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Incorporating behavior in infectious disease models for economic evaluation

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Contents

List of abbreviations

ABM	Agent-based model
AEFI	Adverse events following immunization
ASCID	Antwerp Study Centre for Infectious Diseases
BCM	Behavioral change model
BISS	Behavioral Insights Summer School
CBA	Cost-benefit analysis
CDC	Centers for Disease Control and Prevention
CEA	Cost-effectiveness analysis
CFR	Case-fatality rate
COVID	Coronavirus disease
CUA	Cost-utility analysis
DALY	Disability-adjusted life years
DCE	Discrete choice experiment
DF	Degrees of freedom
DSA	Deterministic sensitivity analysis
DTP	Diphtheria, tetanus, pertussis
E	Exposed (disease state)
ECDC	European Centre for Disease Prevention and Control
EVD	Ebola virus disease
FDA	Food and Drug Administration
FWO	Fonds voor Wetenschappelijk Onderzoek – Vlaanderen / Research Foundation – Flanders
GP	General practitioner
HB	Hierarchical Bayes
HBM	Health belief model
HH	Household
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HRQoL	Health-related quality of life
HTA	Health technology assessment
I	Infected (disease state)
IBM	Individual-based model
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost-utility ratio
ILI	Influenza-like illness

ISCED	International Standard Classification of Education
KCE	Belgian Health Care Knowledge Centre
LAIV	Live attenuated influenza vaccine
LR	Likelihood ratio
MCDA	Multi-criteria decision-analysis
MMR	Measles-mumps-rubella
MNL	Multinomial logit
MPT	Multi-purpose prevention technology
NICE	National Institute for Health and Care Excellence
NPI	Non-pharmaceutical intervention
NHAPS	National Health and Activity Patterns Survey
ODE	Ordinary differential equation
PBAC	Pharmaceutical Benefits Advisory Committee
PML	Panel mixed logit
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life years
R	Recovered (disease state)
R_0	Basic reproduction number
S	Susceptible (disease state)
SARS	Severe acute respiratory syndrome
SIR	Susceptible – infected – recovered
STI	Sexually transmitted infection
Tdap	Tetanus, diphtheria and acellular pertussis
TIP	Tailoring immunization programmes
TPB	Theory of planned behavior
TPrEP	Topical pre-exposure prophylaxis
UK	United Kingdom
US	United States of America
UZA	Antwerp University Hospital
VPD	Vaccine-preventable disease
VRSE	Vaccine-related side-effects
VBD	Vector-borne disease
V	Vaccinated (disease state)
VSC	Flemish Supercomputer Centre
WHO	World Health Organization
WoS	Web of Science
WLS	Weighted least-squares

CHAPTER 1

Introduction

1.1 Infectious diseases

In the year 165 the Antonine Plague broke out in Rome, following the return of the Roman army from Parthia. The impact of this disease was significant in terms of disease burden and fatalities but also in terms of disastrous effects on the economy of the entire Roman empire. Indeed, the number of taxpayers collapsed significantly, up to a 93% decline in some districts, as a result of many casualties and people fleeing from the epidemic [106].

Other examples of infectious disease outbreaks, epidemics or pandemics are ubiquitous. E.g. the Black Death in the middle of the 14th century killing an estimated 30-50% of the European population, resulting in severe economic, social and demographic changes during and following the years of the epidemic [93]. The 1918 influenza pandemic, a global epidemic, also referred to as the Spanish flu, caused the death of an estimated 50-100 million individuals worldwide [181].

All these examples of devastation in history have a common origin, i.e. they are caused by an infectious disease. The World Health Organization (WHO) defines infectious, or communicable, diseases as: "caused by pathogenic microorganisms, such as bacteria, viruses, parasites or fungi; the diseases can be spread, directly or indirectly, from one person to another. Zoonotic diseases are infectious diseases of animals that can cause disease when transmitted to humans [439]". The communicable, or transmissible, character of infectious diseases provides public health policymakers with both assets and liabilities. Needless to say, outbreaks require prompt interventions and, depending on the route of transmission, can quickly result in worldwide catastrophes as mentioned in the examples above. However, if outbreaks can be prevented or contained through interventions, the total burden of the disease can be limited to only a few initial cases. Under certain circumstances, the communicable

character can even facilitate the eradication of certain diseases, when transmission can be halted completely [18]. Still, to date, humankind was only able to eradicate one human disease by vaccination. Smallpox was declared eradicated by the WHO in 1980 thanks to an eradication program and a vaccine with origins dating back to Edward Jenner's findings in the late 18th century [377]. The last natural case of smallpox had been reported in 1977 in Somalia, while in 1978 a final case was confirmed in Birmingham after lab exposure [246].

In developed societies demographical and epidemiological transitions have been observed in the last centuries following the introduction of medical technologies that prevent and treat infectious diseases. Take for instance, the differences in the mortality and population structure by age in England and Wales between 1891 and 1966 as described by William Jack [176]. In figure 1.1, two observations stand out. Namely, i) people become older in 1966 than in 1891, with about 45% of the population reaching the age of 75 and above in 1966, i.e. the population ages; ii) mortality has shifted from childbirth and very young children to older age groups, with the former category only responsible for about 5% of the deaths in 1966, compared to 35% in 1891. Three main health technologies contributed to these dynamics and all three link back to the (reduced) burden of infectious diseases: i) the discovery of Penicillin (an antibiotic) by Alexander Fleming in 1928 and widespread treatment starting in 1942 [231] ; ii) the widespread use of vaccination, first against smallpox – the vaccine was made compulsory in England and Wales in 1853 – and followed by vaccines against other pathogens such as anthrax and rabies [377]; iii) increased hygiene and sanitation such as hand washing, sewerage and safe water supply [175].

Additional and more innovative health technologies have been developed since, yet today infectious diseases still cause a significant burden to public health on a global scale. E.g. measles caused 110 000 deaths in 2017, even though a safe and cost-effective vaccine is available [444]. Moreover, a lot of the infectious disease fatalities are seen in children under the age of 5. E.g. pneumonia caused 15% of all deaths of children under five years old, killing over 800 000 children in 2017, followed by diarrhoeal disease killing around 525 000 children under the age of 5 each year. Furthermore, people living in developing populations are at significantly higher risk of having severe or fatal infection due to limited access to resources [441, 445]. Examples of recent outbreaks are: measles outbreaks in countries that had previously eliminated or interrupted endemic transmission [119], ebola in West Africa in 2013-2014

[132], the 2009 influenza A/H1N1 (or mexican flu) in 2009 [55] and the 2019-20 COVID–19 pandemic [81].

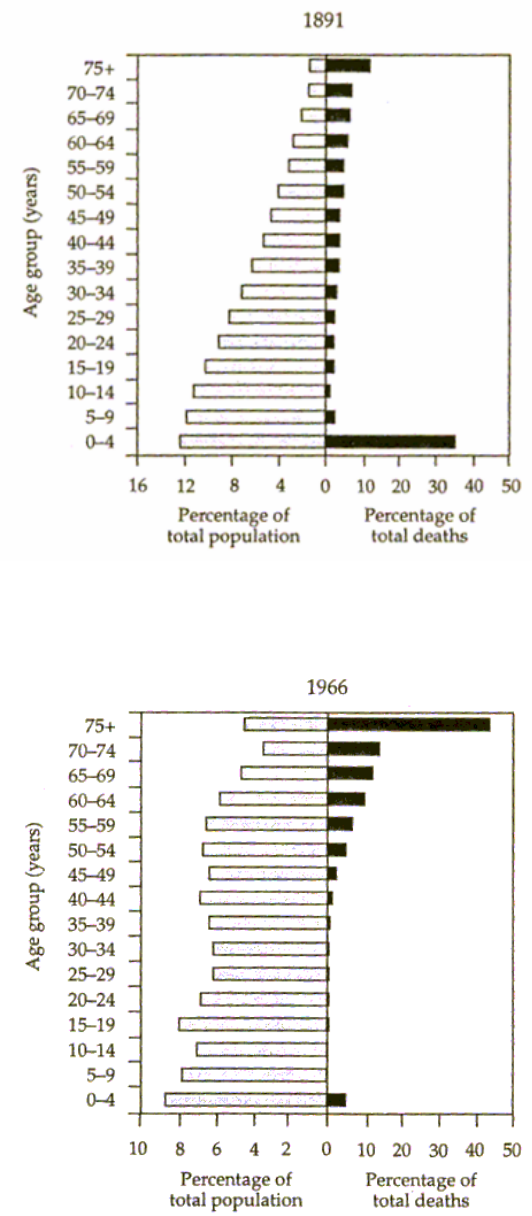

Figure 1.1: Demography and epidemiology in England & Wales in 1891 and 1966, adapted from William Jack [176]

1.2 Immunization, vaccination and vaccine hesitancy

The WHO defines immunization as: "the process whereby a person is made immune or resistant to an infectious disease, typically by the administration of a vaccine. Vaccines stimulate the body's own immune system to protect the person against subsequent infection or disease" [443]. Vaccination is one of the most successful health interventions ever, averting between 2 and 3 million deaths each year. Moreover, vaccination is one of the most cost-effective health technologies ever and known to be a safe way to prevent infection in humans and to halt or limit the spread of pathogens [443].

Vaccination is a textbook example of an externality: if an individual decides to get vaccinated, this decision has, mostly positive, implications on others. Indeed, vaccination is characterized by 'herd immunity', by which the vaccination of one individual decreases not only this individuals' own infection risk, but also reduces the risk of infecting others, as the vaccinated individual is no longer a potential transmission route. As such, the more individuals get vaccinated, the lower the likelihood that a disease will spread among the population. This means that even with a vaccine coverage below 100%, an infectious disease can be contained or eliminated. This is illustrated in Figure 1.2. The indirect protection of unvaccinated people in a largely vaccinated population is essential because it provides a safety net for those who cannot receive vaccination for medical reasons (e.g. too young, immunocompromised, pregnant), those who deliberately reject or delay vaccination or those who are not or no longer immunized by the vaccine they received.

Herd immunity, or herd protection, complicates the decision of whether or not to get vaccinated. As more and more people get vaccinated, the marginal benefit to vaccinate oneself decreases. Theoretical game theory models assume that at some point, when the marginal cost to vaccinate (expressed in terms of either time, monetary units or perceived vaccine adverse events) exceeds the marginal benefit, individuals will rationally refuse vaccination. The decision is further complicated by the uncertain nature of prevention measures: people do not know upfront when, or whether, they will contract a vaccine-preventable disease (VPD). Moreover, vaccination is to a certain extent victim of its own success. Regions with high vaccination coverage experience less VPD burden, and when this occurs over a long period, individuals no longer perceive VPDs as a reasonable threat to their health [472].

Only moments after the introduction of Edward Jenner's cowpox vaccination in the late 18th century, negative sentiments and false information regarding this

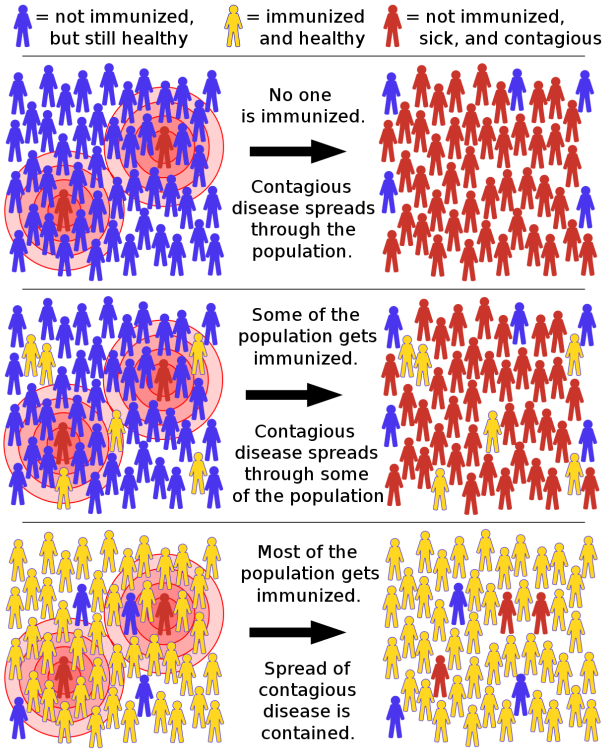

Figure 1.2: In the top box no-one is immunized. As such almost everyone gets infected by the two initial cases. In the middle box, some individuals are immunized. However, the coverage is suboptimal such that the disease can still spread through the population (only immunized individuals can circumvent infection). In the bottom box, almost all individuals are protected from infection, either by immunization or by herd protection (immunized individuals can prevent the disease from spreading to some susceptible individuals). By Tkarcher `https://commons.wikimedia.org/wiki/User:Tkarcher` **and licensed under CC BY-SA 4.0** `https://creativecommons.org/licenses/by-sa/4.0`.

new technique to prevent smallpox infection were spread by the anti-vaccine movement (e.g. see Figure 1.4). Also today, the successes of vaccination are increasingly undermined trough elevated vaccine hesitancy which was identified as one of the 10 global health threats in 2019 by the WHO [442]. Vaccine hesitancy refers to the: "delay in acceptance or refusal of vaccination despite availability of vaccination services" [247]. In essence, the vaccine hesitancy continuum is anywhere between those who accept all vaccines on time and those who refuse all vaccines (Figure 1.3) [247]. Reasons for vaccine hesitancy and refusal originate from a spectrum of controversies, such as: refusal on

religious grounds (e.g. in the Bible Belt in The Netherlands and Amish communities), conspiracy theories, people preferring a "natural infection" - although this strategy being conditional on survival and at the risk of severe complications, perceived severe side-effects (e.g. the alleged, but repeatedly refuted, link between autism and measles-mumps-rubella (MMR) vaccination [140]) and disbeliefs in vaccines' effectiveness. The Wellcome Global Monitor 2018 revealed that only 40% of Eastern Europeans believe vaccines are safe, followed by 59% in Western Europe - with France having the worst score, with only two in three agreeing that vaccines are safe. In Northern Europe and Northern America, figures are slightly higher at 73% and 72%, respectively. Attitudes with respect to vaccines' effectiveness were more positive with worldwide 84% who agree to some extent that vaccines are effective [131]. Another study from 2016, that assessed vaccine confidence in 67 countries found that overall, vaccine sentiments appeared to be inversely correlated with socioeconomic status [217].

The current magnitude of vaccine hesitancy is at least partly attributable to the internet and a variety of social media that have amplified the spread of misinformation and have facilitated the creation of new online anti-vaccine communities [214]. As such, not only pathogens spread globally in a matter of days through ever-increasing human mobility [273], but vaccine scares and hesitancy can propagate even faster online [214, 343]. The communicability of both infections and vaccine hesitancy undermine hard-fought investments to prevent, control and eradicate infectious diseases [217].

Vaccine coverage is insufficient, and falling, in many EU countries and in the US. For example, a large pool of people in the EU are susceptible to measles due to low historical and current vaccination coverage. Remarkably, a safe and effective vaccine is available, that was licensed by the FDA already in 1971 [63]. Only 4 EU countries achieved a vaccination coverage of at least 95% in 2017, compared to 14 countries in 2007. These numbers are very concerning as it causes a decline in indirect protection, or herd immunity, which plays a central role in protecting vulnerable individuals (e.g. the very young or immunocompromised). Unsurprisingly, measles resurgence has recently been observed, with 44,074 cases in 30 EU member states between 2016 and March 2019 [119]. A similar trend has been observed in the US, with over 1276 cases reported in 2019 (even though the US declared elimination of endemic transmission in 2000) [65, 280, 306]. Both supply-side effects and demand-side effects can be held responsible for these dynamics. On the supply side, for example, the time-consuming organization of vaccine visits or clumsy appointment systems can explain lower uptake. Moreover, the transition from

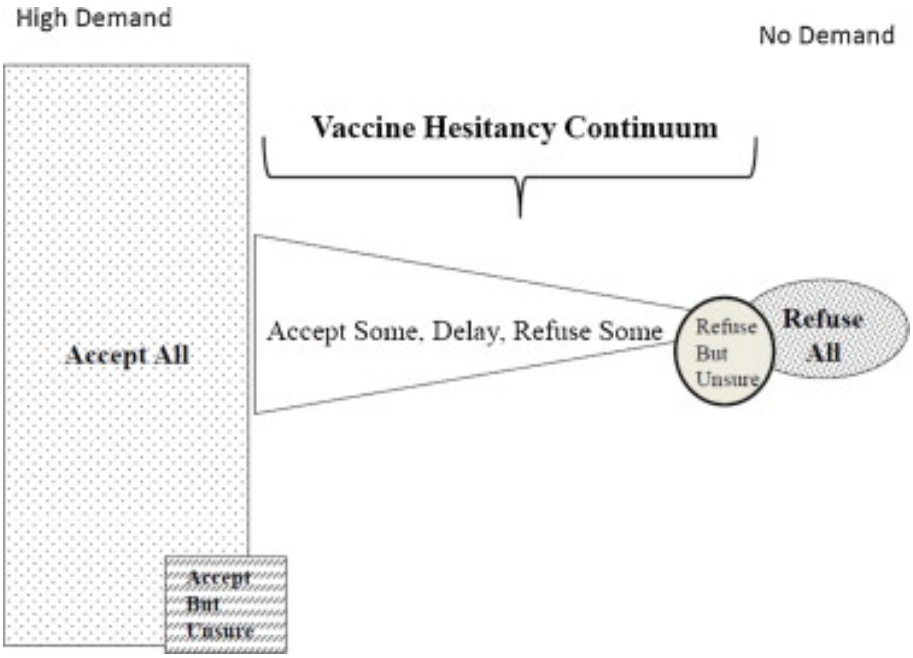

Figure 1.3: The continuum of vaccine hesitancy between full acceptance and outright refusal of all vaccines. MacDonald et al. [247]

natural infection to vaccine-induced immunity, following the introduction of measles vaccine, can lead to suboptimal immunity levels [166]. However, on the demand side, "vaccine hesitancy" also plays an important part in the decreased immunity levels and observed outbreaks in countries that had previously eliminated vaccine preventable diseases such as measles [344].

On the demand side, interventions are needed to restore confidence in vaccines and trust in public health institutions. On the supply side, initiatives should be undertaken by lowering the barriers for people to get vaccinated to an absolute minimum. But first, insights are needed into which elements individuals take into account when deciding about vaccination.

Figure 1.4: Caricature by James Gillray. "The Cow-Pock - or - The Wonderful Effects of the New Inoculation!". Publication of the Anti-Vaccine Society in 1802.

1.3 Modeling infectious diseases

Mainly because of ethical considerations, mathematical and economic models have been proven valuable tools to simulate and evaluate the impact of prevention measures on the spread, burden and economic impact of infectious diseases. These models inform and guide policy-makers to prepare for and respond to (re)emerging infectious diseases, particularly when sufficient information from controlled experiments is lacking.

An important example of such infectious disease model is the susceptible-infected-recovered (SIR) model by Kermack and McKendrick in their 1927 paper: *A contribution to the mathematical theory of epidemics* [196], which was later converted into the basic SIR model and other compartmental models. Compartmental models are typically characterized by a system of ordinary differential equations (ODEs) in which each equation determines the movement in and out the three different compartments. A simple SIR model without demographics, can be represented by the following system of ordinary differential equations:

$\frac{dS}{dt} = -\frac{\beta IS}{N}$,

$\frac{dI}{dt} = \frac{\beta IS}{N} - \gamma I$,

$\frac{dR}{dt} = \gamma I$

People move from the susceptible compartment (S) at a rate depending on β, the number of contacts per time unit per person, the fraction of infected individuals (that can transmit the disease to others) and the fraction of susceptible individuals (that can potentially be infected). This proportion, $-\frac{\beta IS}{N}$, moves individuals into the infected compartment. Lastly, individuals recover at a rate γ and end up in the recovered compartment (R).

The infectiousness of a specific pathogen or disease is often captured by the basic reproduction number (R_0), which is defined as the average number of new infections caused by one infected individual in a fully susceptible population [12]. In the SIR model, the basic reproduction can be calculated as follows: $R_0 = \frac{\beta}{\gamma}$. For example, the basic reproduction numbers for measles and diphtheria are estimated to be in the range of 15-17 and 4-6, respectively [12]. This implies that if one measles case is introduced in a fully susceptible population, on average this case will infect about 15 to 17 other individuals. Using R_0 values, one can estimate, under the assumption of a 'homogeneously mixing population', the critical vaccination coverage to block transmission,

also referred to as the 'herd immunity threshold', using equation: $Cov_{crit} = 1 - \frac{1}{R_0}$. As such, a vaccine coverage of at least 92 to 95% is needed to block the transmission of measles [12]. Unsurprisingly, the WHO target vaccination coverage for measles eradication is set at 95% [119]. See Table 1.1, adapted from Anderson & May [12], for an overview of basic reproduction numbers for a selection of vaccine-preventable diseases.

Infectious agent	R_0	$Cov_{crit}(\%)$
Measles	15 - 17	92 - 95
Pertussis	15 - 17	92 - 95
Mumps	10 - 12	90 - 92
Rubella	7 - 8	85 - 87
Diphtheria	5 - 6	80 - 85
Polio virus	5 - 6	80 - 85

Table 1.1: Basic reproduction numbers (R_0) and critical vaccination coverages in order to block transmission (Cov_{crit}), under a homogeneous mixing hypothesis for a selection of vaccine-preventable childhood diseases. Adapted from [12].

Other models have been developed in order to model the spread of a wide range of infectious diseases and interventions to contain them. For example adding a vaccinated compartment with waning immunity in an SIRVS model, SIS models for pathogens that do not provide long-lasting immunity, or models including an M compartment in order to capture maternal immunity for newborns etc.

1.4 Health economic evaluation

Health interventions are evaluated with respect to both health effects and costs in health economic evaluations or health technology assessments (HTA). The outcome of HTA guides decision makers and policymakers when deciding about the introduction and reimbursement of (new) health technologies. The objective of HTA is to optimize health care outcomes by identifying and selecting the most efficient health care interventions. I.e. to obtain maximum health outcomes for a given health budget. This objective requires comparing different interventions and making choices. Most HTA methods evaluate the health technology in a marginal sense. That is, the technology under study, is compared to a baseline situation, usually a status quo situation or an alternative intervention. Economic evaluation aims to answer questions like: "Is a

million euros really a justifiable price for a new cancer treatment?" or "Is it worth investing in human papillomavirus (HPV) vaccination in boys?".

An important element in health economic evaluations is the point of view – or perspective – that is taken in the analysis. The choice of perspective has an important impact on the cost and benefit components assessed in the evaluation [202]. Some commonly used perspectives are (ordered from broad to narrow): societal, healthcare system, insurer, single perspective (e.g. a hospital) and the patient's perspective. Whereas the societal perspective includes all possible cost and benefit components of a healthcare service or illness – e.g. including caregivers' time to take care of an ill family member – other perspectives focus on fewer components. For example, productivity losses due to illness (presenteeism) would not be included in a healthcare payers' perspective while it forms an integral part of the costs in a societal perspective. Belgian guidelines specify the reference case to use the healthcare payers' perspective that consist of the patients, the federal government and the three Belgian communities [389]. On the contrary, the Dutch guidelines prescribe to take a societal perspective [419]. Naturally, health economic evaluations can only be compared if they apply the same perspective.

The most common approaches to HTA are: i) cost-effectiveness analysis (CEA), ii) cost-utility analysis (CUA) and iii) cost-benefit analysis (CBA).

Cost-effectiveness analysis (CEA)

CEA evaluates health interventions by expressing the additional costs relative to the added health effects. The measurement or valuation of such health effects (E) is expressed in natural units, such as: life-years gained, disability-days saved, number of acute exacerbations averted, points of blood pressure reduced etc. [102]. CEA assesses the marginal costs (ΔC) and the marginally gained health effects (ΔE) in order to obtain the incremental cost-effectiveness ratio (ICER):

$$ICER = \frac{\Delta C}{\Delta E},$$

E.g. an ICER of €2500 per life year gained to introduce and fully reimburse new Hepatitis C antivirals, means that, on average it costs society €2500 per life-year saved in Hepatitis C patients due to the new treatment, compared to an alternative treatment. Given that this measure ignores the quality of life under certain medical conditions and treatments, it is not frequently used in practice.

Cost-utility analysis (CUA)

Instead, CUA is the most commonly used method for health economic analyses, because it takes into account the quality of life in evaluating the health effects. Indeed, instead of a single effect of interest (e.g. life years gained), CUA uses 'healthy life-years', and more commonly, quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs) [102]. Figure 1.5, illustrates that by assessing QALYs, one takes both the life years gained and the quality of life – during and the years following the intervention – into account. A CEA would typically only look at the difference between death with and without the intervention (on the x-axis). In the case of CUA, quality of life at any point in the patients' life too is taken into account (on the y-axis) by a value ranging between 1 (perfect health) and 0 (death). In this specific example, the intervention adds to the patients' health-related quality of life and additionally prolongs the life of the patients. The total QALYs without intervention is equal to the blue surface (A) and the total number of QALYs under the intervention equals the blue and brown surface (A+B). As such, the total number of QALYs gained equals the brown surface (B).

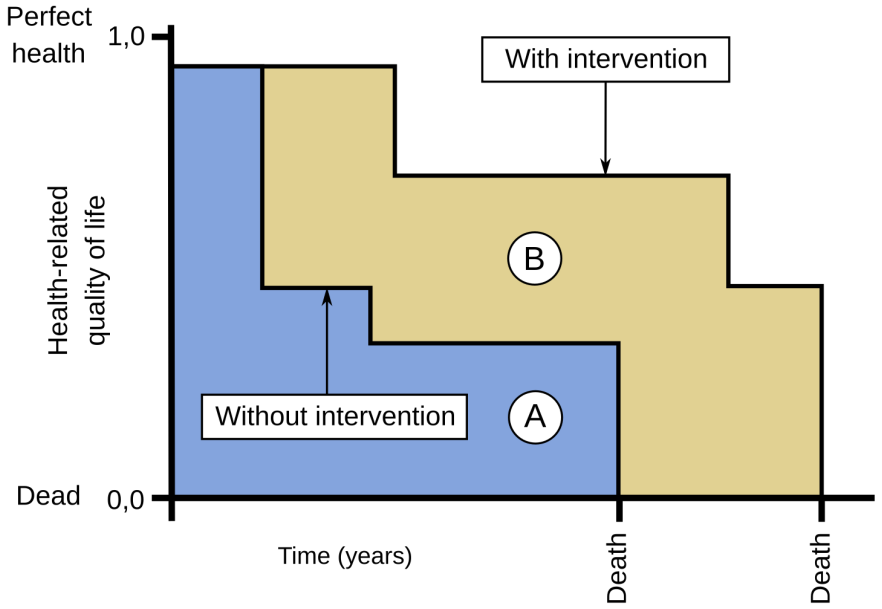

Figure 1.5: Quality adjusted life-years in terms of life years and health related quality of life. The total QALY gain with the intervention is represented by the brown surface (B). By Jmarchn `https://commons.wikimedia.org/wiki/User:Jmarchn` **and licensed under CC BY-SA 3.0** `https://creativecommons.org/licenses/by-sa/3.0/deed.en`**.**

The incremental cost-utility ratio (ICUR) is thus defined as:

$ICUR = \frac{\Delta C}{\Delta QALYs}$,

The ICUR can be interpreted as the cost per quality-adjusted life year, or the cost per healthy life year, relative to the chosen baseline. Compared to CEA, incorporating quality of life in CUA has already improved HTA significantly. However, some important limitations remain, for example: i) CUA cannot determine the total size of the healthcare budget, and ii) CUA does not take inequality into account (i.e, who pays the costs and who benefits from a specific intervention does not matter in CUA).

Cost-benefit analysis (CBA)

Cost-benefit analysis in health care interventions originates from social welfare theory. It allows to incorporate distributional weights and evaluates the net-benefit of an intervention in monetary terms. As such, also health benefits are expressed in monetary terms and there is no need to compute ratios. Instead, in CBA, the outcome is expressed in terms of net-benefits or net-costs.

Net-benefit = total benefits - total costs

If the net-benefit is positive, the intervention is economically interesting. Note, that CBA can be applied to non-health interventions as well, allowing trade-offs to be made between health interventions and other interventions. In theory, CBA allows policymakers to determine the size of the health care budget. Yet, in practice this would require a CBA for all available healthcare interventions, and summing the total costs of the interventions that resulted in a net-benefit. Even if this tedious procedure could be – and would be – performed in practice, the overall size of the health care budget would most likely still be largely determined by political rather than technical considerations. Nevertheless, CBA is rarely used in practice, particularly due to the lack of consensus (among economists) and credibility (among medical professionals) when the value to a statistical life-year is determined as an intrinsic part of the analysis, as is the case with CBA.

Uncertainty in HTA

Every health economic analysis contains at least some degree of uncertainty [202]. Therefore, guidelines recommend that uncertainty analysis forms an inherent part of health economic analysis [168, 207]. We refer to the work by Bilcke et al. for a practical guide that offers an integrated approach to

account for different kinds of uncertainty in decision-analytic models [35]. The authors proposed three broad categories of uncertainty: methodological (e.g. perspective or discounting rate), structural (e.g. types of functions for extrapolation or intervention efficacy in different age classes) and parameter uncertainty (e.g. true value of parameter or bias in parameter estimation) [35]. Sensitivity analysis has been central in the assessment of uncertainty [202]. In a deterministic sensitivity analyses (DSA), one parameter (or methodological choice / model structure) is altered one step at a time in scenario analyses while all other features remain equal (*ceteris paribus*). Other model features are ideally altered in proceeding steps up to a point where all parameter (and methodological choices / model structures) combinations have been analyzed. Probabilistic sensitivity analysis (PSA) requires the distribution of input parameters instead of simple point values [297]. In a PSA, input parameters are randomly sampled from their respective distributions in an iterative process (at least 1,000 iterations). For each iteration a health economic analysis is performed (i.e. modelled) of which the outcome is stored (e.g. ICUR or life-years lost). A PSA provides a distribution of outcomes (e.g. in terms of ICURs) [297]. We refer to the WHO guide for standardization of economic evaluations of immunization programmes for more details about uncertainty and HTA of immunization programmes in general [297].

Equity considerations and the role of HTA in reimbursement decisions

Conventional health economic analyses implicitly consider a utilitarian equity perspective: the societal value of a QALY gained is independent of how it is obtained, or to whom it accrues. That is, QALYs are independent of: age (a QALY gained in a 80 year old is valued equally to a QALY gained in an 8 year old), type of health technology (preventive versus curative), patients' lifestyle (bad luck versus lifestyle-induced illness), the initial health state of the patient etc. Yet the general population's opinions deviate from these implicit ethical assumptions. Indeed, Luyten et al. found patients' lifestyle, age and the type of health technology to be significant attributes in Belgians' preferences with respect to prioritisation of healthcare interventions [245]. The work by Cleemput et al. confirms that societal preferences do not fully correspond to the utilitarian theory embedded in conventional HTA [72]. Yet, several procedures have been developed to integrate equity considerations in health economic evaluations, such as incorporating equity weights and social welfare functions, or by the use of multi-criteria decision-analysis (MCDA) [182, 348].

Health technology assessment is however only one component of reimbursement decision making. Whereas economic considerations have been consistently found influential in reimbursement decision-making in the UK, the strength of clinical evidence for the drug of interest was found more important [101]. Studies in Australia, Britain, Canada and Ireland reported HTA to have had a significant role in reimbursement recommendations as well [73, 281, 353]. Indeed, since the 1990's policymakers increasingly use economic evaluations when making decisions about healthcare programs. Since 1993 it has been mandatory for sponsors to formally include an economic analysis in submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, whereas guidelines for economic evaluation were already introduced in 1990 [102, 152]. In 1999, the National Institute for Health and Care Excellence (NICE) was established in the UK with as a formal role "the appraisal of new and existing health technologies" [321]. The Belgian Health Care Knowledge Centre – that was established in 2002 – performs health technology assessments as one of its five primary objectives. These assessments provide useful information to the Commission on Reimbursement of Health Products (*Commissie Tegemoetkoming Geneesmiddelen*) that is responsible to amend the list of reimbursable pharmaceutical technologies in Belgium since 2002 and formally requires health economic evaluations as a part of reimbursement submissions [424].

The role of infectious disease models

Model based predictions and dynamics serve as a highly valuable tool for the health economic evaluation of infectious disease interventions. The impact of different health interventions (e.g. vaccination, antiviral use etc.) can be assessed by applying these interventions to infectious disease models. Typically, several scenarios are compared to a baseline situation. The model output, often the decrease in the burden of the disease, serves as an input in HTA. For example, a vaccination program against influenza can be simulated in an infectious disease model in order to retrieve $\Delta QALY$ and ΔC under different scenarios.

1.5 Behavioral change models in epidemiology

However, the impact of prevention measures and other policy interventions are subject to individuals' compliance and demand. For that reason, behavioral change models have been developed to incorporate dynamic behavior (i.e. the demand side of prevention measures) into models for infectious disease transmission. As a result of circulating controversies and herd immunity touched

upon in the previous paragraphs, vaccination models have become particularly interesting to take dynamic behavior into account. As a result of herd immunity, the marginal utility of vaccination decreases (non-linearly) as coverage increases. For example, modelers have been integrating this externality into game-theoretical models [127, 411]. These mainly theoretical models assume that individuals are free-riders, enjoying protection from herd immunity and hence no longer have the incentive to become vaccinated themselves if vaccine coverages are already sufficiently high. As more and more individuals engage in this free-riding behavior, diseases reemerge and the incentive for individuals to become vaccinated reappears. Behavioral change models are used for various prevention measures, and can model individuals' decision making under different decision rules and assumptions.

Figure 1.6 graphically illustrates an example of a rather simplistic behavioral change model. Individuals need to decide at some point in time (t) whether or not to take a preventive measure. Some examples of prevention measures are: vaccination, antiviral use, wearing face-masks or social distancing. The individuals are exposed to an information set about the disease and the prevention measure e.g. the susceptibility to the disease and potential side-effects of the prevention measure under study. Note that this information set is subject to bias and, as such, some authors rather use 'perceived' susceptibility, 'perceived' side-effects, 'perceived' vaccine efficacy and so forth. Based on this information, individuals decide whether or not they take preventive measures to protect themselves from being infected based on a pre-determined decision function, whether or not taking others' decisions into account. All these decisions combined, have an effect on disease dynamics, which are typically estimated by infectious disease models (e.g. an SIR model adding a 'vaccinated' compartment). There is a feedback mechanism providing an information set to the individuals deciding about preventive measures in a next step. This feedback mechanism introduces the dynamic character of behavioral change models and can be either direct (upper arrow), or can be spread by third parties such as public health information campaigns, social media, healthcare workers etc. In essence, the preventive measures taken by individuals in time t determine the information set of individuals deciding in time t+1, by applying an infectious disease model to estimate the impact in t+1.

1.6 Behavioral change theories in social sciences

Note that several behavioral change theories have been developed in social sciences – such as in anthropology and medical psychology – as well, and

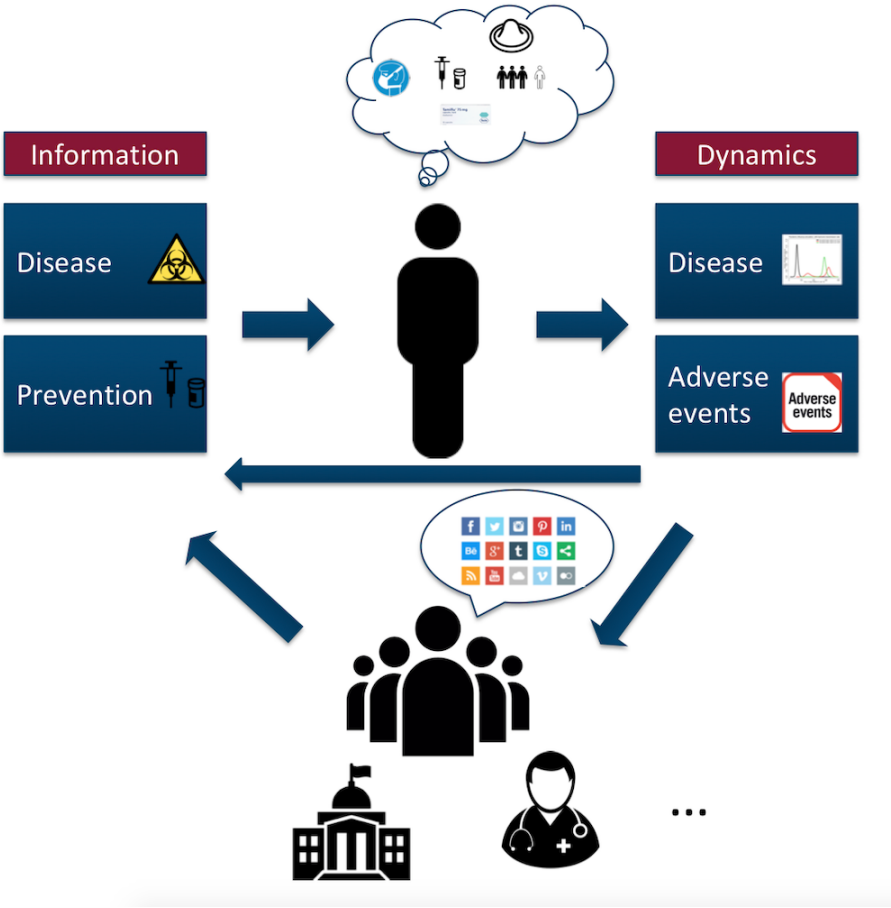

Figure 1.6: A graphical representation of a dynamic behavioural change model that is coupled to an epidemiological model. This illustration presents a rather simplistic – but frequently used – behavioral change model in which individuals change their behavior solely based on information about the disease and/or intervention measures. Other, more realistic models will be tackled in the remainder of this thesis.

are often explicitly used in predicting vaccination uptake [367]. Two behavioral theories stand out: i) the Health belief model (HBM) and ii) the Theory of Planned Behavior (TPB), which we will introduce in more detail in the remainder of this section.

Note that other behavior change theories have been developed: e.g. the health action process approach [355] and the transtheoretical model of health behavior change [316]. In addition, we would like to draw special attention to the "Behaviour Change Wheel" developed by Michie et al. that was published in 2011

[262], which has been used as a foundation of the WHO's recently developed Tailoring Immunization Programmes (TIP) approach [298]. The behavioural change wheel is a framework that involves three essential conditions, namely: capability, opportunity and motivation (referred to as the 'COM-B system'). The authors furthermore propose 9 interventions to resolve deficits in one of these conditions as well as 7 categories of policies to enable such interventions. The application of this theory of behavior change reaches beyond the field of immunization and was successfully used to characterize interventions in the fields of tobacco control and reducing obesity. Further discussion of this model reaches beyond the scope of this thesis. For more details regarding the behaviour change wheel and its' relevance for behavioural insights into immunization programme planning and policy, we would like to invite the reader to consult the work by Michie et al. [262] and the WHO's guide to TIP [298].

The Health Belief Model

The Health Belief Model was developed in the US Public Health Service in the 1950s and "...grew simultaneously with the solution of practical problems" [331]. That is, the HBM was mainly a response to failure in the uptake of disease prevention measures and screening tests (e.g. for the early detection of asymptomatic disease), which were both focal points of the Public Health Service at the time. The model, in one of its earliest forms, describes that in order for an individual to take a preventive action, he or she would need to believe three traits: i) that the individual is susceptible to the disease, ii) that by contracting the disease, the individual would at least suffer from moderate severity in at least one aspect of its' life, and iii) taking preventive action would be beneficial to the individual – hence, either reducing the susceptibility to the disease, reducing the severity when that individual contracts the disease, while not overcoming important psychological barriers (e.g. costs, convenience, pain etc.) [331].

The HBM aims to predict and explain preventive behavior in terms of certain belief patterns [170]. An individual's motivation in taking preventive action can be divided into three categories: individual perceptions, modifying behaviors or factors and the likelihood of action [170]. In more recent descriptions, the HBM consists of 6 constructs (adapted from Strecher & Rosenstock [378]):

1. **Perceived susceptibility:** individuals' subjective perception of the risk of contracting a health condition or, in case of medically established ill-

ness, this construct can include the acceptance of the diagnosis, personal estimates of resusceptibility, and susceptibility in general.

2. **Perceived severity:** individuals' feelings with respect to the seriousness of contracting an illness, or of leaving it untreated, including both medical (e.g. pain, death, disability, discomfort etc.) and social consequences (e.g. family or social life).

3. **Perceived benefits:** individuals' beliefs regarding the effectiveness of available actions in reducing the odds of contracting the disease, or when contracting the disease, the belief that this action would result in a lower severity. That is, "... an individual exhibiting an optimal level of beliefs in susceptibility and severity would not be expected to accept any recommended health action unless that action was perceived as potentially efficacious. [378]".

4. **Perceived barriers:** individuals' subjective perception about the negative attributes of a health action recommended (i.e. that the action may be expensive, dangerous in terms of side-effects, time-consuming, uncomfortable, inconvenient etc.).

5. **Cues to action:** individuals' internal or external triggers to accept the desired course of action (e.g. environmental factors, exposure to a health promotion campaign etc.).

6. **Self-efficacy:** individuals' belief that they "... can successfully execute the behaviour required to produce the outcomes." [19]. I.e. that they are confident they can pursue the desired health action.

The HBM has been implemented in a multitude of studies predicting or explaining vaccination uptake or acceptance. For example, in the context of HPV vaccination [95, 133], for pandemic influenza vaccine [75], but also in more general contexts such as for parents making decisions about childhood vaccinations [366]. Note that, the HBM has been applied in epidemiological BCMs as well – such as in the work by Karimi et al. [190] and Durham & Casman [108], though such applications remain relatively rare to date.

Theory of Planned Behavior (TPB)

The Theory of Planned Behavior was proposed by Ajzen in the 1980s [5, 8], building on the Theory of Reasoned Action proposed earlier by Fishbein & Ajzen [7, 115]. The intention to perform a given behavior is a central factor

to the theory of planned behavior. Indeed, intentions are assumed to capture motivational factors which influence individuals' behavior. That is, " ... how hard individuals are willing to try ... how much of an effort they are planning to exert, in order to perform the behavior." [6].

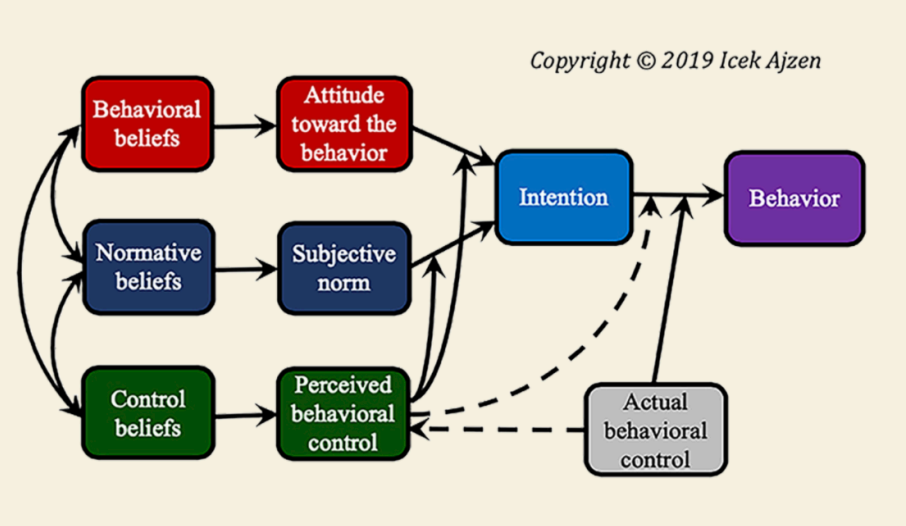

Figure 1.7: Theory of Planned Behavior. A schematic depiction. Copyright ©2019 Icek Ajzen.

The TPB is schematically depicted in Figure 1.7. We briefly elaborate on each of the theory's constructs, based on the work by Ajzen [6]. According to the TPB, three main factors shape an individual's intention to perform a certain behavior and, subsequently, their actual behavior. The first are an individual's beliefs about the probability of a given outcome of the behavior ("behavioral beliefs"), and about the value of performing the behavior ("attitude toward the behavior"). Secondly, an individual's intention is influenced by the social pressure they perceive to perform a certain behavior ("subjective norm"). This subjective norm is, in turn, the result of what an individual thinks is expected of them by people whose opinion they value ("normative beliefs") and their motivation to live up to those expectations. Lastly, an individual's assessment of their own ability to perform a given behavior ("perceived behavioral control"), given the perceived presence of circumstances that may alter how well the behavior can be performed ("control beliefs"), moderates the first two factors to produce an actual intention, and finally, behavior.

The theory of planned behavior has been proven useful to query intentions in the context of vaccination. Indeed, in the context of HPV vaccination,

Catalano et al. used the TPB to predict vaccination intentions of college men [61], whereas Askelson et al. focussed on mothers' intentions to vaccinate their daughters [17], and Fisher et al. queried intentions in both men and women of target age [116]. The theory of planned behavior has moreover been applied to assess the intention to vaccinate against other pathogens as well, such as influenza [3], or Hepatitis B [88].

1.7 Motivation and aim

Although there is increased recognition for the need to incorporate behavioral changes in infectious disease transmission models, a consensus on the proper methodology to do so is lacking. It appears much research is not supported by empirical information but departs from a theoretical foundation with arbitrarily chosen parameter values and no validation process. As a result, there is large heterogeneity in the triggers for behavioral change and the impact on disease transmission, as well as the conclusions of such studies. There is a need for empirical data to support the validity of these models and to guide further research [127, 128, 411]. Surprisingly, even though an extensive selection of behavioral change models is available and demand-side obstacles are increasingly manifested, HTA applications to infectious disease prevention that incorporate such models are lacking. The aim of this thesis is to explore and evaluate behavioral change models for infectious disease transmission and gather empirical data in order to parameterize behavioral change models for vaccination. This way, future models can take empirical data into account. We will apply these empirical data to a behavioral change model for vaccination against, and transmission of, measles. Additionally, we aim to introduce individuals' behavior in the health economic evaluation of infectious disease interventions.

1.8 Introducing the chapters and their objectives

This thesis is composed of three main parts: i) review and exploration of behavioral change models, ii) quantification of vaccination behavior in order to parameterize behavioral change models, and iii) applications to behavioral change models with respect to measles transmission and vaccination and a cost-benefit analysis of employer funded influenza vaccination. Figure 1.8 presents an overview of the topics that are covered in-depth in the chapters. The overall findings of this thesis, as well as the contributions to the research field are reviewed in Chapter 8 (General discussion).

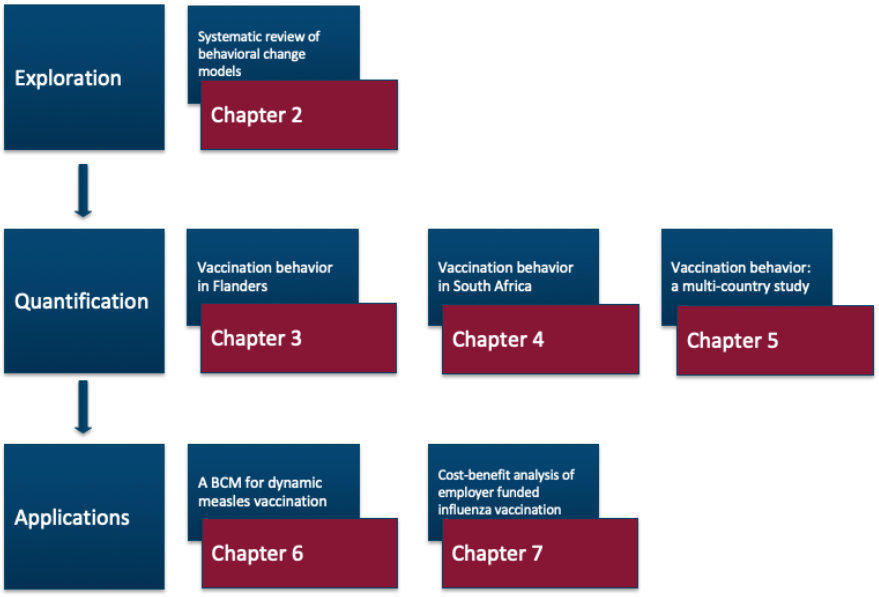

Figure 1.8: Overview of the thesis' structure and chapters.

Behavioral change models (Chapter 2)

Numerous historical infectious disease outbreaks confirm the importance of human behavior in preventing further spread of infectious diseases. For example, during the 2003, severe acute respiratory syndrome (SARS) outbreak people took precautionary actions such as wearing face masks, hand-washing, avoiding public transport, restaurants, shops and other crowded places in Hong Kong [108, 219] and Beijing [29]. Moreover, behavioral interventions seem to be central in combatting the 2019 SARS-CoV-2 pandemic [437]. In addition, the 2009 A/H1N1 influenza pandemic has triggered a significant proportion of the

population to adapt their behavior and take preventive measures such as social distancing [184, 334]. Since the impact of infectious diseases and interventions are indeed depending on behavior, we explore behavioral change models for infectious disease transmission. We systematically identify and analyze models starting from where a previous review in 2010 left off [127]. These models are categorized in order to distinguish their assumptions, methods, disease and transmission-specific applications and implications. Furthermore, a critical point of view is taken when evaluating these models in terms of their real-life applicability. Current pitfalls and opportunities are identified to support the development of more advanced BCMs in the near future. Some BCMs in the setting of infectious disease transmission still use a game-theoretical foundation that caused the development of, for instance, 'vaccination games' [20] and 'epidemic games with social distancing' [323]. In the most recent literature however, only few papers are still using a pure, self-centered game-theoretic model. Despite recent advancements, we remain concerned that most models are purely theoretical and lack representative data and a validation process.

Vaccination behavior in Flanders (Chapter 3)

Given the scarcity of empirical exploration with respect to behavioral change models and in order to investigate whether Flemish individuals involve in free-riding behavior, we performed a discrete choice experiment (DCE) in 1919 respondents in Flanders, Belgium. By means of this DCE, we analyzed vaccination behavior as a multi-criteria decision containing six attributes: i) vaccine effectiveness, ii) vaccine-related side-effects (VRSE), iii) accessibility (in terms of convenience and reimbursement), iv) vaccine-preventable burden of disease, v) local (respondents' network of contacts) vaccination coverage, and vi) population (the population at large) vaccination coverage. Utility levels are calculated for each attribute level, facilitating the parameterization and validation of BCMs for Flanders. We distinguish between individuals making decisions about vaccines that would be administered to themselves, and individuals deciding about vaccines that would be administered to their youngest child. Additionally, this chapter elaborates on the finding that the free-riding assumption as a driver of individual vaccination decisions seems inappropriate.

Vaccine drivers in South Africa (Chapter 4)

Based on the findings in Chapter 3, we fine-tuned and updated the questionnaire. In this chapter, we performed a similar DCE in 1200 respondents in South Africa. A country with a suboptimal vaccination coverage for many

VPD. Furthermore, South Africa is one of the countries that has suffered most from the human immunodeficiency virus (HIV) epidemic. Hence, establishing a high vaccination coverage is essential in order to protect the ones that cannot be vaccinated for medical reasons. By means of this DCE, we gain insight into the most important drivers for South Africans to get vaccinated.

No such thing as a free-rider? (Chapter 5)

Following the survey results described in Chapters 3 and 4, we expand our study population and quantify vaccination decisions by means of a DCE in France, The United Kingdom, The Netherlands and Belgium as a whole. This chapter reveals the most and least important attributes these populations take into account when making decisions about vaccinations. We confirm the inappropriate use of free-riding assumptions with respect to vaccination decisions in all study populations and elaborate on both between and within country differences. Additionally, we highlight the potential of supply side interventions in increasing vaccination coverage.

A BCM for Measles in Flanders (Chapter 6)

We highlighted concerns with respect to the scarcity of real-life data integration in behavioral change models (BCM) in Chapter 2. Therefore, we applied the parameters retrieved from the discrete choice experiment in Chapter 3 to construct a behavioral change model for measles transmission and vaccination in Flanders. Instead of resorting to game-theory and free-riding behavior, we tackled vaccination uptake as a multi-criteria decision, determined by both constant and varying attributes. This BCM simulates the uptake of measles vaccination in children at one year of age, parallel to a compartmental SIRV transmission model that mimics the spread of measles in Flanders. In this chapter we evaluate, among others, the impact of a vaccine scare or a suspension from the immunization schedule, on vaccine uptake and disease transmission. Even though this chapter primarily sketches a proof-of-concept, it provides valuable insights into coupled behavior-disease dynamics under a transparent set of assumptions. We highlight the challenges that remain with respect to data availability.

A return on investment? (Chapter 7)

In this chapter, behavioral changes are applied to the economic evaluation of infectious disease interventions. Absenteeism from work due to influenza causes a large economic burden to society. On the other hand, influenza vaccines

are mostly recommended in specific risk groups, which typically have a low employment rate (e.g. the elderly or chronically ill people). However, a higher vaccination coverage among employees could drastically decrease employee absenteeism both directly (in vaccinated employees) and indirectly (through herd immunity in unvaccinated employees on the workplace and beyond). Therefore, it might be interesting for employers (and perhaps governments) to organize and promote employer-funded vaccination programs for employees, even if the direct protection offered by influenza vaccination is far from perfect. However, to date, the return of such employer investments is largely unstudied, especially in the context of herd immunity. This chapter presents a cost-benefit analysis of employer funded workplace vaccination, incorporating the dynamic (social contact) behavior of symptomatically infected individuals.

CHAPTER 2

A systematic review

This chapter is based on published work: "Verelst F, Willem L, Beutels P (2016). Behavioural change models for infectious disease transmission: a systematic review (2010-2015). Journal of The Royal Society Interface 13 (125): 20160820" [411].

Summary

We review behavioural change models (BCMs) for infectious disease transmission in humans. Following the Cochrane collaboration guidelines and the PRISMA statement, our systematic search and selection yielded 178 papers covering the period 2010-2015. We observe an increasing trend in published BCMs, frequently coupled to (re)emergence events, and propose a categorization by distinguishing how information translates into preventive actions. Behaviour is usually captured by introducing information as a dynamic parameter (76/178) or by introducing an economic objective function, either with (26/178) or without (37/178) imitation. Approaches using information thresholds (29/178) and exogenous behaviour formation (16/178) are also popular. We further classify according to disease, prevention measure, transmission model (with 81/178 population, 6/178 metapopulation and 91/178 individual-level models) and the way prevention impacts transmission. We highlight the minority (15%) of studies that use any real-life data for parametrization or validation and note that BCMs increasingly use social media data and generally incorporate multiple sources of information (16/178), multiple types of information (17/178) or both (9/178). We conclude that individual-level models are increasingly used and useful to model behaviour changes. Despite recent advancements, we remain concerned that most models are purely theoretical and lack representative data and a validation process.

2.1 Introduction

Infectious diseases can have a large impact on society as they can negatively affect, among others, morbidity, mortality, unemployment and inequality. As a result, prevention and control of infectious diseases are important for public health and welfare.

The main objective of infectious disease transmission models is to inform and guide policy-makers to prepare for and respond to (re)emerging infectious diseases, particularly when sufficient information from controlled experiments is lacking. However, the impact of infectious disease transmission and policy interventions are subject to hosts' behaviour. Therefore, there is an interest to incorporate behaviour change in response to disease-related information into models for infectious disease transmission.

Numerous historical infectious disease experiences confirm the existence of a so-called behavioural immune system [350] in humans. For example, during the 2003, severe acute respiratory syndrome (SARS) outbreak people took precautionary actions such as wearing face masks, hand-washing, avoiding public transport, restaurants, shops and other crowded places in Hong Kong [108, 219] and Beijing [29]. In addition, the 2009 A/H1N1 influenza pandemic has triggered a significant proportion of the population to adapt their behaviour and take preventive measures such as social distancing [184, 334].

We refer to models incorporating behavioural immunity as 'behavioural change models' (BCMs), which typically complement models for disease transmission in an attempt to mimic real life dynamics. In essence, a BCM is a model in which individuals are responsive to external information about the disease and as a result take one or more preventive measures to reduce the chance of contracting the disease. The external information individuals respond to can be global (equally available and relevant to all individuals) or local (individual availability and relevance determined by physical or social proximity to the information source). Furthermore, this information can be specified in terms of actual risks ('prevalence-based') or of perceptions of these risks ('belief-based'), as well as a mixture of all the above [127]. Vaccination is a common prevention measure with varying uptake, given historical fluctuations in the trade-off between the perceived risks of vaccine-related side effects (VRSEs) and of vaccine-preventable disease. Other common prevention measures include social distancing and condom use.

A widely used theoretical foundation for the formation and dynamic nature of individuals' behaviour comes from game theory. Game theory has a rich

history in social sciences with the Prisoner's Dilemma being a frequently used illustration (see [137] for a comprehensive introduction). Game theory assumes individuals take rational decisions based on a trade-off that embodies the anticipated rational decisions of all other individuals in society. Even though these assumptions are often not observed in real life [421], a multitude of BCMs in the setting of infectious disease transmission still use a game-theoretical foundation that caused the development of, for instance, 'vaccination games' [20] and 'epidemic games with social distancing' [323].

Another foundation for behaviour change is found in the fields of network science and individual-based modelling (IBM), where there are opportunities to develop more realistic models by introducing (more) heterogeneity. The challenge here is to find a balance between model complexity and computational boundaries. Some examples of behavioural change research for which network science has been used include models using adaptive contact networks [408], vaccinating behaviour in social contact networks [258] and social distancing in sexual contact networks [328].

Although there is increased recognition for the need to incorporate behavioural changes in infectious disease transmission models, a consensus on the proper methodology to do so is lacking. It appears much research is not supported by empirical information but departs from a theoretical foundation with arbitrarily chosen parameter values and no validation process. As a result, there is large heterogeneity in the triggers for behavioural change and the impact on disease transmission, as well as the conclusions of such studies. There is a need for empirical data from, for instance, surveys or discrete choice experiments to support the validity of these models and to guide further research [127, 128].

The main goal of this paper is to systematically review and document how and to which extent behavioural immunity has been explored in infectious disease transmission models over the past 5 years. In brief, we aim to investigate to which extent: (i) technological advancements and increased data availability have enriched BCMs, (ii) the literature has coped with the fact that behavioural immunity is often contingent on the disease and not coupled to disease dynamics, (iii) modelling efforts are validated with quantifiable observations and parameterized, (iv) the current models have assessed the importance of social networks in individual decisions, (v) the process of transferring information to behaviour is managed and (vi) irrational behaviour is demonstrated.

In the following sections, we systematically identify and analyse BCMs applied to infectious disease transmission, starting from where a previous review in 2010 left off [127]. These models are categorized in order to distinguish their

assumptions, methods, disease and transmission-specific applications and implications. Furthermore, a critical point of view is taken when evaluating these models in terms of their real-life applicability. Current pitfalls and opportunities are identified to support the development of more advanced BCMs in the near future.

2.2 Methods

The strategy and reporting in this review are based on Cochrane guidelines for systematic reviews of intervention [167] and the PRISMA statement [269]. The eligibility criteria and the search query were determined by consensus between all authors, covering expertise in infectious disease modelling and economics.

Search

We searched PubMed and Web of Science (WoS) for records published between January 2010 and December 2015. After discussing and defining the inclusion and exclusion criteria, we obtained our final search query which we used in PubMed on 12 January 2016 and in WoS on 13 January 2016: '(behavio* OR decision*) AND (change* OR influence* OR dynamic* OR adapta* OR adapt OR adaptive OR strategic*) AND (infect* OR epidemic OR epidemics OR epidemiology OR epidemiological OR epidemiologic OR pandem* OR outbreak*) AND (disease* OR vaccin*) AND (model OR models OR modelling OR modeling OR simulat* OR transmission*)'.

Selection

In a first step, F.V. screened the results of the search query based on title and abstract in accordance with the following pre-specified eligibility criteria:

Infectious diseases. Only records that concern infectious diseases are included in the selection. Infectious diseases are defined using the WHO definition: infectious diseases are caused by pathogenic microorganisms, such as bacteria, viruses, parasites or fungi; the diseases can be spread, directly or indirectly, from one person to another [439].

Model. Records should consist of a mathematical model for behavioural change, for infectious disease transmission or a coupled model combining these two.

Individual behaviour. Behaviour is considered the consequence of personal and voluntary choices made by an individual, i.e. we exclude studies tackling forced interventions such as school closure or mandatory vaccination, but include government interventions creating awareness, education in prevention, etc.

External trigger(s). At least one trigger for modelled individuals to change their behaviour is external and has to be related to infectious disease. We exclude models with exclusively intrinsic triggers from the selection (e.g. an individual's own human immunodeficiency virus (HIV) status).

Preventive measure. A preventive measure is central to the analysis (e.g. vaccination or social distancing). The behaviour of the individual is defined by the decision (not) to take preventive measures.

Humans. We are interested in diseases in humans and behaviour of humans regarding these diseases, and therefore exclude research on plants, animals, the behaviour of the model itself or the behaviour of governments or institutions.

Original research. We exclude review articles, letters, editorials and comments.

English language. Excluding articles written in other languages.

In a second step, the remaining articles' full texts were screened to confirm eligibility, independently by F.V. and L.W. Whenever there was doubt about eligibility, agreement was sought through discussion.

Data extraction

Using a common data extraction protocol for each eligible article, F.V. and L.W. independently retrieved from the full text: (i) infectious disease; (ii) disease category (sexually transmitted infection (STI), influenza-like illness (ILI), childhood disease, vector-borne disease (VBD) or other); (iii) prevention measure (vaccination, social distancing etc.); (iv) source of information (global, local or multiple); (v) type of information (prevalence-based, belief-based or multiple); (vi) effect on the model (disease state, model parameters, contact structure or multiple); (vii) disease transmission model description; (viii) BCM description; (ix) whether there was interaction between the behaviour and disease transmission model; (x) whether the analysis incorporated real-life data; and (xi) movement of individuals in the model. When applicable, other interesting information was extracted using free form fields. Again, discrepancies in interpretation were resolved through discussion.

2.3 Results

Search results

Our search query resulted in 7193 records from Web of Science and PubMed (figure 2.1). We identified and removed 1434 duplicates, resulting in 5759 unique records that were screened based on title, abstract, keywords and full-text if necessary. Exclusions were mostly related to (i) topic, including the study of non-infectious diseases or infections in animals, plants and crops; (ii) discipline, including microbiological and clinical trial studies, and to a lesser extent to (iii) language and article type. Eventually, 178 articles were included for full-text analysis.

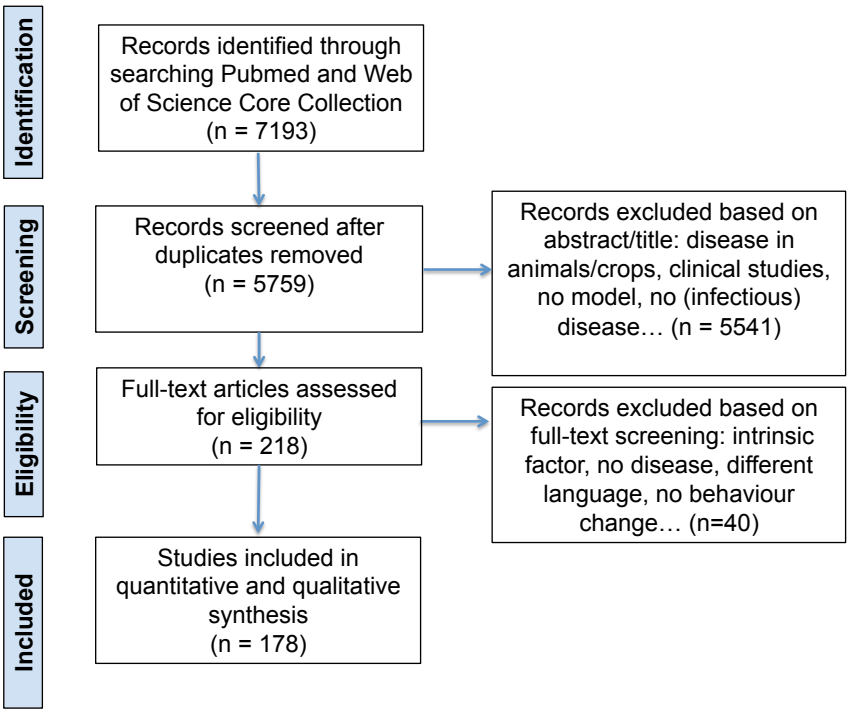

Figure 2.1: Prisma flow diagram.

The number of articles matching our eligibility criteria increased from 18 in 2010 to 38 in 2015, but there was a single year downward deviation from the trend in 2014 (with 22 eligible studies; figure 2.2). Compared with Funk et al. [127], we observe a marked increase in BCM publications. Over the 9 year period between 2002 and 2010, Funk et al.'s search yielded 27 eligible articles (i.e. about 15% of our yield over 6 years), but their search and selection procedure lacks transparency to compare these results in depth.

Models applied to influenza or ILI stand out, together with 'general' models. In the latter category, a hypothetical infectious disease is modelled, without specification of which disease (but often including optimistic statements about the generalizability of the application).

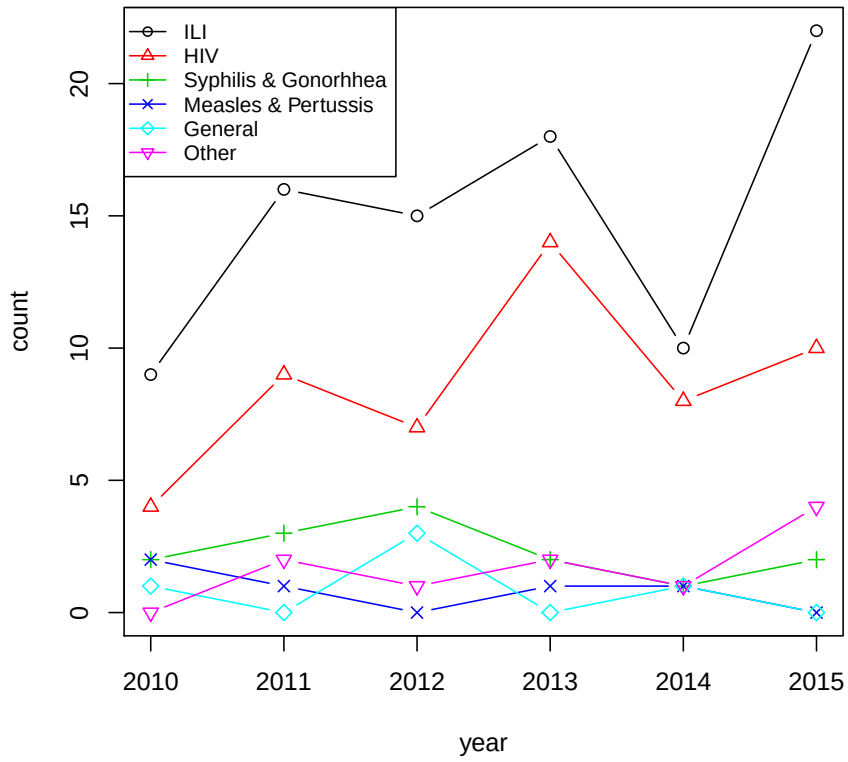

Figure 2.2: Number of studies over time.

Model structure categories

In table 2.1, we categorized the studies according to disease, prevention measure (topic) and whether the model is implemented at the population level or at the individual-level (i.e. using an IBM or contact network) to simulate infectious disease transmission. Metapopulation models for disease transmission were also identified and are labelled in bold. Furthermore, the columns indicate at which level the impact of prevention measures is modelled, distinguishing whether behavioural change is implemented through a switch in infectious

disease state (e.g. vaccination immunizes previously susceptible persons, and this can be modelled by moving them from the susceptible to the immune state), a change in model parameters (e.g. hygiene measures may be assumed to reduce the effectiveness of transmission) or in social contact structure (e.g. social distancing may be mimicked by a link-breaking or rewiring process between susceptible and infectious individuals in contact networks). Studies can appear in multiple categories, as some have multiple prevention strategies or multiple effects on the disease transmission model. For the transmission model category, we interpreted to which extent heterogeneity is introduced in the model. All references are categorized and represented in a spreadsheet that can be found as electronic supplementary material (see [411]). The model type is often disease-dependent. For instance, all retrieved models for measles and/or pertussis are population models with vaccination as a preventive measure that affects the disease state in the transmission model. Moreover, the models are often prevention-dependent. We observe that most of the models that use vaccination as a prevention strategy will impact the model through a switch in disease state. For instance, in many compartmental susceptible-infectious-recovered (SIR) disease models, vaccinated individuals move to the R compartment. General models with social distancing as a prevention strategy usually impact the model in terms of a modified contact structure, contingent on the disease transmission model. Whereas for influenza applications, this only applies for one out of seven references.

Prevention measures

Most of the eligible articles use models with vaccination or social distancing as a prevention measure, though other strategies have been considered. The choice of prevention measure naturally depends on the disease under study. For instance, the discovery and implementation of antivirals as a prophylactic for influenza and HIV has resulted in the publication of models with pre-exposure antiviral use as individual behaviour. A minority of models does not specify the preventive action taken by individuals. When an effect on the contact rate was mentioned, we assumed that the preventive action was social distancing. It appears some authors use the term 'social distancing' as a synonym for all non-pharmaceutical interventions (NPIs) [323]. In this review, social distancing is interpreted as reducing physical (or sexual) contacts between individuals and their environment.

Diseases

In table 2.1, we classified the records based on four specific disease categories, one category for general models (not specifying a disease) and one category for other diseases. Most models retrieved were on influenza or influenza-like illness (ILI) and HIV. Other frequent diseases studied with BCMs are 'measles & pertussis' and 'syphilis & gonorrhoea'. Historically, perceptions of high risks, associated with measles and pertussis vaccination, have adversely affected the uptake of these vaccines. As a result, these are topical applications for transmission models incorporating behavioural changes, as discussed in [32]. The literature on measles is becoming more diverse as VRSE perceptions evolve; Bhattacharyya & Bauch [31] describe a model in which parents delay vaccinating their children as a result of an exogenous vaccine scare, whereas the same authors use social networks of imitation behaviour for VRSE perception spread in response to a vaccine scare [23], and d'Onofrio et al. [99] introduce public interventions in their model to increase vaccine uptake. Diseases in the 'other' category are: SARS, smallpox-like disease, malaria, hepatitis B, Ebola, pneumococcus, pneumonic plague, toxoplasmosis and cholera. General models do not explicitly specify a disease, often assuming general applicability. As noted earlier, models tend to be disease-specific. In the case of influenza or influenza-like illness, some models look at seasonal changes in behaviour with backward looking individuals evaluating the success of their (vaccination or social distancing) strategy during previous season(s) [59, 125, 157, 239, 457, 468, 471]. HIV BCMs are often coupled with a public health information/education campaign aimed at evaluating public health measures to control epidemic spread or to study the cost-effectiveness of these control measures [180, 191, 256, 287, 288]. An example of a more advanced, game-theoretic model is the model by Tully et al. [396]. They use an agent-based model (ABM) for the spread of risk perception, sexual behaviour and HIV transmission in the context of individual sexual encounters evaluating the behaviour of (potential) partners.

Table 2.1: Model structure categories. References in bold represent metapopulation models. References in italics represent references that use empirical data for parameterisation and/or validation. PrEP:Pre-Exposure Prohylaxis. References in category "Other" specify a disease other than the above. Hygiene measures include face-mask use, increased hand washing etc.

Disease	Prevention measure	Population level		Network / IBM		
		Infectious Disease State	Model Parameters	Infectious Disease State	Model Parameters	Contact Structure
Influenza / ILI	Vaccination	Bhattacharyya and Bauch [32], Breban [43], Laguzet and Turinici [211], Liu et al. [239] & *Cohen et al. [76], Shim et al. [362], Xia and Liu [459]*	Vardavas et al. [410]	Cardillo et al. [59], Cornforth et al. [80], Fu et al. [123], Fukuda et al. [124, 125], Han and Sun [157], Liao and You [229], Liu et al. [239], Loganathan et al. [241], Wells and Bauch [434], Wells et al. [436], Wu and Zhang [457], Xia and Liu [458], Zhang et al. [466], Zhang [471] & *Andrews and Bauch [14]*	Marathe et al. [255], Mei et al. [259], Zhang et al. [469] & *Karimi et al. [190]*	-
	Social Distancing	Mummert and Weiss [278], Poletti et al. [313] & *Zhong et al. [472]*	Greer [149], Larson and Nigmatulina [218], Liu et al. [236], Morin et al. [271], Wang [428] & *He et al. [162], Poletti et al. [312], Springborn et al. [370]*	-	Barrett et al. [21, 22], Karimi et al. [190], Mei et al. [259], Wang et al. [432] & ***Bayham et al. [25]***	Chen et al. [68]
	PrEP Antivirals	-	-	Liao and You [229]	Barrett et al. [22], Chen et al. [68], Liao and You [229], Mao and Bian [253], Mao and Yang [254], Marathe et al. [255], Mei et al. [259] & *Andrews and Bauch [14]*	-
	Hygiene measures	-	Larson and Nigmatulina [218], Parikh et al. [305] & *Poletti et al. [312]*	-	Mei et al. [259], Parikh et al. [305], Wang et al. [432]	-
	Other & General	-	*Pawelek et al. [307], Xiao et al. [460]*	Liao et al. [230] & *Collinson et al. [77]*	Zhang et al. [468] & *Fierro and Liccardo [112]*	-

Table 2.1 Continued: Model structure categories. References in bold represent metapopulation models. References in italics represent references that use empirical data for parameterisation and/or validation. PrEP:Pre-Exposure Prohylaxis. References in category "Other" specify a disease other than the above. Hygiene measures include face-mask use, increased hand washing etc.

Disease	Prevention measure	Population level		Network / IBM		
		Infectious Disease State	Model Parameters	Infectious Disease State	Model Parameters	Contact Structure
HIV	Condom Use	-	*Johnson et al. [180], Nyabadza et al. [288]*	-	Vieira et al. [420]	-
	Reduce sexual risk	-	-	Alimadad et al. [9]	Tully et al. [396, 397]	-
	Social Distancing	-	Nyabadza et al. [287, 288], Reluga and Li [325], Reniers and Armbruster [326] & *Viljoen et al. [422]*	-	Tully et al. [396]	-
	Other & General	Kassa and Ouhinou [191, 192]	-	-	Marshall et al. [256]	-
Syphilis & Gonorrhea	Condom use	-	Morin et al. [270]	-	*Gray et al. [146]*	-
	Vaccination	-	Milner and Zhao [265]	-	-	-
	Reduce sexual risk	-	Milner and Zhao [265]	-	-	-
	Social distancing	-	Aadland et al. [1]	-	*Gray et al. [146]*	*Althouse and Hebert-Dufresne [10]*
Measles & Pertussis	Vaccination	Bhattacharyya and Bauch [31], Shim et al. [363] & *Bauch and Bhattacharyya [23], d'Onofrio et al. [99], Oraby et al. [293]*	-	-	-	-
Other	Social distancing	Greenhalgh et al. [148], Perra et al. [309], Sharma and Misra [360]	Cooper et al. [78], Del Valle et al. [89], Wang et al. [429]	-	*Fast et al. [110]*	*Robinson et al. [328]*
	Vaccination	Sharma and Misra [360], Sykes and Rychtar [382]	-	-	-	-
	Other & General	Misra et al. [267]	Cooper et al. [78]	Williams et al. [450]	-	-

Table 2.1 Continued: Model structure categories. References in bold represent metapopulation models. References in italics represent references that use empirical data for parameterisation and/or validation. PrEP:Pre-Exposure Prohylaxis. References in category "Other" specify a disease other than the above. Hygiene measures include face-mask use, increased hand washing etc.

Disease	Prevention measure	Population level		Network / IBM		
		Infectious Disease State	Model Parameters	Infectious Disease State	Model Parameters	Contact Structure
General models	Social distancing	Funk et al. [126], Misra et al. [266, 268], Samanta et al. [347], Wang et al. [427], Zuo and Liu [477]	Brauer [41], Buonomo et al. [52], Fenichel et al. [111], Li et al. [226, 227], Liu et al. [235], Liu [237], Lubuma and Terefe [243], Morin et al. [272], Reluga [322], Wang et al. [426], Xiao et al. [461]	Sahneh and Scoglio [339]	Cao [58], Wang et al. [430], Wu et al. [454], Zhang et al. [470] & *Schumm et al. [354]* & **Bichara et al. [34], Liu and Zheng [238], Meloni et al. [260], Sun et al. [381]**	Dong et al. [96], Jolad et al. [183], Juher et al. [186], Liu et al. [234], Maharaj and Kleczkowski [248], Noble et al. [286], Rogers et al. [329], Shaw and Schwartz [361], Szabo-Solticzky et al. [384], Tunc and Shaw [398], Valdez et al. [402, 403], van Segbroeck et al. [408], Zhang et al. [467] & **Nicolaides et al. [285]** & *Maharaj et al. [249]*
	Vaccination	Bauch et al. [24], Bhattacharyya et al. [33], Buonomo et al. [51, 53], d'Onofrio and Manfredi [97], d'Onofrio et al. [98], Oraby and Bauch [292], Reluga and Galvani [324], Voinson et al. [423], Wu et al. [453], Xu and Cressman [462]	Barbagallo and Cojocaru [20]	Cai et al. [56], Campbell and Salathé [57], Dong et al. [96], Han et al. [158], Helbing et al. [164], Liang and Juang [228], Mbah et al. [258], Morsky and Bauch [274], Ruan et al. [333], Schimit and Monteiro [352], Wells et al. [435], Wu et al. [455, 456]	Zhang et al. [465]	-
	Hygiene measures	Funk et al. [126]	-	-	-	-
	Other & General	Joshi et al. [185]	Liu and Stechlinski [240], Reluga [323], Samanta and Chattopadhyay [346], Sega et al. [357]	Goyal and Vigier [142], Guo et al. [151], Hatzopoulos et al. [161], Juher et al. [187], Liu et al. [232], Miller [263], Sahneh and Scoglio [340], Sahneh et al. [341], Yuan et al. [464] & *Chen et al. [67]*	Goyal and Vigier [142], Kitchovitch and Lio [205, 206], Ni et al. [283], Rutherford et al. [336], Shang [358, 359]	-

Emergence-driven research

The Centers for Disease Control and Prevention (CDC) defines emerging infectious diseases as: "those whose incidence in humans has increased in the past 2 decades or threaten to increase in the near future. These diseases, which respect no national boundaries, can challenge efforts to protect workers as prevention and control recommendations may not be immediately available" [62]. Between 2010 and 2015, a number of studies appear to have been emergence-driven. That is, the research field responds by focusing on infectious disease events that are of major interest because of a change in the threat they present to public health. The influenza A/H1N1 pandemic of 2009 has largely influenced the development of BCMs for influenza. For example, Poletti et al. [312] use the influenza A/H1N1 pandemic of 2009/2010 to parametrize an influenza transmission model with behavioural changes focusing on the spread of risk perceptions in the population. In addition, a model on Ebola virus disease (EVD) was published in 2015 in response to the epidemic outbreak in Liberia [110]. The authors use WHO and CDC data to parametrize the model suggested in an attempt to mimic disease transmission and to identify behavioural changes as drivers of the disease dynamics. Note that, in the current review, we relate 'emergence' not only to disease emergence, but also the emergence of a vaccine scare (such as observed with measles-mumps-rubella (MMR) vaccination and pertussis whole-cell vaccination [23]) or the emergence of new interventions for endemic diseases (such as the development of a multi-season influenza vaccine [410]).

Disease transmission models

We identify three major categories of models: population-level models, metapopulation and individual-level models. Population-level models traditionally formulate compartments according to health state (e.g. susceptible, infectious and recovered) and simulate transitions between the compartments over time using population averages. These models are often based on the mass-action principle to designate the transmission probability. Each individual has an equal probability of contracting disease given the disease state levels in the population. Metapopulation models split the population into different subpopulations with their own (spatial) general characteristics and disease-related parameters. The individual-level category consists of network models and IBMs. Network models represent disease transmission on a network where nodes (individuals) are connected to each other using links. This allows to model individuals with different degrees, representing how many links a node has (i.e. number of neighbours/direct contacts). IBMs or ABMs typically incor-

porate more heterogeneity and stochasticity on individuals' characteristics such as spatial location, age, gender, sexual orientation, etc. The model selection depends on disease characteristics, data availability, modelling purpose (i.e. what outcome figures are you interested in?), computational resources, etc.

Individual-level models are gaining interest in the BCM literature since they can introduce heterogeneity in behaviours, tackle clustering of vaccine sentiments and look at stochastic and local outbreaks of infectious diseases with a high vaccination coverage (e.g. measles). Moreover, given an underlying contact structure, individual-level models are well suited to model social distancing behaviour in terms of reduced contacts as a prevention strategy. Remarkably, for measles and pertussis we found deterministic models only, despite the widely acknowledged stochastic nature of outbreaks in highly vaccinated populations. Note that, in table 2.1, we also made a distinction between individual-level and population-level models in the category 'disease transmission model'. Metapopulation models are displayed in bold.

Information gathering

In order for individuals to change their behaviour in relation to prevention measures, they require disease-related information. As defined in the eligibility criteria, we only included papers in which this information is external to the individual. Examples of disease-related, external information include: news broadcasts on a disease outbreak or rumours among friends and family about VRSEs or vaccine-preventable disease. Funk et al. [127] proposed a classification based on type and source of information, distinguishing global and local information as source and prevalence-based and belief-based information as type of information. Global information is defined as information available to all individuals in the population, for example, TV stations and public health campaigns. Local information is information individuals gather from their direct contacts or neighbourhood. Examples are rumours from neighbours or infective individuals in their close contacts. Prevalence-based information is defined as 'directly relating to disease prevalence', whereas belief-based information is 'not directly relating to disease prevalence'. Belief-based information can therefore have its own dynamics, to some extent independent of the disease dynamics. For example, rumours can inflate the perception of disease prevalence, even if the true prevalence is low. In table 2.2, we classify the studies we identified in a matrix, using the same definitions.

Table 2.2: Information gathering.

Source of information	Type of information: Belief-based	Prevalence-based	Multiple
Local	Alimadad et al. [9], Barbagallo and Cojocaru [20], Cardillo et al. [59], Fukuda et al. [125], Funk et al. [126], Han and Sun [157], Liu et al. [239], Mbah et al. [258], Tully et al. [397], Wang et al. [432], Wu and Zhang [457], Xia and Liu [458, 459], Zhang et al. [468], Zhang [471]	Althouse and Hebert-Dufresne [10], Cai et al. [56], Cao [58], Dong et al. [96], Fu et al. [123], Fukuda et al. [124], Han et al. [158], Helbing et al. [164], Juher et al. [186, 187], Liu et al. [232], Maharaj et al. [249], Morsky and Bauch [274], Noble et al. [286], Reniers and Armbruster [326], Rogers et al. [329], Ruan et al. [333], Sahneh and Scoglio [339, 340], Sahneh et al. [341], Schumm et al. [354], Shaw and Schwartz [361], Szabo-Solticzky et al. [384], Tunc and Shaw [398], Valdez et al. [402, 403], van Segbroeck et al. [408], Wells et al. [435], Wu et al. [456], Zhang et al. [470]	Andrews and Bauch [14], Guo et al. [151], Mao and Bian [253], Mao and Yang [254], Miller [263], Shang [359], Wells et al. [436], Wu et al. [455], Zhang et al. [466]
Global	Bauch and Bhattacharyya [23], Bhattacharyya and Bauch [31, 32], Cooper et al. [78], Cornforth et al. [80], Durham and Casman [108], Fast et al. [110], He et al. [162], Johnson et al. [180], Joshi et al. [185], Karimi et al. [190], Laguzet and Turinici [211], Li et al. [227], Mannberg [251], Marshall et al. [256], Milner and Zhao [265], Misra et al. [267], Oraby et al. [293], Parikh et al. [305], Poletti et al. [313], Shim et al. [362, 363], Sykes and Rychtar [382], Vieira et al. [420], Voinson et al. [423], Zhang et al. [465]	Aadland et al. [1], Barrett et al. [21], Bichara et al. [34], Buonomo et al. [51, 52], Chen et al. [67, 68], Collinson et al. [77], Del Valle et al. [89], d'Onofrio and Manfredi [97], d'Onofrio et al. [98], Fenichel et al. [111], Goyal and Vigier [142], Greenhalgh et al. [148], Greer [149], Jolad et al. [183], Kassa and Ouhinou [191], Li et al. [226], Liu et al. [234, 235, 236], Liu [237], Liu and Zheng [238], Liu and Stechlinski [240], Lubuma and Terefe [243], Meloni et al. [260], Misra et al. [266, 268], Morin et al. [270, 271, 272], Mummert and Weiss [278], Nyabadza et al. [287, 288], Pawelek et al. [307], Poletti et al. [312], Reluga [322, 323], Reluga and Galvani [324], Reluga and Li [325], Samanta and Chattopadhyay [346], Samanta et al. [347], Sharma and Misra [360], Sun et al. [381], Viljoen et al. [422], Wang et al. [426, 427], Wang [428], Wang et al. [429, 430], Wu et al. [453], Xiao et al. [460, 461], Xu and Cressman [462], Yuan et al. [464], Zhang et al. [467, 469], Zhong et al. [472], Zuo and Liu [477]	Bauch et al. [24], Bayham et al. [25], Bhattacharyya et al. [33], Breban [43], Buonomo et al. [53], Liao et al. [230], Oraby and Bauch [292], Sega et al. [357]
Multiple	Campbell and Salathé [57], Cohen et al. [76], d'Onofrio et al. [99], Loganathan et al. [241], Ni et al. [283], Nicolaides et al. [285]	Barrett et al. [22], Kassa and Ouhinou [192], Kitchovitch and Lio [205, 206], Larson and Nigmatulina [218], Maharaj and Kleczkowski [248], Marathe et al. [255], Schimit and Monteiro [352], Shang [358], Vardavas et al. [410]	Fierro and Liccardo [112], Hatzopoulos et al. [161], Liang and Juang [228], Liao and You [229], Mei et al. [259], Perra et al. [309], Tully et al. [396], Wells et al. [436], Wu et al. [454]

We observe that most BCMs are using information that is globally available and prevalence-based. These models are frequently game-theoretic (or pay-off maximizing) behavioural change frameworks coupled with disease transmission models at the population level. Studies that met our eligibility criteria, but are unclear about the information individuals use [41, 146, 328, 336, 370, 450] were excluded from figure 2.2. Given the increasing individual heterogeneity in disease transmission models, it is becoming more interesting to incorporate local information in BCMs. In network models and IBMs, one could for instance model the local spread of information through direct contacts with crucial implications in terms of clustering of both disease prevalence and opinions [283].

In addition, we observe that more articles are using multiple information types and/or sources, making individual behaviour more realistic. For instance, Barrett et al. [22] constructed a model where 'individual behaviour is triggered by the prevalence level of the virus in the overall society (global prevalence) as well as within one's own demographic class (local prevalence)'. Highly relevant are articles introducing both multiple sources and multiple types of information such as the model by Liang & Juang [228], which introduces different forms of information in the individual's risk perception of an epidemic, embodying all four information categories.

How is the transfer from information to behaviour managed?

Based on full-text analysis, we extracted how individuals were modelled to translate the information they receive into behavioural change. Traditionally, behaviour formation models were composed of a game-theoretic framework in which individuals have perfect information on disease-related data and prevention effectiveness. Individuals are then assumed to use this information in a utility-maximizing game by comparing the expected costs of infection with the expected costs of the prevention measure. However, more advanced and different BCMs have been developed since. We identified five distinct categories for characterizing the decision-making process of individuals, listed from a) to e) (see also electronic supplementary material to Verelst et al. [411]). Some referenced papers contain multiple BCMs.

a) Exogenous behaviour formation (16/178)

We retrieved 16 papers [41, 78, 89, 146, 149, 180, 185, 190, 256, 270, 305, 328, 336, 370, 420, 450] describing BCMs in which there is no two-way interaction with a disease transmission model. Morin et al. [270] provide an example of such a

model by assessing the impact of policies encouraging condom use, on gonorrhoea transmission dynamics; i.e. behaviour (condom use) is parametrized based on different empirical studies and model projections are made to estimate consequential disease transmission and model equilibria. Similarly, Brauer [41] assessed disease model implications of a constant fractional reduction in the number of contacts. A third example is the model by Joshi et al. [185] where a time-dependent education function moves susceptible individuals into lower susceptibility classes with lower transmission rates, independent of disease dynamics. These models are relatively rare and most often focus on policy implementations and short-term effects of behaviour on disease transmission.

b) Information threshold (29/178)

We retrieved 29 BCMs in which behaviour change is modelled conditional on exceeding a predefined information threshold [10, 21, 22, 57, 68, 96, 112, 151, 183, 186, 187, 191, 232, 234, 253–255, 286, 326, 329, 354, 361, 384, 398, 402, 403, 408, 455, 461]. The information the individual assesses can be obtained in a direct way (e.g. through prevalence in neighbours) or in an indirect way (e.g. through rumours or opinions). These models do not elaborate on how behaviour is rationally determined or influenced by relevant factors. Instead, behaviour formation is a result of a predefined threshold function. Examples include switching to social distancing when the number of infectives exceeds a threshold [461], social distancing by rewiring once a non-infected node connects to an infected node [361], and – as in Wu et al. [455] – to have an individual's vaccination decision exercised through a risk function exceeding a threshold, which in turn depends on the number of infected neighbours. Mao & Yang [254] used an individual risk function incorporating the proportion of 'adopters' among contacts, the perceived pressure of 'adoption' and the proportion of infective neighbours. Again, once the risk function exceeds a threshold, individuals adopt preventive behaviour, which in this case consisted of taking prophylactic antivirals.

c) Information as dynamic parameter (76/178)

The largest category embodies 76 references managing information as a dynamic parameter [9, 25, 34, 51–53, 58, 68, 77, 97, 99, 108, 110, 112, 126, 148, 158, 161, 162, 183, 192, 205, 206, 218, 226–230, 235–238, 240, 241, 243, 248, 259, 260, 263, 265–268, 278, 283, 287, 288, 307, 309, 333, 339–341, 346, 347, 357–360, 381, 422, 423, 426–430, 454, 456, 459, 460, 464, 467, 470, 472, 477]. In this category, instead of a threshold, the information is a continuous input in the decision-making process of individuals. At the population level, we can characterize these BCMs as information driving the flow in and out the prevention

taking compartment. Two subcategories can be distinguished: models with a direct relation between infectious disease parameters and behaviour formation (i.e. behaviour changes vis-à-vis disease dynamics), and models with an indirect relation, through an information spread medium. For the former subcategory, the behaviour or decision-making process is predefined as a functional relation depending on disease transmission parameters. The functional form does not need to be linear. Some examples are vaccination coverage as a positive decreasing function of perceived risk of VRSE [97], the percentage of the susceptible population engaging in avoidance actions increases as the disease becomes more prevalent [472] and a model where the effective contact rate reduces with the number of infectives [226].

The latter subcategory requires a third-party spreading the information for individuals to receive. For instance through mass media, neighbours, formation of opinions in the population, etc. A multitude of these models introduce an 'aware' compartment in the model where aware and unaware individuals are assigned distinct disease transmission parameters such that aware individuals have lower susceptibility of acquiring infection. See for example Funk et al. [126], in which a rate introduces people in an 'aware' class after which the awareness spreads through the population, coupling disease transmission with a BCM. Interestingly, some models introduce information spread models with characteristics from disease transmission models where individuals are, for example, susceptible to or infected with disease-related information. Misra et al. [266] use a model with media coverage creating awareness in the population, also introducing an 'aware' compartment in a population model. Social impact is introduced in a model by Ni et al. [283], where they use a variety of complex networks for the spread of opinions driving the individual probability of prevention behaviour. The use of a network is convenient to model these dynamics as they allow clustering of, for instance, vaccine-related sentiments in the population. Most often these models assign additional characteristics to nodes (which represent individuals), apart from disease state. An example could be that a node is assigned a disease state and an opinion which is either provaccination or contravaccination. When simulating the disease and behaviour dynamics in this network, when nodes interact, transmission of both disease and opinions can occur. Such that if a provaccine node is surrounded by many vaccine sceptics, it might change its opinion towards the opinions of its links (i.e. neighbours) and as a result this will influence the individual's probability of taking vaccination as a prevention measure.

d) An economic objective function (37/178)

This 'economic' class of BCMs is also quite common with 37 articles being retrieved [1, 14, 20, 24, 32, 33, 43, 67, 76, 80, 111, 142, 164, 211, 249, 251, 258, 260, 271, 272, 274, 285, 322–325, 352, 362, 363, 382, 396, 397, 410, 423, 432, 434, 465]. This approach assumes individuals take their prevention decision based on an objective function, which they attempt to optimize (i.e. by maximizing benefits and/or minimizing costs). Game theory grounded models form an integral part of this category. By way of example, one can assume that individuals have knowledge about both the disease and their options for prevention and make rational decisions based on this knowledge. People accordingly possess a (perceived) cost of infection (c_i) and a (perceived) cost of the prevention measure (c_p), which can, for instance, be assumed to be 100% effective. Another important input in people's decision-making, their probability of infection (λ) can be assumed to be dependent on disease prevalence, which evolves over time. For instance, one can define this using an SIR model under the mass action principle as the force of infection, i.e. $\lambda = \beta$I, where β is the per-contact transmission rate, and I is the fraction of infectives in the population. This way the behavioural change framework can be coupled to the disease dynamics. The individual makes the following trade-off, with P, the choice of taking the prevention measure

$$P = \begin{cases} 1 \text{ if } c_i\lambda > c_p \\ 0 \text{ if } c_i\lambda < c_p \end{cases} \tag{2.1}$$

In a study by Bhattacharyya & Bauch [32], individuals take their vaccination decision based on the perceived vaccination cost in the context of the 2009 A/H1N1 influenza pandemic. Their BCM model exhibits a 'wait and see' Nash equilibrium where individuals incorporate the concept of herd immunity in their prevention behaviour, resulting in free-riding represented by a 'delayer' strategy. The model developed by Morin et al. [271] embodies individuals' behaviour by the maximization of expected utility determined by adapting the contact level (i.e. social distancing). Aadland et al. [1] introduce a BCM maximizing an individual's expected lifetime utility by choosing the number of sexual partners, hereby explaining the re-emergence of syphilis.

e) An economic objective function with social learning/imitation. (26/178)

We retrieved 26 papers [23, 31, 56, 59, 96, 98, 123–125, 157, 239, 258, 292, 293, 312, 313, 435, 436, 453, 457, 458, 462, 466, 468, 469, 471] describing a BCM

with an objective function with imitation. It is recognized that some social or peer influence should be incorporated in the decision-making process of the individuals (see also models with information as a dynamic parameter). As a response to this concern, the (rational) 'game-theoretic' model has been adapted to include social influence or imitation behaviour. In these models, it is assumed that people compare their own prevention-related behaviour with that of other individuals in society. Through comparison, individuals learn whether their own behaviour is optimal and, to which extent they should adapt it. Typically, a sampling rate is assumed for individuals sampling other individuals from the population. After sampling an individual from the population, the trade-off is compared and people switch strategies with a probability as a function of the pay-off difference. Often, a Fermi-like function is used, guiding the adoption to the better strategy depending on the magnitude of the pay-off difference. Other switching functions/strategies are used, but naturally, the larger the beneficial pay-off difference, the higher the probability of switching your behaviour. An example of a Fermi function, taken from [125] is given in this section. If we represent the pay-off of the strategies of individual i (with strategy s_i) and individual j (with strategy s_j) as ε_i and ε_j respectively, and the pay-off difference is defined by $\Delta\varepsilon_{ij} = \varepsilon_i - \varepsilon_j$. Then, the probability of individual i switching to the strategy of individual j is

$$Pr(s_i \leftarrow s_j) = \frac{1}{1 + exp[\frac{\Delta\varepsilon_{ij}}{\kappa}]} \tag{2.2}$$

where κ denotes the selection pressure representing the sensitivity of individuals to switch strategies in response to a pay-off difference [125]. Parameter κ can be interpreted as expressing 'stickiness' in behaviour. Figure 2.3 indicates that individuals are very responsive even to small differences in the pay-off when κ is low, and that for large values of κ (e.g. 0,9) their behaviour becomes 'sticky'. Sticky, in the sense that they need to observe a very large pay-off difference before they opt to change. For intermediate values of κ, people have sticky behaviour but when the potential benefit in the pay-off is large enough, people switch to the strategy of individual j. If the behaviour is not assumed to be very sticky, then it could be that individual i still adopts the strategy of individual j even if the pay-off of strategy j is worse. The underlying assumption is here that for some individuals peer influence and social conforming behaviour is -to a certain extent- more important than pay-off maximization. Note that in the majority of these models, assumptions rather than real-life observations guide the choice and distribution of the 'stickiness' parameter κ.

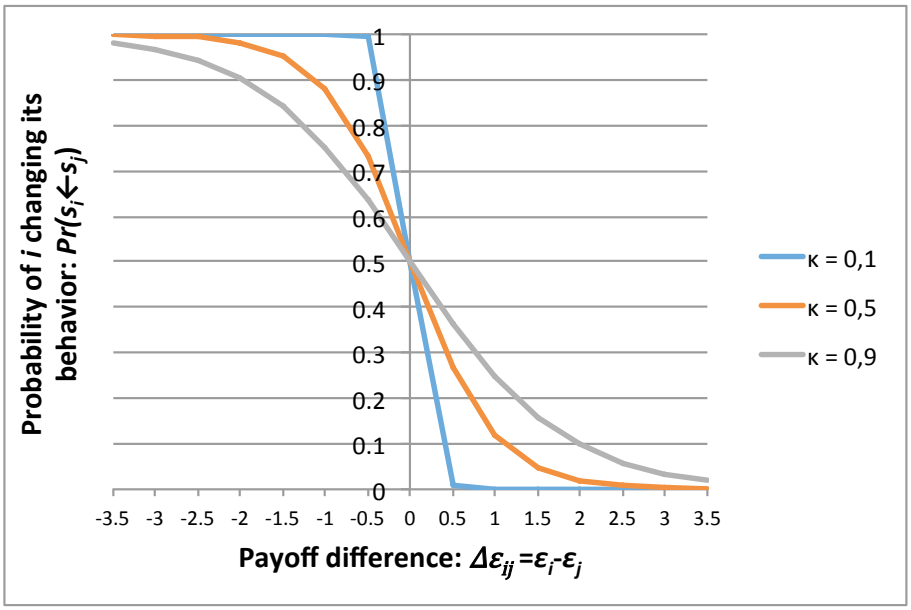

Figure 2.3: Fermi function for different values of κ

Model parameterisation and validation

One may question how well BCMs approach reality, as there is a paucity of empirical data on behavioural responses to disease-related information informing these models. We examined whether and how data were used to parameterize BCMs, and to which extent these data support the underlying theoretical model. Moreover, we critically assessed model parameterization, distinguishing data-driven from assumption-driven parameterization, for the disease model, the BCM and the complete integrated model. A first, striking observation is that most models are solely theoretical because they are constructed independently from empirical observations. Often a stability analysis is performed, and equilibria are obtained in order to grasp the dynamics of the model in the absence of parameter values. Others perform numerical simulations with either assumptions on parameters or referring to other studies supporting their choice of parameters. Less than 20% of the studies has (partially) fitted or validated their model to behavioural and/or disease transmission data. Retrospective studies on disease emergence are particularly useful when real-time data on behavioural change and disease transmission during an outbreak are available over a sufficiently long time. Social media data and other electronic sources of information are also increasingly used, thus creating opportunities for 'big data' collection on disease transmission, behaviour formation and spatial location [25, 307, 459]. Next, we briefly describe studies constructing their models using

observational data, i.e. studies not exclusively making assumptions or taking parameters from literature.

To underpin BCMs, participatory experiments have been performed to capture social distancing. Maharaj et al. [249] and Chen et al. [67] collected data through a game in which participants trade-off social contacts versus their risk of infection. Such data can be used to parameterize game-theoretic models of social distancing and adaptive networks with link deletion. In addition, survey data have been used to assess behavioural change. Zhong et al. [472] used survey (Public Risk Communication Survey, 2009) data to parameterize their BCM. Robinson et al. [328] surveyed sexual attitudes and lifestyle to build a sexual contact network. The IBM in Gray et al. [146] for syphilis transmission was also informed with survey data on sexual behaviour. Additionally, disease transmission parameters were calibrated from syphilis diagnosis among gay men in Victoria, Australia. A survey on altruism and self-interest was conducted by Shim et al. [362] to calibrate the behavioural change parameters regarding influenza vaccination. In Schumm et al. [354], the BCM is represented by a dynamic social contact network with social distancing, constructed from a survey and census data. Cohen et al. [76] surveyed a convenience sample of students about their risk perceptions for influenza A/H1N1 to estimate the utility values of different behaviours. The study by Fierro & Liccardo [112], used data on awareness and concern about the risk of contagion to populate their model on A/H1N1 influenza transmission with behavioural parameters. Moreover, they also validated their output through comparisons with Italian influenza surveillance data from 2009. The health belief model (HBM) [170] is frequently used to retrieve prevention behaviour and parameterize BCMs. The parameters in the HBM in Durham & Casman [108] were calibrated, using survey data on perceived severity and susceptibility during the 2003 SARS outbreak in Hong Kong. Karimi et al. also use the HBM for their ABM on influenza in 2015 [190]. For validation, the authors compare their model output with similar influenza ABMs in the literature. Another model tackling the influenza A/H1N1 pandemic in 2009 is the model by Bayham et al. [25], who used data from the American time-use survey and the National Health and Activity Patterns Survey (NHAPS). Moreover, Google Trends data are represented as a proxy for subjective risk perception and weather data are used to control for the effects of extreme weather phenomena. Xia et al. [459] constructed a social network using data of an online Facebook-like community to construct a BCM for disease and vaccine awareness on the 2009 influenza A/H1N1 pandemic in Hong Kong. The same pandemic has inspired Springborn et al. to use home television viewing as a proxy for social distancing [370]. Pawelek et al. [307] used Twitter data of self-reporting for awareness spread and ILI surveillance

data (UK Health Protection Agency) of the 2009 A/H1N1 influenza pandemic for disease transmission. In addition, Collinson et al. [77] constructed a model on influenza A/H1N1, incorporating mass media report data from the Global Public Health Intelligence Network.

Incidence and outbreak data have been useful to inform the disease dynamics parallel with BCMs. For the 2009 influenza pandemic, Zhong et al. [472] parameterized their transmission model with outbreak data from Arizona and Xiao et al. [460] estimated parameters using outbreak data (laboratory-confirmed cases) from Shaanxi province in China. Schumm et al. [354] focused on observational census and survey data from rural areas. Andrews & Bauch [14] calibrated both disease and behaviour parameters to vaccine coverage and disease incidence data. Althouse & Hébert-Dufresne [10] used surveillance-based incidence rates for syphilis and gonorrhoea from 1941 to 2002. Gray et al. [146] calibrated disease transmission parameters from data on syphilis diagnosis among men who have sex with men in Victoria, Australia. An HIV transmission model including adaptive condom use and sexual partnerships in South Africa is fitted to HIV prevalence data in Nyabadza et al. [288]. The publication makes projections for disease dynamics when scaling up condom use and reducing the number of sexual partners stepwise with 10%. Behavioural change parameters are not calibrated in this publication. The HIV model of Viljoen et al. [422] is fitted to prevalence data in South Africa and Botswana to look at the effect of awareness on disease spread.

BCMs on vaccination dynamics have also been supported by real-life observations. Bauch & Bhattacharyya [23] informed model parameters with historical vaccine coverage and disease incidence data from two vaccine scares (MMR and whole-cell pertussis). The behavioural change framework introduced in the model has a game-theoretic foundation with inclusion of imitation. Likewise, a model for the dynamics of vaccine uptake with a public intervention was proposed by d'Onofrio et al. [99]. Pertussis vaccination uptake and disease dynamics data for the UK are used to fit the model by Oraby et al. [293], which focuses on the inclusion of injunctive social norms in the context of vaccinations for paediatric infectious diseases. The model is validated comparing the model prediction with observed vaccination uptake data during both the UK vaccine-scare period and high coverage period.

Model fitting has been performed through maximum-likelihood and least-squares methods [108, 162]. Poletti et al. [312] use ILI incidence data in Italy to calibrate the disease dynamics in their game-theoretic model using least-squares. In addition, data on antiviral drug purchase were used to calibrate the

model. In [110], a model of social mobilization is fitted to weekly case counts from CDC and WHO for EVD in Lofa County, Liberia. He et al. [162] investigated three possible explanations for multiple waves of the 1918 influenza pandemic, with one consisting of human behaviour responses. Three proposed models are fitted to historical mortality data using maximum-likelihood in order to determine the extent they can justify the observed disease dynamics. Johnson et al. [180] used prevalence data, antenatal clinic surveys and household surveys for parameterization in order to determine the effects of increased condom use and antivirals on disease dynamics. They calibrated both disease and behaviour parameters to age-specific data using a Bayesian approach for two distinct models.

2.4 Discussion

What are current BCMs capturing?

It is intuitively logical to include human behaviour in mathematical models for the spread of infectious diseases. After all, disease dynamics are, in essence, dependent on human behaviour dynamics: people interact and take preventive measures on a regularly basis. Because there is much heterogeneity in the ways in which behaviour is included and parameterized in BCMs, it seems the real question is: 'How should behaviour be taken into account?' We found that model output may depend on the model specification, to the extent that the selection and development of a model leads in a predictive way towards a predefined conclusion. That is, it seems many of these models serve to justify a theory. For instance, in many pure game-theoretic models, free-rider behaviour emerges resulting in suboptimal vaccination coverage levels, whereas in models including imitation behaviour, the results are often ambiguous. Validation of models with real-life observations is desperately needed to specify an appropriate model, conditional on disease characteristics. Note that model selection implicitly determines the characterization of individuals in the population; models with an economic objective function often assume rational decision-makers, whereas models with imitation or information spread introduce some 'irrational' behaviour such as peer influence and social responsibility.

In addition, purely rational game-theoretic models fail to capture important notions highlighted by Tversky & Kahneman. That is, such models do implicitly rely on expected utility theory – in which it is assumed that "... individuals choose in such circumstances as if they were seeking to maximize the expected value of some quantity." [122]. Kahneman & Tversky criticized this theory and proposed an alternative, called prospect theory. Prospect theory incorporates

flaws in individuals' decision making, such as the certainty effect (people are risk averse for choices involving sure gains and risk seeking for choices involving sure losses) and the isolation effect (people discard aspects that are shared by all alternatives) [188]. Moreover, they do not capture other notions of cognitive bias which have been found to influence human decision making [399]. Cognitive biases influences our judgment and perception under uncertainty, and hence our decision making. For example, omission bias – the finding that a potential loss due to inaction is valued less than the same potential loss due to action – has been found significant in parents making decisions about pandemic flu vaccination to their children [47, 327].

Primary sources such as surveys are needed to empirically underpin the foundations of the models used. The study of Skea et al. [364] on MMR vaccination decisions uses an online chat forum to assess vaccination sentiments and the importance of social responsibility in the parental decision process. The authors find that: 'participants expressed a desire to both (i) protect their own child and (ii) help protect others by contributing to herd immunity' [364]. This finding suggests that people are not purely self-interested and herd immunity is not taken as a means to opt for free-riding, on the contrary, establishing herd immunity is seen as an additional incentive, protecting others. A similar conclusion can be drawn from Vietri et al. [421], who tested whether college students consider either free-riding or altruistic motives to decide on (not) receiving vaccinations. They find that individuals both incorporate their own risk of infection and altruistic motives in their decision of whether or not to vaccinate. Determann et al. [92] suggest that these behaviours – and as a result the decision-making process – are country-dependent. They find that focus group participants tend to 'base their vaccination decision on the trade-off between perceived benefits and barriers of the vaccine'. Although, in their vaccination strategy, Swedish participants also incorporate: following the rules, doing the right thing, solidarity with other citizens and social influences. The latter drivers are less important in Dutch and Polish participants. This implies that studies may have to be diversified by country-specific characteristics to tackle the inhabitant's behaviour. Dorell et al. [100] conclude that one of the most important factors for vaccination is the healthcare provider's recommendation, which is a determinant that is not included in any of the approaches in the models we found in this extensive review.

In general, there is a need for empirical research to underpin the development of valid models approximating real-life behaviour and disease transmission. Some attempts for recent BCMs illustrate the difficulty of finding suitable observational data. For instance, Springborn et al. [370] used television viewing

habits (average viewing time) as a proxy for social distancing, although this proxy is far removed from a direct estimation of social distancing in an outbreak situation. More promising sources of information include: survey data using, for instance, the HBM framework (also see [147, 170, 332]) or time-use surveys [25, 67, 76, 108, 146, 180, 190, 328, 354, 362, 472] or digital sources such as social media [25, 249, 307, 342, 459]. Real-life data collection during the influenza A/H1N1 pandemic in 2009 has been a milestone for the parametrization of BCMs with increased collection of both behaviour and disease-related information. For instance, Van Kerckhove et al. [406] studied social contact patterns of symptomatic ILI cases during the pandemic. We encourage the collection of such real-time data in future outbreaks to guide policy-makers in the establishment of an optimal response strategy. For some models, data are just not available, and one needs to resort to assumptions to model behavioural change. Note also that excluding behavioural change from infectious disease models equates to assuming behaviour is unaffected by risk perceptions and disease incidence, and vice versa. Ignoring behavioural responses in the face of substantial changes in risk perceptions is probably worse than making assumptions within a theoretical model in the first place. This review has also met with important limitations in clarity of assumptions and methods in many publications, notwithstanding transparency is an essential part of publishing credible and replicable research.

Disease-dependent model specification

We observed that the specification of BCMs largely depends on the disease being investigated and the prevention measures considered. Clearly, the transmission characteristics (e.g. air and saliva borne versus STIs), the potential prevention measures (e.g. social distancing versus condom use) and the epidemic stage (e.g. emergence versus endemic equilibrium versus elimination) are interdependent, and determine both the utility and specification of a BCM. For instance, many influenza models use vaccination as a prevention measure with individuals evaluating their previous influenza vaccination decisions to determine the current season's strategy. It would seem unrealistic to require more data to parameterize both behavioural change and disease transmission models with the aim to develop more general models that suit any infectious disease, albeit that behavioural change in response to one disease's risk perceptions could change the risk perceptions of another. At the current stage of BCM development and parameterization, generalized BCMs accommodating multiple pathogens and different transmission routes seem unrealistic. However, it would be easier to combine multiple diseases with the same transmission and prevention properties. For instance, BCMs assessing the combined effects of

vaccination scares on MMR and diphtheria, tetanus, pertussis (DTP) disease seem intuitively possible and relevant, though technically challenging and high on data demands.

Developing BCMs with multiple prevention measures is also challenging. Again, we take influenza as an example where we discovered a multitude of prevention measures in our selection (also see table 2.1): vaccination, social distancing, pre-exposure prophylaxis by antivirals, hygiene measures and others. Interdependencies between these prevention strategies may occur. For instance, a person vaccinated for seasonal influenza may put less effort into hygienic measures such as hand-washing. However, individuals taking hygiene measures may also be more inclined to engage in social distancing if these individuals are more risk-averse. Researchers need to take into account that focusing health policy on one prevention measure may induce 'crowding out' of other prevention measures because of such interdependencies. Hence, it is useful to assess the total effect of combined prevention efforts when evaluating policies to reduce the incidence of a disease. Models introducing behavioural change with interdependencies between different prevention measures are influenced by both intrinsic and extrinsic factors.

The popularity of emergence-driven research has many drivers: often new research funding and data collection opportunities arise as an emergence unfolds for the development and parameterization of new models to inform health policy.

Social networks and IBMs

We observed a rise in the number of studies using (complex) social networks and IBMs to represent disease spread and individual behavioural changes. Social network models impose a structure in the population enabling the identification of model subjects at the individual-level. The implementation of these networks creates a coherent environment to model: social distancing as a prevention measure, the spread and clustering of disease- and prevention-related information and disease dynamics itself. In addition, neighbours can be identified to implement game-theoretic models with imitation dynamics, potentially resulting in clustering of prevention measures. It is clear that the development of these networks has increased the feasibility of modelling local or combined local-global information sources in a BCM. Nevertheless, the selection of an individual-level model is often a trade-off between the desirability for heterogeneity and IBM-specific hurdles such as the computational burden, greater risk of coding errors and potential loss of transparency and reproducibility.

Here too, data availability is key to develop relevant models. For example, one could use the POLYMOD study on mixing patterns to construct a synthetic population or a network [276]. Still, more research is needed to enrich the validity of synthetic populations as a representation of real-life dynamics. We refer to a review by Wang et al. [431] focusing on coupling disease dynamics with behaviour in complex networks. A more general work covering BCMs is the book by Manfredi & D'Onofrio [250].

Some models use a single social network for both the disease transmission process and the formation of behaviour. Nonetheless, depending on the background, separate networks may be needed to model the spread of risks and the spread of information influencing behaviour. Take for instance anti-vaccine sentiments. These are often spread through blogs, Facebook groups and other social media [342]. Unlike these sentiments, infections are not spread through the Internet, and as a result require an additional network of physical contacts (see also Grim et al. [150], who make the case for modelling multiple networks). Additionally, the timescale of disease transmission can differ substantially from that of information spread leading to behaviour change. The models by Fukuda et al. [125], Helbing et al. [164] and Maharaj & Kleczkowski [248] are useful examples to guide further development of BCMs with separate parallel and sometimes interacting networks.

Internet and social media

Information gathering by individuals has evolved over the past decades with the introduction of the Internet, mobile phones and associated social media applications. It is well documented that web-based information can provide a distorted picture about disease risks and adverse events from vaccinations [28, 83, 215]. For instance, the search term 'MMR vaccine' in Google is automatically complemented by the suggestions 'autism' or 'side effects'. We know individuals retrieve information using these sources for disease-related or prevention-related information and as a result, individuals are exposed to a wide variety of biased information. We recommend policy-makers to implement measures to help individuals to distinguish between evidence-based and unsubstantiated information. A quality label for health-related websites and public health information campaigns are two examples of such measures. Surveys can help understanding how individuals form their perceptions and where they obtain their information.

Another challenge we are faced with, given the popularity of social media, is whether we can still make a distinction between global and local information

and how to use these sources of information to construct BCMs. We motivate by example: are Tweets local or global information? In essence, this information can be accessed by anyone, so that they are global. However, at the same time, Tweets are primarily shared among contacts that 'follow' each other, which defines local information. In addition, Facebook contacts are not necessarily close in a geographical sense, such that 'local' relates more to the possibility of clustering, moving beyond geography. This evolution reinforces the need for having distinct networks in the same model. While social media require reconsidering how information spread is modelled, they also present an opportunity to gather data on behaviour and behavioural changes. A number of studies we identified already integrated social media data [25, 307, 342, 459]. We expect future modelling studies to increasingly use social media as a data source to parameterize BCMs.

Irrational behaviour and altruism

BCMs have evolved from the perspective of a fully rational 'Homo economicus' to a more reasonable, empathic 'Homo sapiens'. This evolution is conform the findings of surveys examining individuals' drivers to take vaccination [92, 364, 421] and common sense in general. The study of Shim et al. [362] even considers altruism explicitly as a driver of individuals to take vaccination. In the most recent literature, only few papers are still using a pure, self-centred game-theoretic model. Instead, in the majority of the papers, some form of irrational behaviour has been introduced by the inclusion of social influences or imitation. It is striking, however, that most of the imitation BCMs did not empirically justify their choice of stickiness parameter.

Level of detail of behaviour.

Many BCMs today capture, to some extent, heterogeneity in behaviour; individual-level networks can, for instance, introduce heterogeneity in the number of neighbours that can influence a person to adopt preventive measures. Some population models split the population into compartments representing different levels of risk attitude [31]. Some IBMs introduce personal experiences with disease or prevention measures in behaviour change models [123].

Moreover, heterogeneity in behaviour can be split into two categories: heterogeneity in information an individual receives (e.g. the social contact network of the individual) and heterogeneity in the response to this information (e.g. assigning individual values of stickiness of response in models with imitation). The majority of the publications include individual heterogeneity as the information they are exposed to, whereas only few include the latter category.

The desirability of heterogeneity in behaviour depends on the circumstances and characteristics observed. We illustrate by example: for measles in a highly vaccinated population, it has been observed that unvaccinated individuals and anti-vaccine sentiments are clustered and, as a result, heterogeneity in behaviour should be introduced in behaviour models. For example, one can introduce a distinction between vaccine sceptics and vaccine believers [363].

Again, the availability of real-life observations determines to a large extent the feasibility of introducing heterogeneity in BCMs. Why develop a complex model with large heterogeneity if the parameters cannot be informed by real-life observations? A trade-off needs to be made in terms of computational efficiency, data availability and desirability of heterogeneity given the context of the disease [128].

Limitations and strengths

Our search was limited to the past 6 years. However, a previous review ended where we start, and since this field is transitioning fast with rapidly increasing computational and research capacity, we believe the most recent years are the most informative. This is also testified by the evolution of our search yield over the 6 year period we covered. Our strength lies in the transparent and systematic way we have searched and analysed the literature according to the standards of systematic review. Nevertheless, as with any systematic review, our search string strikes a balance between completeness and feasibility. Given the current lack of a consistently used common term for the models we review, it is inevitable that we missed some admissible research. Indeed, it came to our attention that, for instance, [252, 257, 474] terms were not retrieved by our search, although they would satisfy our eligibility criteria. This emphasizes the need for a specific terminology. We therefore propose the use of the term 'behavioural change model' in title, abstract or keywords to facilitate more accurate identification of relevant studies by researchers in different fields.

2.5 Conclusions

We have systematically reviewed the literature on BCMs published from 2010 until 2015. We analysed and classified 178 references after full-text processing. We proposed a classification of the BCMs based on the decision-making process of the individual. We can summarize our findings in line with the six aims we listed in the introduction. Regarding the technological advancements and increased data availability (i), we find that social media and big data are useful to parametrize BCMs and present an as yet insufficiently explored source

of information. Social media can, however, introduce a bias in individuals' prevention- or disease-related perceptions. In addition to the health recommendations they make, policy-makers can optimize their influence by enabling the collection and accessibility of government-owned data (such as surveillance) and by establishing a quality label for disease-related websites. Further, we can confirm that behavioural immunity is often contingent on the disease (ii): BCMs are disease and situation-dependent, which we strongly support. Regarding model validation and parametrization with quantifiable observations (iii), we can state that additional data sources are needed to specify relevant BCMs. Although the 2009 influenza pandemic presented an opportunity for parametrization and validation of both disease transmission and BCMs for flu-like illnesses, there is still much room for improvement in other disease areas. Current models have, without a doubt, assessed the importance of social networks in individual decisions (iv). Individual-level models such as IBMs are extremely useful to tackle behaviour changes and to mimic disease transmission better. More specifically, (v) the diversity observed in BCMs has increased the feasibility of introducing social influences and irrational behaviour (vi). In terms of policy recommendations, it is highly important to think about the total effect of an intervention, with possible implications on all prevention strategies.

The expansion of BCMs has been remarkably valuable. We encourage researchers to incorporate behaviour changes in future disease transmission models and to be transparent about the assumptions they make if data sources for parametrization or validation are sparse.

2.6 Author contributions statement

P.B. initiated the study. F.W., L.W. and P.B. conceived and designed the inclusion criteria. F.V. and L.W. performed the screening. All authors reviewed the manuscript.

2.7 Funding statement

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CHAPTER 3

A discrete choice experiment (DCE)

This chapter is based on published work: "Verelst F, Willem L, Kessels R and Beutels P. (2018). Individual decisions to vaccinate one's child or oneself: A discrete choice experiment rejecting free-riding motives. Social Science & Medicine, 207, 1-9." [413] and: "Verelst F, Willem L, Kessels R and Beutels P. (2018). Corrigendum to 'Individual decisions to vaccinate one's child or oneself: A discrete choice experiment rejecting free-riding motives'. Social Science & Medicine, 217, 31." [412]

Summary

It is essential for public health to understand what drives people's hesitance towards vaccination. Theoretical models of vaccination decisions are ubiquitous, often incorporating herd immunity, perceptions of vaccine-related side-effects (VRSE) and of vaccine-preventable burden of disease, but with little to no empirical exploration. Herd immunity is a (usually) positive externality where vaccinated individuals influence others' risks by their reduced capability to transmit an infectious disease to them. It is often assumed that (rational) individuals incorporate this externality in their strategic vaccination decision, from which free-riding behavior arises. We performed a Bayesian D-efficient discrete choice experiment in February-March 2017 to study vaccination behavior in 1919 Belgian respondents. Choice sets with vaccine profiles were constructed using six attributes: vaccine effectiveness, VRSE, accessibility (in terms of convenience and reimbursement), vaccine-preventable burden of disease, local (respondents' network of contacts) vaccination coverage, and population (the population at large) vaccination coverage. VRSE and accessibility are the most influential attributes, followed by vaccine effectiveness and burden of disease. Both population and local coverage are less important than the other attributes, but show a significant direct linear relationship with vaccine utility. This supports the existence of peer influence (more incentivized as more and more vaccinate), rather than free-riding on herd immunity. These findings were independent of whether respondents made vaccine choices for themselves or for their child. Around 40% of the respondents indicated accepting vaccination with little or no questioning. These 'acceptors' were less sensitive to changes in the vaccine-preventable burden of disease for their child's vaccination choices (but not for themselves). Public health institutions are critical in stimulating vaccine uptake by making vaccines conveniently available at an affordable price and by communicating pro-actively on perceived VRSEs. The free-riding assumption as a driver of individual vaccine decisions, seems inappropriate, but this observation needs confirming in other populations.

3.1 Introduction

Infectious disease prevention is increasingly challenged by globalization [173]. Not only pathogens spread globally in a matter of days through ever-increasing human mobility [273], but vaccine scares and hesitancy can propagate even faster via social media [214, 343]. The communicability of both infections and rumors undermine hard-fought investments to prevent, control and eradicate infectious diseases [217]. Hence, understanding individual vaccination decisions is highly relevant for policy-makers and vaccine program managers in order to anticipate and respond to drops in vaccination coverage. Empirical information on how individuals decide about vaccinating themselves or their children is however lacking [128, 411].

Yielding uncertain benefits in the future, prevention differs fundamentally from cure. People do not know upfront when (or if) they will contract a preventable disease. Other vaccine-specific aspects further complicate an individual's decision to accept vaccination [79]. Widespread vaccination yields (mostly positive) externalities through herd immunity [114]. Herd immunity – the indirect protection of unvaccinated people in a largely vaccinated population – provides a safety net for those who cannot receive vaccination for medical reasons (e.g. too young, immunocompromised, pregnant), those who deliberately reject or delay vaccination or those who are not or no longer immunized by the vaccine they received. Some theoretical models assume herd immunity is incorporated by individuals in their vaccination decision, implying many individuals are assumed to deliberately free-ride on others' vaccination (e.g. [20, 352, 471], see [411] for a systematic review). Though rarely discussed, it remains unresolved whether herd immunity contributes more to vaccine acceptance through altruistic motives (to protect the vulnerable) than to rejection or hesitance through free-riding motives [317, 364, 421]. Moreover, vaccination is to a certain extent victim of its own success. Regions with high vaccination coverage experience less vaccine-preventable disease (VPD) burden, and when this occurs over a long period, the need for a high vaccination coverage may be questioned to the extent that large VPD outbreaks occur until coverage rises again [475].

Discrete choice experiments (DCEs), which are well-established in health economics [71, 85], have been used before to elicit preferences for vaccines [36, 84, 91, 138, 154, 303, 338], but none of these compared adults' vaccine choices for themselves with those for their children, and only one investigated free-riding motives [154].

In Belgium, the administration of childhood vaccines up to age 15 months is organized at the regional level through well-baby clinics, which are attended

by about 70% of infants [203]. During five vaccination consults, these infants receive up to 13 vaccine doses (jabs and oral intakes combined) against 12 pathogens. Only poliomyelitis vaccination is mandatory in Belgium. Most recommended vaccines are available on site for free. Only the oral rotavirus vaccine requires parents to first get a prescription, buy the vaccines at the pharmacy (co-payment of 11.90 euro per dose), and take the vaccine to the well-baby clinic or general practitioner (GP) for its administration. School-age children are vaccinated through a regional-level institution of school nurses and physicians. In general, vaccination coverage of recommended vaccines (i.e. in the basic immunization schedule) in children is stable and high (92.9-96.2%) [409]. Despite the above practical hurdles and personal costs, even rotavirus vaccine coverage attained 89.7% in Flanders, the Dutch speaking part of Belgium [409]. As such, the Flemish population remained up till now largely indifferent to vaccine controversies [217, 409], except for some clusters of susceptibles interfering with measles elimination (e.g. measles outbreak linked to an antroposophic school [40]). Nonetheless, an understanding of the individuals' "vaccination blackbox" is important to inform simulation models, and to guide policy-makers in case of spill-overs of vaccine hesitancy or refusals from other countries [159, 217, 308].

Flemish adults are familiar with vaccination decisions as well. More specifically, they are familiar with seasonal influenza vaccine (recommended for risk groups and elderly), booster doses for tetanus, diphtheria and acellular pertussis (Tdap) every 10 years (with additional recommendations for future parents) and travel vaccinations such as typhoid fever, yellow fever and hepatitis A. Pneumococcal and shingles vaccines are licensed for adults, though the uptake remains low. Tdap is offered for free and is available at the vaccinator, while others require a subscription or a visit to the pharmacy or travel clinic [27].

In this chapter we explore determinants of Flemish individuals' decision-making on vaccination by means of a DCE. As such, the decision-making process is represented as a multi-criteria decision in which we can determine the importance individuals assign to each attribute. We discuss the relevance of our findings for modeling and vaccine policy-making.

3.2 Methods

We conducted a survey among Flemish-Dutch speaking Belgian inhabitants in February-March 2017, recruiting respondents from a registered consumer panel. Multiple techniques guaranteed a high-quality panel, such as consistency checks, mobile phone ID verification and the identification of 'straightliners' (respondents answering the same for each question) and 'speeders' (respondents completing the survey much faster than a reference time). Only one respondent per household could take part. Participation was incentivized through credit rewards, transferable into coupons, airline miles, etc. No physical samples were collected and the ethical committee of the Antwerp University Hospital (UZA) approved the study protocol.

A representative sample was drawn in terms of gender, age group and province with Flemish-Dutch native speakers. Respondents filled out the survey for themselves or for their youngest child (<18 years), which we distinguish as the 'adult' and 'child' group, respectively. Preferences elicited in the child group reflect parents' preferences with respect to vaccinations for their child. Demographic and household info was used to include and assign panel members until the sample quota were reached (table 3.1). In total, 1919 panel members completed the full survey through a web-link directing them to an online version of the questionnaire. We surveyed 1091 respondents in the adult group and 828 in the child group. The participation rate was 88% (in a multi-source, routed environment with efficient participant allocation), implying 12% of respondents started but chose not to complete the survey. Other respondents completed the full survey or were dropped out automatically, when pre-defined sample quota were reached.

Table 3.1: Comparison of sample characteristics with pre-defined sample quota and population characteristics.

Characteristic	Adult group (%)	Child group (%)	Pre-defined quota (%)*	Sample (%)	Flemish population (%)
Gender					
Male	55	46	50	51	49
Female	45	54	50	49	51
Age group					
18-34	23	35	25	28	26
35-49	15	50	25	30	25
50-64	27	14	25	21	26
65-85	35	1	25	20	22
Educational attainment					
Low	5	3	NA	4	25
Medium	50	48		49	41
High	45	47		46	34
Other	0	1		1	
Province					
Antwerp	31	29	28	30	28
Limburg	14	14	13	14	13
East Flanders	23	24	23	23	23
West Flanders	16	17	18	17	18
Flemish Brabant	14	13	17	13	17
Brussels	2	1		2	
Other	1	1		1	
Sample size	**N=1091**	**N=828**	**N=1500**	**N=1919**	

Source for Flemish population rates: Algemene Directie Statistiek - Statistics Belgium: http://statbel.fgov.be/nl/statistieken/cijfers/bevolking/, retrieved on May 16, 2017.
*Pre-defined quota were made on the full sample in absolute numbers (e.g. minimum 375 respondents aged between 65-85). Another pre-defined sample characteristic was a 70/30 ratio of child group respondents with their youngest child between [0-11] and [12-18] years respectively.

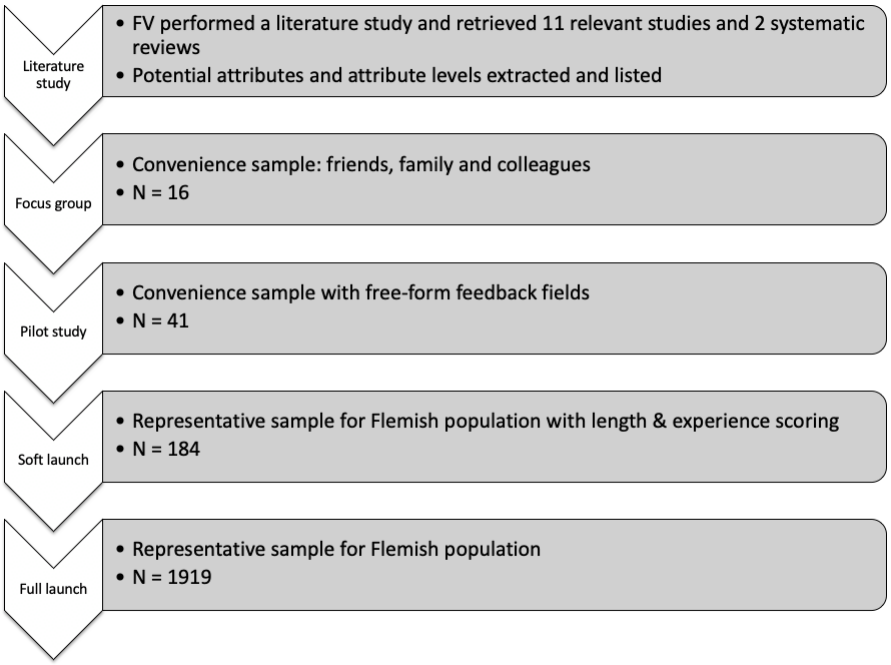


Figure 3.1: Flow chart representing the selection and tuning of DCE attributes and attribute levels.

DCE Attributes

The construction of choice sets with vaccine profiles by means of attributes is a trade-off between completeness and cognitive feasibility. We retrieved relevant elements from the literature [48–50, 84, 91, 127, 138, 154, 245, 303, 338], departing from systematic reviews [317, 411] in order to make vaccine profiles and to match attributes to the parameterization of vaccine-decision models. Attributes were then ranked and categorized through a focus group discussion. Final selection and tuning of relevant attributes occurred through a pilot study with free-form feedback, followed by a soft launch in the study population with respondent feedback scoring. Feedback from the focus group and the pilot study resulted in a reduced number of attributes (from 8 to 6) and an adapted DCE design with only 10 choice sets (instead of 15) of two vaccine profiles. Feedback from the respondents of the soft launch confirmed feasibility of the DCE with an average score of 8.1/10 based on survey length and experience (survey company tool). The details of the attribute and attribute level selection are displayed in Figure 3.1. Table 5.1 lists the final attributes and corresponding levels, the rationale of which can be summarized as follows:

1. Vaccine effectiveness is described as the proportion of vaccinated persons

protected by the vaccine and has two levels: 50% and 90%. These levels were chosen to represent vaccines with moderate effectiveness, such as seasonal influenza vaccination [117, 195] and high effectiveness, such as hepatitis B [385] and measles [379] vaccination.

2. Burden of disease is a combination of disease prevalence and severity. Both these subattributes have two levels, implying four levels describe the burden of disease attribute: rare/common and mild/severe (see table 5.1). Mild/severe disease is further specified as hospitalization occurring exceptional/often and being not life-threatening/life-threatening. We chose two extreme levels for both prevalence and severity to facilitate the choice task. Our pilot study validated the feasibility of this four level representation, with no reported interpretative difficulties.

3. VRSE are described by two possible levels: common and rare. The focus group discussion and cognitive feasibility considerations led us to represent risk of vaccination by frequency rather than severity of VRSE.

4. Accessibility was included as an attribute to represent practical hurdles of vaccine administration, represented by broad reimbursement policy and time cost. We defined two levels based on current vaccination practice in Flanders: 'The vaccine is provided for free and available at the vaccinator ...' versus 'The vaccine is not reimbursed and is only available with a prescription'. The first represents most current universal childhood vaccinations, such as Tdap vaccination. Without naming them, the latter describes non- or partially reimbursed vaccines (depending on target group), such as rotavirus vaccine, seasonal influenza vaccine, or travel vaccines against hepatitis A, tick-borne encephalitis or typhoid fever, and many new vaccines when they first enter the market.

5. Local coverage was specified as 30%, 60% and 90% of close acquaintances (friends and family) already being vaccinated. In the absence of previous explorations of this attribute, we retained the above specific description based on (1) the focus group study, confirming attribute importance in vaccine decisions, and (2) the pilot study where respondents indicated they clearly understood the attribute and different levels. We also intended to quantify to which extent individuals adhere varying degrees of importance to local and population coverage as a main driver for vaccination choices, as often assumed in vaccine-decision models [127, 411].

6. Population coverage, i.e. vaccination coverage in the intended target group, was also included as an attribute.

Table 3.2: DCE attributes and levels.

Attribute	Level description
1. Vaccine effectiveness	a) Protects **50%** of vaccinated b) Protects **90%** of vaccinated
2. Burden of disease	a) The disease, against which the vaccine protects is **rare** and often **mild**: hospitalisation is exceptional and the disease is not life-threatening b) The disease, against which the vaccine protects is **rare** and often **severe**: often with hospitalisation and the disease is life-threatening c) The disease, against which the vaccine protects is **common** and often **mild**: hospitalisation is exceptional and the disease is not life-threatening d) The disease, against which the vaccine protects is **common** and often **severe**: often with hospitalisation and the disease is life-threatening
3. VRSE	a) Side-effects are **common** b) Side-effects are **rare**
4. Accessibility	a) The vaccine is provided for **free** and **available at the vaccinator** (GP, well-baby clinic, school- or occupational physician) b) The vaccine is **not reimbursed** and is **only available with a prescription**
5. Local coverage	a) **30%** of your acquaintances (friends and family) is already vaccinated b) **60%** of your acquaintances (friends and family) is already vaccinated c) **90%** of your acquaintances (friends and family) is already vaccinated
6. Population coverage	a) **30%** of the population in general is already vaccinated b) **60%** of the population in general is already vaccinated c) **90%** of the population in general is already vaccinated

Survey

The four-part questionnaire probed for background characteristics, vaccine-related attitudes, the DCE-preferences and risk perceptions on infectious diseases and vaccination. We circumvented disease- or vaccine-specific sentiments by not specifying (e.g. naming) an infectious disease until the fourth part on risk perception. The questionnaire was developed and honed through literature [50, 245], focus group discussion and a pilot study. The survey started with a general introduction, the questionnaire's outline and its estimated time to completion (20 minutes). Individuals were sampled employing a routing environment with efficient allocation of the respondents.

Background characteristics were derived on gender, age, ZIP code, educational attainment, job status, family situation, family size, age of youngest child, mother's country of birth, professional experience in the health care sector, experience with severe illness, experience with seasonal influenza vaccination, smoking status and religion. Respondents were then assigned to the adult or child group in accordance with our quota. Unconditional assignment to the adult group was performed until sample quota (based on the total sample) were reached, but to the child group assignment was conditional on parenting a child under the age of 18 at the time of recruitment. Parents of children under 18 were not excluded from the adult group. From this point onwards, child group respondents were instructed to fill out the questionnaire making hypothetical vaccine decisions regarding their youngest child. Adult group respondents filled out the questionnaire making these decisions for themselves. Background characteristics were tested as covariates with the DCE estimates to examine preference heterogeneity.

Vaccine attitudes were surveyed by means of 13 statements about vaccination sentiments and habits on a five-point Likert scale. We displayed these statements sequentially to minimize nonresponse [233]. Vaccine attitudes were tested as covariates with the DCE estimates to examine preference heterogeneity.

The DCE started with a general description and an illustrative example of a simplified choice set to familiarize the respondents with the choice tasks ahead. We then used 10 choice sets of two partial profiles each. Partial profiles vary the levels of only a subset of the attributes to limit cognitive burden [70, 198]. We presented three attributes with varying levels and three with constant levels (see figure 3.2). For each choice set, respondents indicated which vaccine profile they were most inclined to choose. Similar to several previous DCEs [82, 198, 200, 201, 245], the evaluation of the choice sets was made easier and

Vaccine A	Vaccine B
Protects 50% of vaccinated individuals	Protects 50% of vaccinated individuals
The infectious disease, against which the vaccine protects is rare and often mild: hospitalization is exceptional and the disease is not life-threatening	The infectious disease, against which the vaccine protects is rare and often mild: hospitalization is exceptional and the disease is not life-threatening
Side-effects are rare	Side-effects are frequent
The vaccine is not reimbursed and is only available with a prescription	The vaccine is not reimbursed and is only available with a prescription
60% of your acquaintances (friends and family) is already vaccinated	30% of your acquaintances (friends and family) is already vaccinated
30% of the population in general is already vaccinated	90% of the population in general is already vaccinated
○	○

Figure 3.2: Example of a choice set in the DCE, consisting of 2 vaccine profiles based on 6 attributes. The attributes with differing levels between the two vaccine profiles are displayed in yellow.

clearer by marking the varying attributes in yellow. However, we explicitly instructed respondents to also consider the constant, non-yellow attributes and to compare all the attributes jointly for a given profile. This helps preventing respondents imagining levels for the constant attributes, which improves the validity of the preference estimates [90] and enables estimating interaction effects.

In addition to the main effects of the attributes, we aimed to estimate all two-way interactions between the attributes 'vaccine effectiveness', 'VRSE' and 'accessibility'. To guarantee that these preference parameters could be estimated with maximal precision, we opted for a partial profile design that is D-optimal (as measured by the log-determinant of the information matrix) for the basic multinomial logit (MNL) model [199]. Because there are 34 model terms (10 main and 24 interaction effects), we constructed a sufficiently large design of 50 choice sets and divided it into five survey versions of 10 choice sets (described in Appendix A.1), about evenly presented to respondents. The three varying attributes in the design differ between choice sets. For each survey we determined them using the attribute balance approach that, for the given design dimensions, comes down to a balanced incomplete block design that enables each attribute to vary in exactly five choice sets and each pair of attributes in exactly two choice sets [198].

The D-efficient partial profile design in Appendix A.1 is Bayesian because it includes prior knowledge. For example, the design assumes that 90% is favored

over 50% vaccine effectiveness and that VRSE are desired to be rare rather than common. For all attributes, we similarly ranked the levels in order of expected importance. Based on literature [48–50, 91, 127, 245, 303] and discussion, we also made a prior ranking of attributes. Table A.2 in Appendix A.2 displays the attributes and their levels in the resulting descending order of priority. We expressed our uncertainty regarding these a priori rankings in a prior multivariate normal distribution. A Bayesian D-efficient design maximizes the information content of the DCE when averaged over that prior distribution. This state of the art approach generally leads to the smallest possible standard errors in model estimation at the smallest sample sizes [37, 199, 330]. We chose to generate a Bayesian D-efficient design for the MNL model because Bliemer and Rose [37] have shown that such a design also performs well for the precise estimation of the more sophisticated panel mixed logit (PML) model, which we used for our main analysis.

Risk perception questions were adapted from Bults et al. [50] inquiring about the perceived relative severity and susceptibility of measles compared to influenza, leukemia and bladder infection. The respondent's relevant sources of information, and knowledge about VRSE of the measles-mumps-rubella (MMR) vaccine were also queried. Risk perception responses were tested as covariates with the DCE estimates to examine preference heterogeneity.

Data analysis

To determine the relative importance of the attributes and attribute levels, we estimated for both the adult and child group a PML model using the Hierarchical Bayes (HB) technique in the JMP 13 Pro Choice platform [179] (based on 10,000 iterations, with the last 5,000 used for estimation). For each model we assumed normally distributed preference parameters without correlation between attributes. These random parameters accommodate unobserved heterogeneity in the respondents' preferences.

The average utility function of the adult and child group is the sum of the average values of the attributes' main and interaction effects. We computed the overall significance of the attributes using likelihood ratio (LR) tests and measured the relative importance of the attributes by the logworth statistic, i.e. -$\log_{10}$(p-value of the LR-test). We started our analysis by estimating the a priori PML model for each group, i.e. the model with the attributes' main effects and all two-way interactions between 'vaccine effectiveness', 'VRSE' and 'accessibility'. Next, we dropped the insignificant model terms until we obtained two final models in which all effects had significant explanatory value

at the 5% level. We explored the presence of observed preference heterogeneity (i.e. structural differences in the parameters by different respondent groups) by estimating interaction terms one by one, based on background characteristics, vaccine attitudes and risk perception questions. Finally, we tested the (individually significant) covariates in a joint model, dropping the insignificant ones until only significant covariates remained.

3.3 Results

The bar charts in figure 3.3 show the relative importance of the attributes' significant main effects and interactions with respondent covariates. All six attributes are statistically significant, but none of the anticipated two-attribute interactions are significant. The bar charts express the logworth statistic of each of the significant model terms relatively to the logworth statistic of 'VRSE', which is the most important attribute in both the adult and child model. For the two models, 'VRSE' is followed by 'accessibility', 'vaccine effectiveness' and 'burden of disease'. Lastly, the local and population coverage attributes are statistically significant, but with limited effect on decision-making. There are three significant covariate terms in the adult model and one in the child model.

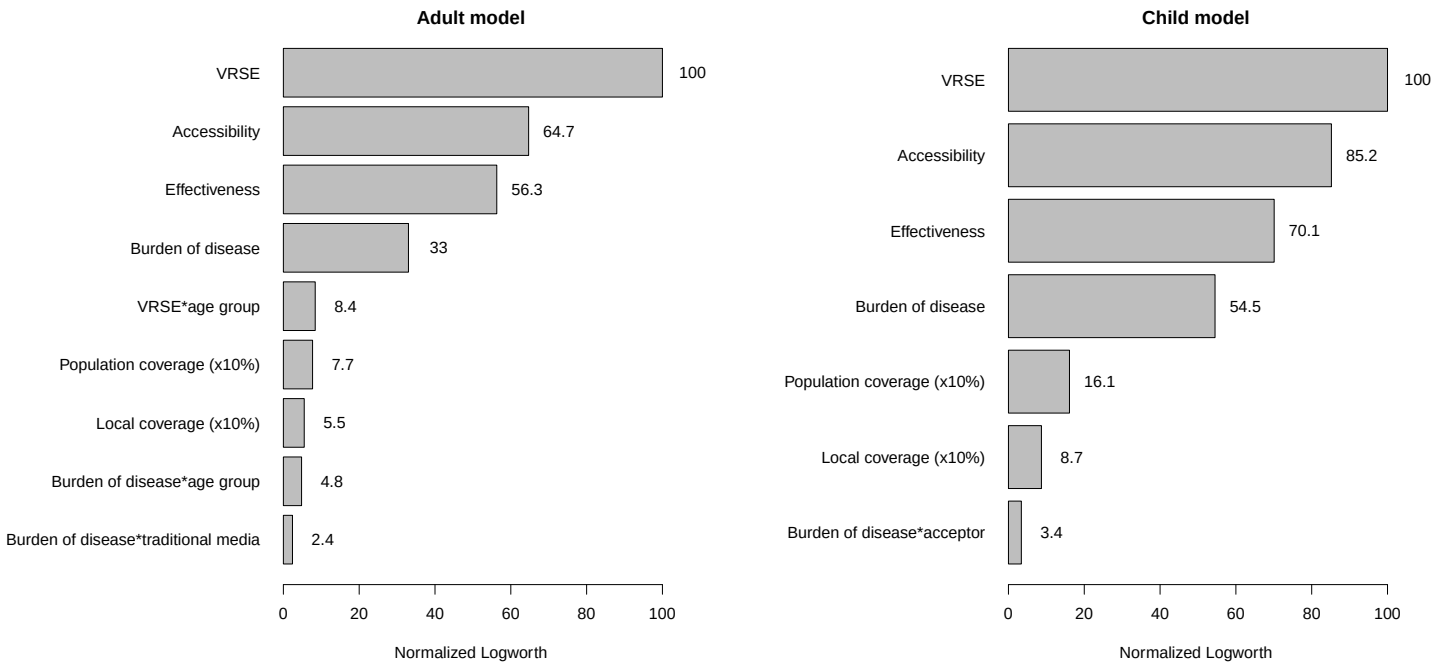


Figure 3.3: Importance of the main and interaction effects of the six attributes in the panel mixed logit model relative to the most important attribute 'VRSE'.

Adult model

'VRSE' is about 40% more important than 'accessibility' and 'vaccine effectiveness', and three times more important than 'burden of disease'. Table 3.3 presents the PML model estimates for the adult group. A positive marginal utility indicates a more preferable vaccine profile. For instance, the marginal utility for rare VRSE is 0.563, and -0.563 for common VRSE. Hence, the most favored vaccine profile has the following characteristics (ranked according to the logworth statistic): rare side-effects, free & accessible at the vaccinator, 90% protective effectiveness, prevents common & severe disease, with its population and local coverage at their highest level. Note that the coverage attributes are treated in a linear manner, such that a 10% rise in local vaccination coverage is associated with a 0.047 utility increase. The maximum attribute utility is reached when 100% of the person's acquaintances is vaccinated (yielding a marginal utility of 0.47). Hence, a vaccine that is already used at high levels of coverage, is preferred to a vaccine for which coverage is low. The marginal utility of the burden of disease attribute levels can be ranked as follows (from least to most desirable level): rare & mild, common & mild, rare & severe and common & severe, indicating that disease severity is more influential than disease prevalence in assigning a preference to a vaccine profile.

There are three significant covariate effects in the adult model. First, respondent's age interacts significantly with the VRSE attribute (figure 3.4a). The impact of VRSE variation on the marginal utility is lower for respondents in the youngest age group [18-34] compared to those in older age groups. The [50-64] age category is the most risk-averse for side-effects: their marginal utility of common VRSE is -0.696 compared to -0.348 for the [18-34] age group. Note that with its larger logworth statistic (see figure 3.3: 8.4 vs 7.7 and 5.5), this interaction can be considered more important than the two main effects attributes on coverage.

Second, respondent's age is also significant with the burden of disease (figure 3.4b). The oldest age group is the most risk-averse, in the sense that they prefer a vaccine against rare & mild disease, more than younger age groups do. By contrast, younger respondents express greater utility when the burden of disease is large (common & severe) than the oldest respondents do. Overall, figure 3.4b shows that differences in burden of disease levels have less impact on individuals' utility in the oldest age group [65-85] compared to younger age groups.

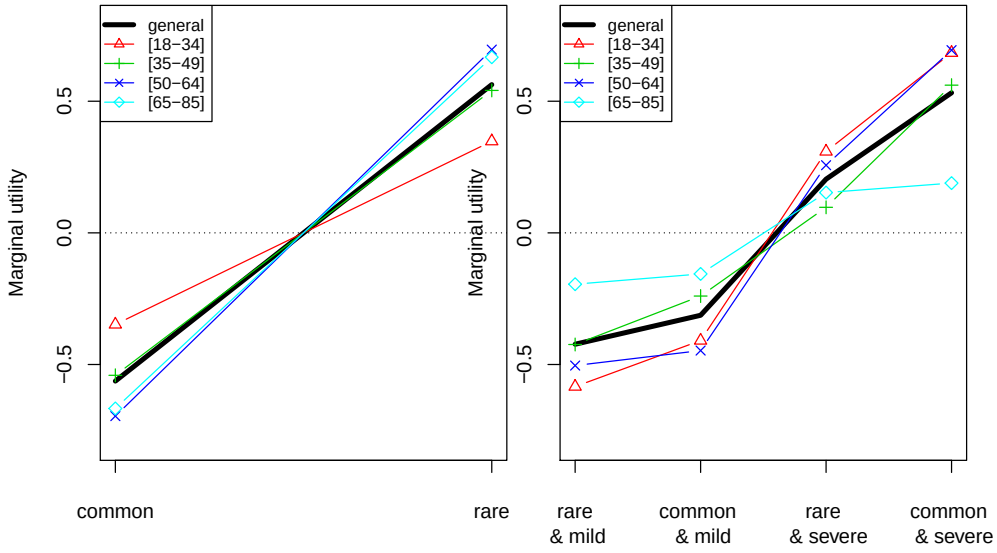
The third covariate interaction effect is between the burden of disease attribute and the (non-) selection of 'traditional media' as a source of information (figure

3.4c). Individuals who use traditional media are less in favor of a vaccine that protects against rare & mild disease, compared to individuals not using traditional media as an information source on infectious diseases and vaccination. However, when the vaccine preventable disease burden is greater, the traditional media subgroup are more in favor of the vaccine. For intermediate levels of the disease burden, the two subgroups have similar preferences.

Child model

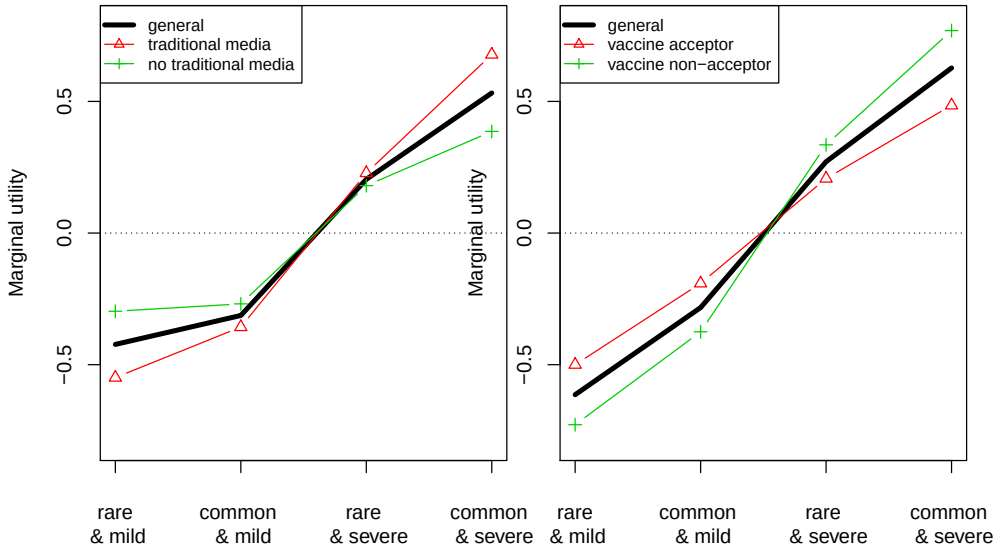
Similar as in the adult model, VRSE, accessibility, vaccine effectiveness, and burden of disease are the most important considerations in the decision-process on childhood vaccination (see figure 3.3 and table 3.4). Although the population and local coverage attributes are more important than in the adult model, they remain less important than the other attributes, and the ordering of main attributes is unaffected. Side-effects are considered about twice as important as burden of disease, and accessibility is considered to be the second most important attribute. Again, more utility is attached to severity compared to frequency of occurrence in the burden of disease attribute.

The interaction between burden of disease and being an 'acceptor' is the only significant covariate term in the child model (see figure 3.4d). An acceptor is defined as a respondent indicating 'strongly agree' or 'agree' (5-point Likert scale) on the statement: 'I do not question vaccination, it's just something I do when it is offered to me'. Differing levels of the burden of disease have a smaller impact on the marginal utility of 'acceptors' compared to 'non-acceptors'. For instance, the marginal utility in the case of a common & severe (rare & mild) disease is 0.485 (-0.500) for 'acceptors' compared to 0.769 (-0.728) for 'non-acceptors'.



(a) Adult model. VRSE and age group.

(b) Adult model. Burden of disease and age group.



(c) Adult model. Burden of disease and traditional media as information source.

(d) Child model. Burden of disease and (dis)agree with acceptor statement.

Figure 3.4: Marginal utilities for the significant covariate interaction terms: a), b) and c) represent the three covariate terms in the adult model, and d) represents the single covariate term in the child model.

Table 3.3: Panel mixed logit model estimates (means and standard deviations) and significances of the attribute effects obtained from likelihood ratio (LR) tests. Adult Model.

Term	Mean estimate (std dev; subject std dev)	LR Chi-square	DF	P-value
VRSE				
Common	-0.563 (0.023; 0.058)	640.612	1	< 0.0001
Rare	0.563			
Accessibility				
Co-payment & prescription	-0.410 (0.023; 0.058)	412.568	1	< 0.0001
Free & accessible	0.410			
Vaccine effectiveness				
50%	-0.487 (0.023; 0.075)	358.211	1	< 0.0001
90%	0.487			
Burden of disease				
Rare & mild	-0.423 (0.042; 0.070)	218.655	3	< 0.0001
Common & mild	-0.313 (0.042; 0.049)			
Rare & severe	0.204 (0.040; 0.034)			
Common & severe	0.532			
VRSE*age group				
Common*[18-34]	0.215 (0.028; 0.044)	57.915	3	< 0.0001
Common*[35-49]	0.022 (0.035; 0.051)			
Common*[50-64]	-0.133 (0.033; 0.051)			
Common*[65-85]	-0.104			
Rare*[18-34]	-0.215			
Rare*[35-49]	-0.022			
Rare*[50-64]	0.133			
Rare*[65-85]	0.104			
Population coverage (x10%)	0.055 (0.007; 0.044)	45.431	1	< 0.0001
Local coverage (x10%)	0.047 (0.008; 0.040)	31.638	1	< 0.0001
Burden of disease*age group				
Rare & mild*[18-34]	-0.161 (0.061; 0.089)	48.614	9	< 0.0001
Rare & mild*[35-49]	-0.001 (0.083; 0.094)			
Rare & mild*[50-64]	-0.081 (0.081; 0.074)			
Rare & mild*[65-85]	0.228			
Common & mild*[18-34]	-0.096 (0.060; 0.074)			
Common & mild*[35-49]	0.073 (0.068; 0.070)			
Common & mild*[50-64]	-0.134 (0.050; 0.067)			
Common & mild*[65-85]	0.157			
Rare & severe*[18-34]	0.105 (0.055; 0.056)			
Rare & severe*[35-49]	-0.107 (0.076; 0.055)			
Rare & severe*[50-64]	0.053 (0.059; 0.050)			
Rare & severe*[65-85]	-0.051			
Common & severe*[18-34]	0.152			
Common & severe*[35-49]	0.029			
Common & severe*[50-64]	0.162			
Common & severe*[65-85]	-0.343			
Burden of disease*traditional media				
Rare & mild*not selected	0.126 (0.033; 0.054)	17.930	3	0.0005
Rare & mild*selected	-0.126			
Common & mild*not selected	0.044 (0.034; 0.049)			
Common & mild*selected	-0.044			
Rare & severe*not selected	-0.024 (0.044; 0.032)			
Rare & severe*selected	0.024			
Common & severe*not selected	-0.146			
Common & severe*selected	0.146			

Note: Mean estimates corresponding to the last level of an attribute, either as a main effect or involved in an interaction, are calculated as minus the sum of the estimates for the other levels of the attribute.

Table 3.4: Panel mixed logit model estimates (means and standard deviations) and significances of the attribute effects obtained from likelihood ration (LR) tests. Child Model.

Term	Mean estimate (std dev; subject std dev)	LR Chi-square	DF	P-value
VRSE				
Common	-0.516 (0.027; 0.118)	452.542	1	< 0.0001
Rare	0.516			
Accessibility				
Co-payment & prescription	-0.447 (0.026; 0.155)	384.639	1	< 0.0001
Free & accessible	0.447			
Vaccine effectiveness				
50%	-0.519 (0.034; 0.121)	315.617	1	< 0.0001
90%	0.519			
Burden of disease				
Rare & mild	-0.614 (0.052; 0.090)	255.510	3	< 0.0001
Common & mild	-0.283 (0.036; 0.103)			
Rare & severe	0.271 (0.041; 0.045)			
Common & severe	0.627			
Population coverage (x10%)	0.077 (0.009; 0.053)	69.391	1	< 0.0001
Local coverage (x10%)	0.058 (0.008; 0.052)	35.822	1	< 0.0001
Burden of disease*acceptor				
Rare & mild*agree	0.114 (0.041; 0.168)	18.069	3	0.0004
Rare & mild*disagree	-0.114			
Common & mild*agree	0.092 (0.037; 0.116)			
Common & mild*disagree	-0.092			
Rare & severe*agree	-0.064 (0.038; 0.046)			
Rare & severe*disagree	0.064			
Common & severe*agree	-0.142			
Common & severe*disagree	0.142			

Note: Mean estimates corresponding to the last level of an attribute, either as a main effect or involved in an interaction, are calculated as minus the sum of the estimates for the other levels of the attribute.

3.4 Discussion

Our study confirms that the decision to vaccinate or not is made by trading off different attribute levels, i.e. it is a multi-criteria decision [154]. VRSE are pivotal in this process. Rapid dissemination of VRSE misperceptions, through social or traditional media [343] can undermine vaccination programs. In addition to continuously providing scientific evidence to counter VRSE misperceptions, health policy institutions and program managers are instrumental in achieving and sustaining high vaccination coverage, by making vaccines as accessible as possible. Indeed, accessibility – inversely related to the opportunity costs (in terms of both time and money) faced by an individual to receive vaccines – as well as effectiveness and disease burden are important determinants of whether or not people become vaccinated. The fact that people are more inclined to demand vaccination when a disease becomes more prevalent supports the idea of a behavioral feedback mechanism. That is, as the prevalence of a vaccine preventable infectious disease increases, more and more people become vaccinated. Through the success of vaccination, the incentives to get vaccinated, along with disease prevalence, decrease to the point where they no longer outweigh perceived VRSE, and the cycle starts all over again. However, the (perceived) severity of disease leads to a larger gain in vaccine utility than disease prevalence does. This finding is supported by Sadique et al. [338], who performed a DCE in 369 UK mothers, and found that severity of disease exerted an important influence on vaccination demand, in contrast to frequency of disease, that was found not to be significant. We estimated both models with a decomposition of the burden of disease into severity of disease (severe/mild) and frequency of disease (common/rare), and found no substantial differences in results from using the joint attribute (Appendix A.3). While also significant, population and local vaccine coverage turned out to be less important attributes compared to the previous four. The propensity to vaccinate was shown to increase with increasing local and population vaccination coverage.

A previous Belgian DCE investigating the public's preferences on how the government should prioritize health care interventions [245], found patients' lifestyle and age to be the most important attributes. Although the research question and some attributes under investigation were different, three other significant attributes were similar, but they were ranked in descending order of importance as effectiveness, severity of illness, and adverse effects, compared to VRSE, vaccine effectiveness, and burden of disease in the current study. Hence, adverse effects seem more influential when the DCE is framed around vaccinations, compared to an unspecified curative or preventive intervention

as in Luyten et al. [245]. The specific context of vaccination seems to make people more cautious about adverse effects. However, this may change in pandemic emergency situations, as suggested by Determann et al. finding vaccine effectiveness is more influential than VRSE, institutional advice, out of pocket costs and media coverage for pandemic vaccination in The Netherlands [91], and some other European countries [92]. Explicitly specifying risk ratios associated with rotavirus and pneumococcal vaccines, Sadique et al. found severity, but not frequency, of VRSE to be a significant attribute [338]. Limiting our VRSE attribute to a cognitively much less demanding category of frequency, we found it to be highly significant, given the limitation that we did not attempt to describe the severity of these VRSE.

The importance of vaccine effectiveness in vaccine decisions was documented in other studies as well [36, 91, 303]. We distinguished - as the first DCE to our knowledge - two vaccination coverage attributes: local and population coverage. Vaccination coverage was incorporated in two other studies [138, 154] as a single (statistically significant) attribute. The specification of the accessibility attribute incorporating both monetary cost and time cost differs from other studies as well, but yields a highly significant estimate in line with others (out-of-pocket cost, cost per visit etc.) [36, 91, 138, 154, 338].

We found no considerable differences in the decision-making process of the adult versus the child group. The rank order of the attributes is the same but there are differences in the attributes' relative importance, marginal utility, and significant covariate terms. Preference heterogeneity, investigated by estimating interactions between the attributes and covariates based on socio-economics, demography, vaccine attitudes and risk perception, is limited to four significant terms. In the adult model, significant interactions exist between VRSE and age group on the one hand, and burden of disease and age group on the other. Older age categories tend to be more risk-averse with respect to VRSE compared to younger age categories (figure 3.4a). This is in line with psychological literature [113] documenting declines in risk-taking by age. One could argue also that younger adults might be willing to risk more (side-effects) today as they benefit longer from the vaccine compared to older individuals. Older people may also have a more severe perception of VRSE, given that they are more vulnerable to them.

However, when it came to burden of disease (in terms of prevalence and disease severity), our oldest age-group (65-85 years) was less sensitive to risk than the other, younger age groups (figure 3.4b). For the elderly, the difference in utility between a vaccine that protects against a rare & mild disease, and a

vaccine that protects against a common & severe disease is much smaller. An explanation could be that younger individuals are generally in better health and less vulnerable to mild disease, and have comparatively more to lose from severe disease. The oldest age group seems more indifferent to the vaccine preventable disease burden, as long as the vaccine is safe.

We also found that those who use traditional media are more risk-sensitive than those who do not rely on these media for information on infectious diseases and their prevention (figure 3.4c). Presumably those using traditional media are better informed about which specific diseases could correspond to our descriptions of mild, common, severe and rare vaccine preventable diseases, and other information related to specific vaccines. This may help explain why they attach relatively more utility to a vaccine protecting against a common & severe disease, as opposed to a vaccine protecting against a rare & mild disease.

In the child model, we only found one significant covariate effect (figure 3.4d), when we observe a difference in risk sensitivity between 'acceptors' and 'non-acceptors'. Quoting Brunson [49]: 'Acceptors rely on general social norms as the basis of their decisions. They accept these norms with little or no questioning. They do not investigate vaccination.' We singled-out an acceptor subgroup by the two most positive response levels on a five-point Likert scale for the statement: 'I do not question vaccination, it's just something I do when it is offered to me'. They represented 40% of respondents in the child group, and 35% in the adult group. Unsurprisingly, 'acceptors' are less sensitive to vaccine-preventable disease burden. They just seem to accept each recommended vaccine offered to their child, trusting it is safe and effective as part of the package that comes with having an infant undergoing regular health check-ups. The fact that adult vaccination is less of a routine undertaking may explain why we do not observe this covariate for the adult group.

The Belgian population remained relatively unfazed by international vaccine controversies and corresponding drops in vaccination coverage in other countries [217, 409]. Yet, it is important to understand underlying attitudes towards vaccination in times of global exposure to fake facts through social media [107]. The identification of the accessibility attribute as an important contributor to vaccine acceptance provides public health institutions with further leverage to improve vaccination coverage. When a vaccine is available at first contact with the vaccinator (GP, occupational physician, pediatrician etc.), it is more likely to be taken, especially if it is offered to large groups simultaneously (e.g. at school or in the work place, such as influenza and HPV [222] vaccines).

This avoids the time-consuming process of sequentially visiting a physician for a prescription, a pharmacy for buying the vaccine, and again a physician for vaccine administration. The basic recommended childhood vaccines are currently available at the vaccinator in Belgium. Naturally, policymakers can raise uptake by fully or partially reimbursing vaccines [222] (e.g. only Tdap booster vaccine is fully reimbursed for Belgian adults [134]).

The authorities should communicate timely and transparently on VRSE - the most important attribute for vaccine decisions - to better align the public's perceptions with reality and to build trust. Numerous historical examples exist where misperceptions on VRSE have lowered vaccine coverage substantially, opening a window for outbreaks and re-emergence of vaccine-preventable disease. For instance, the MMR vaccine scare originating from a fraudulent paper, linking MMR vaccination with autism [140] has significantly decreased the coverage in England & Wales from about 92% in 1995 to about 80% in 2003, resulting in measles re-emergence in subsequent years [23]. Other examples include the whole cell pertussis vaccine scare in the UK, lowering vaccine coverage from around 80% in 1971 to under 40% in 1976 [23], and the HPV vaccine crisis in Japan [159]. Establishing and maintaining vaccine confidence requires many parallel activities, including clear communication about vaccines in general [214], or about post-marketing safety surveillance [60], and a constructive dialogue with those who hesitate or refuse vaccinations [79, 214].

Moreover, rapid and wide media communication about infectious disease outbreaks can help rationalize vaccination behavior. Especially, information on disease risk and severity (i.e. the burden of disease attribute) lacks in regions where vaccination coverage was high for a long time. The interaction effect of traditional media with burden of disease in our DCE confirms the potential of media to help rationalize vaccination decisions. Scrutinized information on the true burden of disease can function as a compensatory mechanism against potentially inflated misperceptions of VRSE in the individuals' trade-off.

'Free-riding on herd immunity' is often an assumption in (game-theoretical) vaccine-decision models. The reasoning is as follows. Individuals face some cost of vaccination (monetary, time and health cost (including VRSE)) and some cost of contracting the disease. They use these perceived costs to make a trade-off between vaccinating or not vaccinating, incorporating the choice of other individuals (either in his/her community, or on a population level). That is, individuals are assumed to calculate how herd immunity arising from vaccination in others affects their own risk of infection. As part of game-theoretical analysis, the decision whether or not to take vaccination, depends on

the potential to free-ride on established herd immunity. Many examples exist of models explicitly applying free-riding on vaccine-induced herd immunity [20, 24, 32, 142, 211, 324, 363], despite empirical studies suggesting there might also be an altruistic motive in vaccination behaviour [15, 362, 364, 421], i.e. the partial intention to protect others.

One would expect, following the above reasoning, that individuals would be less inclined to take vaccination if more and more people are already vaccinated against the disease. In line with the observation of Hall et al. [154] on varicella vaccination coverage in a 'child group'-like Australian sample of 50 respondents, we observe this is not the case – neither locally nor for the population coverage – in Flanders for vaccination in general. Peer influence dominates free-riding on herd immunity, such that an individual prefers a vaccine against which a larger proportion of the population is already vaccinated (keeping the other attributes constant). Gidengil et al. [138] also find coverage to be significant and positively associated with the demand for combination vaccines in the US. Importantly, we observe this for both the child and adult group, and find a direct linear relation between the utility of vaccination and local and population vaccination coverage. These results suggest it is more appropriate for modellers to integrate herd immunity implicitly through (clinical) disease prevalence rather than through vaccination coverage. The individuals' reasoning is thus replaced by 'not many people contract the disease, so the chances are low for me too'. This fits with the notion that demand for vaccines is prevalence-elastic, but is completely removed from an underlying free riding consideration. Note that vaccination coverage influences primarily the risk of infection, and not only the risk of disease, a distinction which is essential in modelling infectious disease dynamics.

Study limitations

Our sample represents the Flemish population well on all intended characteristics, with the possible exception of educational attainment. The lower-educated seem underrepresented, though this is somewhat difficult to interpret since the age intervals of the government statistics on educational attainment (15-64 years) and our sample (18-85 years) do not completely overlap. Note that interaction terms were estimated based on educational attainment, though this was not found to be a significant characteristic for subgroup preference heterogeneity.

Regarding the partial profile design, we colored the varying attributes yellow and asked respondents to also consider the constant, non-yellow attributes.

However, it would be interesting to explore in future studies to what extent respondents actively study the levels of the constant attributes in the presence of the yellow highlighting, which is important for estimating interaction effects. Furthermore, we did not include VRSE severity as an attribute, next to VRSE frequency. In the vaccine-related DCE literature VRSE frequency is a much more widely used attribute than VRSE severity (7 versus 1 studies [338]). However, since VRSE frequency was the most influential attribute, the addition of VRSE severity could have benefited the interpretation of our analysis, likely decreasing the logworth statistic, and hence the importance of VRSE frequency. Furthermore recent guidance recommends the use of natural frequencies to represent risks [139]. Nonetheless, we opted to use terms like 'rare' & 'common' to describe our attribute levels, based on the focus group and the pilot study showing this offered a clear and interpretable understanding. Finally, sample quota were pre-determined for the full sample (see table 3.1). As such, subgroup-level samples do not necessarily reflect population characteristics.

CHAPTER 4

Vaccine behavior in South Africa

This chapter is based on published work: "Verelst F, Kessels R, Delva W, Beutels P and Willem L. (2019). Drivers of vaccine decision-making in South Africa: A Discrete Choice Experiments, Vaccine 37(15):2079-2089" [414].

Summary

To increase vaccination coverage, it is essential to understand the vaccine decision-making process. High population coverage is required to obtain herd immunity and to protect vulnerable groups in terms of age (e.g. the very young) or health (e.g. immunodeficiency). Vaccine confidence and coverage in South Africa are relatively low, opening the window for sustained outbreaks of vaccine-preventable diseases in a country facing one of the most severe HIV epidemics in the world. To capture the vaccine-related decision-making process in South Africa, we performed a discrete choice experiment with 1200 participants in December 2017. We asked for their preferences with respect to (1) vaccine effectiveness, (2) vaccine-preventable burden of disease, (3) accessibility of the vaccine in terms of co-payment and prescription requirements, (4) frequency of mild vaccine-related side-effects, (5) population vaccination coverage and (6) local vaccination coverage. We distinguished between decision-making for vaccines administered to the participant, and for vaccines administered to their youngest child. We analyzed the data for each of these groups using a panel mixed logit model and found similar results for decisions to vaccinate oneself or one's child. Vaccine effectiveness was the most important attribute followed by population coverage and burden of disease. Local coverage and accessibility were also important determinants of vaccination behavior, but to a lesser extent. Regarding population and local coverage, we observed a positive effect on vaccine utility indicating the potential of peer influence. As such, social normative influence could be exploited to increase vaccination confidence and coverage. With respect to vaccine-preventable burden of the disease, the marginal utilities showed disease severity to be more important than frequency of disease. Policymakers and health care workers should stress the effectiveness of vaccines together with the severity of vaccine-preventable diseases.

4.1 Introduction

Decades of progress made in control and prevention of infectious diseases are currently under threat by a worldwide increase in vaccine hesitancy and refusal [217]. The number of people perceiving vaccines as unsafe or unnecessary is growing, fueled by a false sense of security due to a decline in vaccine-preventable diseases, amplification of anti-vaccine messages through social media [105] and continued anti-vaccine exploitation of a fraudulent paper linking the measles-mumps-rubella vaccine to autism [140]. Decreasing vaccination coverage is even more concerning as it causes a decline in indirect protection, or herd immunity, which plays a central role in protecting vulnerable individuals (e.g. the very young or immunocompromised) [114]. Understanding what drives individuals' vaccination-related decisions is highly relevant to inform policymakers and vaccine administrators in their efforts to increase or maintain vaccination coverage.

The voluntary nature of most vaccines substantiates the need to take the decision-making process into account. Information deficiencies make it difficult for the public to grasp the potential burden of vaccine-preventable diseases and hence to understand the need for protection. As such, vaccination is to a certain extent victim of its own success; many regions experienced sufficiently high vaccine coverage for several years, leading to very low prevalence or even elimination. I.e. many regions are no longer confronted with the image of the corresponding vaccine-preventable diseases. This could lead to a false sense of safety and the idea that vaccination is otiose. In addition, many studies assume that vaccine decisions are influenced by free-riding behavior, through which individuals would be less inclined to opt for vaccination when they perceive vaccination coverage to be high [411]. As such, they have the opportunity to obtain "free", indirect protection through herd immunity.

Global vaccine confidence was recently examined in 67 countries by Larson et al. [217]. Overall, vaccine sentiments appeared to be inversely correlated with socioeconomic status. The European region was found to have the lowest vaccine confidence regarding vaccine safety. For the African region, pediatric vaccines were found less important in South Africa than in Ethiopia, Algeria, Ghana, Nigeria and DR Congo. Other studies on vaccine refusal in South Africa refer to the use of the monovalent MeasBio® vaccine that contains porcine gelatin, which is poorly accepted in some religious communities [118, 144]. The country-level coverage of the measles-containing vaccine in South Africa is estimated to be around 60% for the first and second dose [440], which is below the herd immunity threshold of 95% to stop endemic measles transmission

[405]. Achieving and maintaining high vaccination coverage is especially important to sustain herd immunity and avoid outbreaks of diseases like measles and protect vulnerable subpopulations like human immunodeficiency virus (HIV) positives. In January-September 2017, 129 laboratory-confirmed measles cases were detected in South Africa in three major outbreaks [118].

At the same time, South Africa faces one of the most severe HIV epidemics in the world, with an estimated 6.4 million people living with HIV in 2012 [476]. Infants born to HIV-infected mothers have lower maternal passive immunity and are likely to acquire HIV. HIV-infected children are more at risk of severe and lethal vaccine-preventable diseases, including measles [275, 356], partly because they are also less responsive to vaccination [120]. Hence, herd immunity is pivotal in protecting this large vulnerable group in South Africa, and this depends largely on whether other South Africans decide to receive vaccination or not. Despite indications of vaccine distrust and skepticism reported by Larson et al. [217], there is to our knowledge no published study on the drivers of individual vaccination decisions in South Africa.

Discrete choice experiments (DCEs) have been used to investigate societal preferences regarding vaccinations in multiple countries and revealed the importance of vaccine-related side-effects [84, 91, 154, 303, 338, 413], vaccine efficacy [36, 84, 91, 154, 303, 413] and vaccine cost [91, 138, 154, 338, 413]. A DCE is a surveying technique where respondents are asked to make choices between specified profiles in consecutive choice sets to extract attribute importance and utility values for each attribute level [199]. These utilities represent preferences for an attribute level relative to all other attribute levels.

In this paper we describe the results of a DCE that explored the vaccine decision-making process for a general, unnamed vaccine among 1200 respondents in South Africa. We identified the most influential vaccine attributes and analyzed preference heterogeneity. We distinguished between decisions about a vaccine that would be administered to the participant versus decisions about vaccination of their youngest child. We discuss our findings in the context of policy-making and modeling vaccination behavior.

4.2 Methods

We surveyed individuals in South Africa in December 2017 from an online panel using pre-defined quota on gender, age and ethnicity based on national statistics [2]. Details on the quota and background characteristics are presented in Table 4.1. The survey was launched on an established panel platform, where only the average time required and credit rewards for filling out the survey were displayed. Panel members opted-in for this survey based on this information only. Only one respondent (>18 years) per household could take part. Respondents filled out the survey for themselves or for their youngest child (<18 years), and accordingly, we classified respondents in an 'adult' or 'child' group. Preferences elicited in the child group reflect parents' preferences with respect to vaccinations for their child. Individuals were first randomly assigned to a group. If a respondent in the 'child' group indicated not to have a child under the age of 18, (s)he was moved to the adult group. In total 2958 panel members started the survey of which: 1431 completed the survey successfully, 725 chose not to complete it, 122 were screened out because they were identified as 'speeders' (completed the survey much faster than the reference time) or 'straight-liners' (responded the same for each question), and 680 were halted after the first part of the survey with background questions when pre-defined sample quota were reached to optimize participant allocation. From the 1431 completed surveys, we selected 600 participants from the adult and child group, separately, to approximate the pre-defined quota for age, gender and ethnicity. Given the state-of-the-art Bayesian optimal design [199] of this study, a sample size of 600 is sufficient to estimate all attribute and covariate effects. Participation was incentivized through credit rewards which are, after a delay of 72 h, transferable into coupons, gift cards, airline miles, etc. The study protocol was approved by the ethics committee of the Antwerp University Hospital, Belgium, (Reference number: 15/2/12) and no physical samples were collected. Data collection was performed according the ICC/ESOMAR International Code on Market, Opinion and Social Research and Data Analytics. Given the observational and anonymous nature of our study, and by resorting to this regulated survey panel, no additional approval from a South African regulator was required.

The survey consisted of four parts probing for participants' background characteristics, vaccine-related attitudes, discrete choice preferences and risk perception on infectious diseases and vaccination. Background characteristics included gender, age, postal code, educational attainment, job status, family situation, family size, age of youngest child, mother's country of birth, ethnicity, professional experience in the health care sector, experience with severe illness,

Table 4.1: Sample characteristics and national statistics for South Africa from Stats SA Community survey 2016 [2]. (* age group "18-34 years" from the survey is compared with age group "20-34 years" from Stats SA.)

Characteristic	Adult group (%)	Child group (%)	Sample (%)	South African population (%)	Pre-defined quota (%)
Gender					
Male	52.0	44.8	48.4	49.0	50.0
Female	48.0	55.2	51.6	51.0	50.0
Age group					
18-34 (*)	55.6	42.0	48.8	44.5	$\geq$30.0
35-49	21.7	49.2	35.5	29.3	$\geq$30.0
50+	22.8	8.8	15.8	26.2	$\geq$20.0
Educational attainment					
No schooling	0.2	0	0.1	6.0	
Primary education	0.3	0	0.2	59.3	
Secondary education	33.3	28.5	30.9	31.4	NA
Bachelor's degree	62.2	65.3	63.8	3.3	
Other	4.0	6.2	5.1	NA	
Ethnicity					
Black African	48.8	52.3	50.6	80.7	>50.0
Coloured	5.7	8.8	7.3	8.7	>4.0
Indian/Asian	4.0	3.5	3.8	2.5	>1.0
White	40.8	33.7	37.3	8.1	>4.0
Other	0.7	1.7	1.2	NA	NA
Province					
Guateng	47.0	45.7	46.4	24.1	
North West	2.7	3.8	3.3	6.7	
Limpopo	2.0	2.8	2.4	10.4	
Mpumalanga	5.0	4.5	4.8	7.8	
KwaZulu-Natal	11.8	15.0	13.4	19.9	NA
Eastern Cape	8.3	6.5	7.4	12.6	
Western Cape	18.3	16.0	17.2	11.3	
Northern Cape	1.8	1.3	1.6	2.1	
Free State	3.0	4.2	3.6	5.1	
Sample size	**N=600**	**N=600**	**N=1200**		

experience with seasonal influenza vaccination, smoking status and religion. The second part of the survey contained 12 statements regarding vaccination that participants were asked to rate on a 5-point Likert-scale ranging from 'strongly agree' to 'strongly disagree'.

In the third part, the DCE was surveyed using 10 choice sets with 6 attributes to balance between completeness and cognitive feasibility for the respondent. We derived the attributes and their levels (Table 4.2) from the literature on DCEs in the context of vaccination [36, 84, 91, 138, 154, 303, 338, 413] and health economics in general [71, 85, 245]. Burden of disease was introduced in a DCE on vaccination risk perceptions in the UK [338] and in a DCE on health prioritization in general [245]. Vaccine effectiveness was included in

four studies we retrieved from the literature [36, 91, 245, 303]. We found an attribute describing VRSE in two studies [91, 338] and accessibility was included in a variety of descriptions (willingness-to-pay, number of visits, out-of-pocket costs etc.) in five studies [36, 91, 138, 154, 338]. We only retrieved two studies that included an attribute on vaccine coverage [138, 154], but found the need to include both local coverage as well as population coverage based on the literature covering behavioral change models in infectious disease epidemiology [411]. We adopted the survey design from [413], which was created for a multi-country DCE study, except for the description of the attribute on vaccine-related side-effects (VRSE). In the current DCE, we only varied VRSE frequency by explicitly specifying VRSE as being mild in both of its attribute levels.

Table 4.2: DCE attributes and levels.

Attribute	Level description
1. Vaccine effectiveness	a) Protects **50%** of vaccinated persons b) Protects **90%** of vaccinated persons
2. Burden of disease	a) The disease, against which the vaccine protects is **rare** and often **mild**: hospitalisation is exceptional and the disease is not life-threatening b) The disease, against which the vaccine protects is **rare** and often **severe**: often with hospitalisation and the disease is life-threatening c) The disease, against which the vaccine protects is **common** and often **mild**: hospitalisation is exceptional and the disease is not life-threatening d) The disease, against which the vaccine protects is **common** and often **severe**: often with hospitalisation and the disease is life-threatening
3. VRSE	a) Mild side-effects **commonly** occur and severe side-effects are highly unlikely b) Mild side-effects **rarely** occur and severe side-effects are highly unlikely
4. Accessibility	a) The vaccine is provided for **free** and **is directly available at the vaccinator** (GP, well-baby clinic, school- or occupational physician) b) The vaccine is **not reimbursed** and is **only available with a prescription**
5. Local coverage	a) **30%** of your acquaintances (friends and family) is vaccinated b) **60%** of your acquaintances (friends and family) is vaccinated c) **90%** of your acquaintances (friends and family) is vaccinated
6. Population coverage	a) **30%** of the population in general is vaccinated b) **60%** of the population in general is vaccinated c) **90%** of the population in general is vaccinated

Protects 90% of vaccinated persons	Protects 50% of vaccinated persons
The disease, against which the vaccine protects is common and often mild: hospitalisation is exceptional and the disease is not life-threatening.	The disease, against which the vaccine protects is common and often mild: hospitalisation is exceptional and the disease is not life-threatening.
Mild side-effects commonly occur and severe side-effects are highly unlikely	Mild side-effects commonly occur and severe side-effects are highly unlikely
The vaccine is not reimbursed and is only available with a prescription	The vaccine is provided for free and is directly available at the vaccinator (GP, well-baby clinic, school- or occupational physician)
90% of your acquaintances (friends and family) is vaccinated	60% of your acquaintances (friends and family) is vaccinated
60% of the general population is vaccinated	60% of the general population is vaccinated
○	○

Figure 4.1: Example of a choice set with three variable and three constant vaccine attributes.

The feasibility of the survey was confirmed through a 'soft launch' in a small sample of the panel. The DCE was introduced to the respondents by a general description and an illustrative choice set with two attributes. Subsequently, we asked the respondents for their preference between two vaccine profiles in 10 choice sets (Figure 4.1 shows one choice set). We avoided using a technical/epidemiological lexicon to describe attribute levels, resulting in a good understanding by 80 respondents in the soft-launch. We varied three out of six attributes in each choice set and marked the varying attributes in yellow to limit the cognitive burden on the respondents. However, we stressed the importance of taking all attributes into account, corresponding to the methodology described in the literature [82, 198, 200, 201, 245]. We designed the DCE to estimate the main attribute effects and all two-way interactions between any of the six attributes, and 'vaccine effectiveness', 'VRSE' and 'accessibility' with maximum precision. To capture all model terms (10 main effects and 24 interaction effects), we constructed a Bayesian D-optimal design [199] of 50 choice sets, divided into five subsets of 10 choice sets (see Appendix A.1 for the choice design and Appendix A.2 for the specification of the prior parameter distribution). These subsets were evenly presented to the participants in both the adult and child group.

The last part of the questionnaire asked participants about their perception of relative severity and susceptibility of measles compared to influenza, leukemia and bladder infection, based on the work of Bults et al. [50]. Finally, we asked about their relevant sources of information and their knowledge about measles

and measles containing vaccines.

We used the JMP Pro 13 Choice platform [179] to obtain the relative importance ranking of the attributes and the utility values of their levels by estimating a Panel Mixed Logit (PML) model using Hierarchical Bayes. We assumed normally distributed preference parameters without correlation between attributes to accommodate unobserved heterogeneity in the respondents' preferences. Results were obtained after 10,000 iterations, with the last 5000 used for estimation. The total utility of a vaccine profile is the sum of the attributes' main and interaction effect estimates. We computed the overall significance of the attributes using likelihood ratio (LR) tests and measured the relative importance of the attributes by the logworth statistic, i.e. -$\log_{10}$(p-value of the LR-test). We started the data analysis with a PML model for each group (adult and child), i.e. the model with the main attribute effects and all two-way interactions between an attribute and 'vaccine effectiveness', 'VRSE' and 'accessibility'.

To explore structural differences in the observed preference heterogeneity among subsets of respondents, we estimated two-way interactions between vaccine attributes and background characteristics, vaccine attitudes and risk perception. We first tested the interaction effects with each covariate in separate models. We then constructed a joint model by including all individually significant covariates (p-value <0.05). In this model, some of the covariates turned out to be insignificant, which we then dropped through an iterative process until only significant ones remained.

We obtained additional relative importance rankings of the attributes by sampling 100 sub-datasets without replacement of 700 respondents for which the ethnicity distribution matched that of the population (i.e. increasing the proportion of Black African respondents to 80.7% and decreasing the proportion of White South Africans to 8.1%). We generated models for each of these sub-datasets, computed and recorded the logworth statistics and calculated the mean and 95% confidence interval for the importance of each attribute using the percentile method.

4.3 Results

For the full sample (N=1200), around 90% of the respondents were found to be pro-vaccine, based on a dichotomized 5-point Likert response on the statement 'If a vaccine is available against a certain disease, vaccination is mostly a good method to protect individuals against this disease'. Likely based on commonly rumored measles vaccine side-effects, 4.6% thought measles vaccine could cause autism. Also, 8.5% indicated chronic fatigue syndrome and 11.7% an overloaded immune system as possible side-effects. On the other hand, 58% perceived measles as a severe to very severe disease. About half of the respondents indicated they 'do not question vaccination, it's something I do when it is offered to me'. About 28% agreed with the statement 'The vaccine-related decisions of friends, other parents and/or family affect my own decision'. Henceforth, we will use the term 'relier' to refer to the individuals agreeing with this statement (see also Brunson et al. [49]). Conversely, we refer to 61% of the respondents agreeing with the statement 'I deliberately weigh the advantages and disadvantages of a vaccine against the disadvantages of the disease, before making a decision', as 'thinker'. With respect to the household structure, our sample consisted of 16% single parents, 26% singles without children, 15% living together without children and 43% living together with one or more children. We found no significant associations between risk perception and vaccine preferences.

The summary of background characteristics from our DCE sample of 1200 individuals in Table 4.1 shows that, in terms of educational attainment, individuals with no schooling or only primary schooling were not reached. Hence, our results are only representative for a subpopulation in South Africa that attained at least secondary school. With respect to ethnicity, we performed additional analyses using 100 sub-datasets to meet the population statistics, as explained in the methods section.

For the ethnicity-adjusted analysis, Figure 4.2 displays the relative importance of the attributes by means of the normalized logworth values, i.e. the logworth values relative to the most important attribute, which is vaccine effectiveness. We found all six attributes to be significantly associated with vaccine-related decisions. Vaccine effectiveness is followed by accessibility and population coverage which both had a relative importance of about 60% compared to vaccine effectiveness. Note also that in some of the 100 analyses the rank order of accessibility and population coverage switched, hence the large overlap in confidence intervals. Furthermore, vaccine-preventable burden of disease ranked fourth, with a relative importance of about 40%. Local vaccination

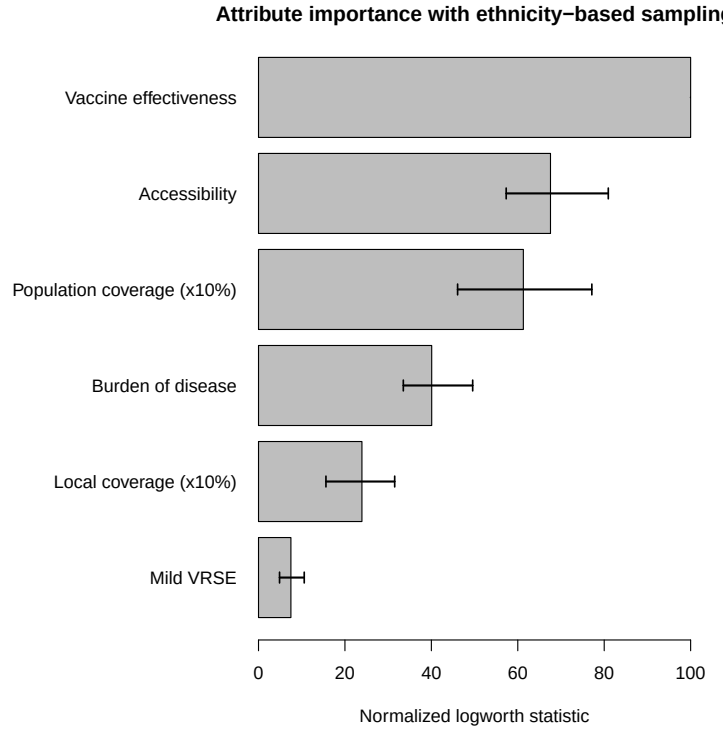


Figure 4.2: Importance of the main effects of the six attributes in the multinomial logit model relative to the most important attribute 'Vaccine effectiveness'. Bars represent the mean and normalized Log-Worth values for 100 samples of 700 observations correcting for ethnicity levels.

coverage and frequency of mild VRSE were found to be less decisive, with a relative importance of 25% or less.

Covariate interactions were estimated with the full survey data for both the adult and child group (both N=600). The model results are shown in Figure 4.3, Table 4.3 and Table 4.4, and are comparable with those of the ethnicity-adjusted analysis. We elaborate on the main findings in the next paragraphs and the discussion section.

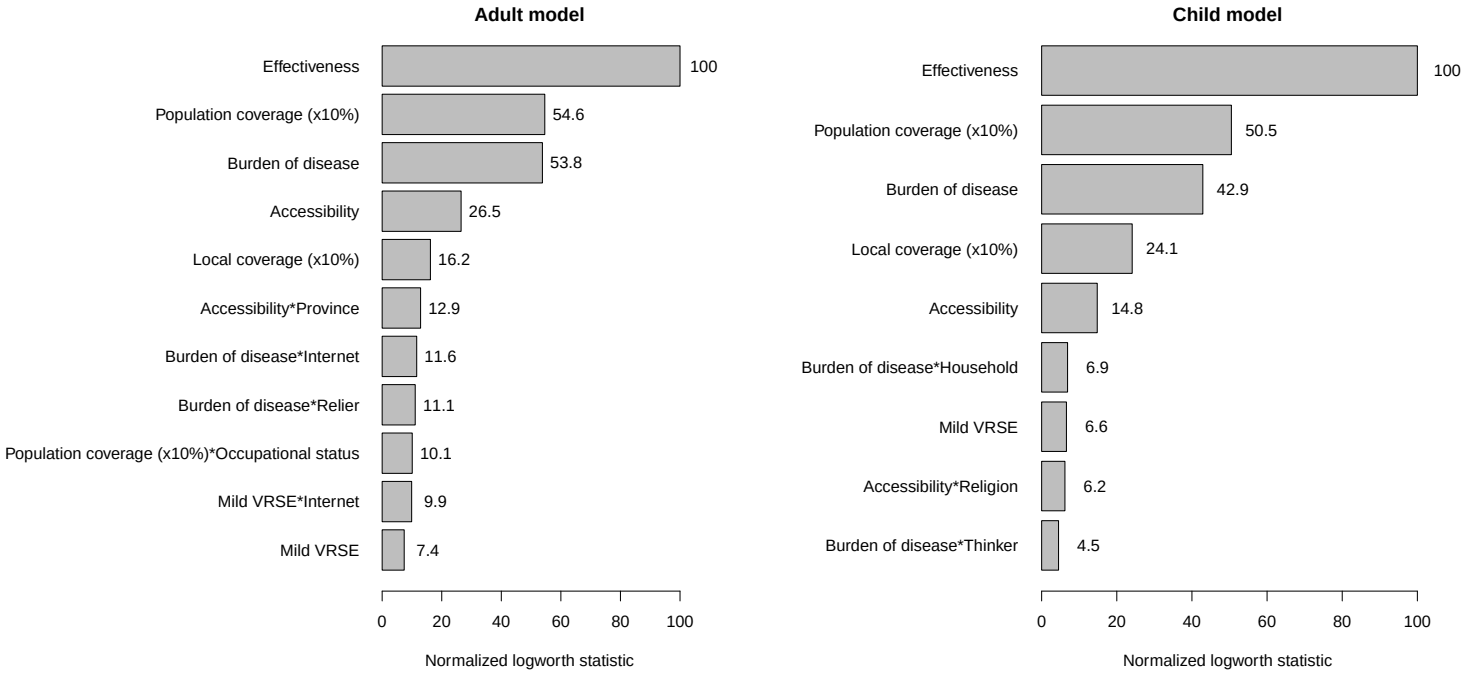


Figure 4.3: Importance of all statistically significant main and interaction effects (p-value $<$ 0.05) relative to the most important attribute 'vaccine effectiveness'.

Adult model

For respondents in the adult group, i.e. for individuals making vaccine choices for themselves, all six attributes were significantly associated with vaccine-related decisions (p-value$<$0.05) (Figure 4.3). Vaccine effectiveness was by far the most important attribute, followed by population coverage and burden of disease, which were ranked as about half as important. Accessibility and local coverage were also influential attributes, although to a lesser extent (26.5% and 16.2%, respectively). Mild VRSE was found to be relatively unimportant as it ranked last, after several covariate interaction terms, with a relative importance of 7.4%. We observed substantial preference heterogeneity demonstrated by significant covariate interactions with accessibility, burden of disease, population coverage and mild VRSE. We elaborate on preference heterogeneity further in this section. In Table 4.3, we display the estimates for the adult model, which represent marginal utilities assigned to the different (combinations of) attribute levels. For example, a vaccine protecting 90% of vaccinated individuals (as opposed to 50%) increased vaccine utility by 0.906. Note that the coverage attributes are treated in a linear way. For example, the marginal utility of a population coverage of 50% was 5 x 0.113 = 0.565. Our analysis indicated that the most favored vaccine profile was a vaccine with 90% vaccine effectiveness, 100% population and local coverage, protecting against a common & severe disease, that was free & accessible and with mild VRSE rarely occurring (yielding a total utility of 3.176). Note that the estimates of the coverage attributes were positive, suggesting that individuals were more inclined to opt for vaccination if more people were vaccinated. Note also that for the burden of disease attribute, which was expressed in terms of susceptibility and severity, the marginal utilities of a vaccine protecting against a rare & severe disease and a common & severe disease were positive and those of a vaccine protecting against a rare & mild disease and a common & mild disease negative. This implies that respondents assigned more weight to severity of disease than to susceptibility.

Regarding the observed preference heterogeneity, we found the most significant covariate interaction between accessibility and province (Table 4.3). Respondents in some provinces (Western Cape, Northern Cape and North West) were more sensitive to accessibility characteristics of vaccines than the average respondent. They attached a relatively lower value to a vaccine that requires patient co-payment and a prescription, and a relatively higher value to a vaccine that is free & accessible.

Figure 4.4 visualizes three other significant covariate interactions. Respondents selecting the internet as a source of information regarding infectious diseases

and prevention seemed more sensible in their choice between preventing a rare & mild versus a common & mild disease, indicating more often their preference for the latter than other respondents (Figure 4.4a). Preference heterogeneity based on internet use for information gathering was also observed for mild VRSE (Figure 4.4b). Individuals not using the internet as a source of information hardly attached any value to mild VRSE as opposed to those who did use the internet. The significant covariate interaction with 'relier' relates to the dichotomized response (agree vs. disagree) on the statement 'The vaccine-related decisions of friends, other parents and/or family affect my own decision' (Figure 4.4c). People who disagreed with the statement were less sensitive to the description of the burden of disease. On the other hand, individuals who did agree with the statement attached relatively more value to a vaccine protecting against a common & severe disease. Also, they were less inclined to opt for vaccination if the disease against which the vaccine protects was common & mild.

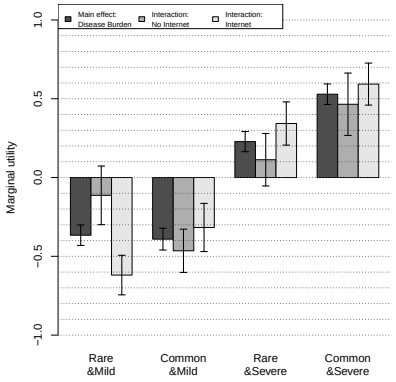
The last significant covariate interaction appeared between occupational status and population coverage (Table 4.3). The positive estimate of 0.042 for individuals that were unemployed implied that they attached a relatively higher value to population coverage and hence were more prone to peer influence or social norms in their vaccine-related decisions.

Child model

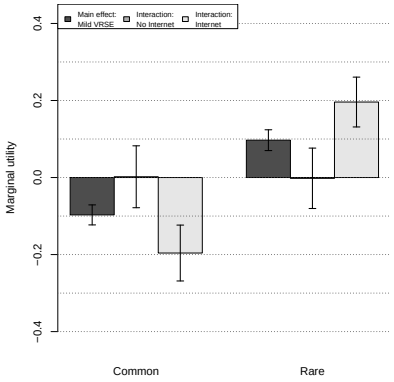
When respondents completed the questionnaire for vaccines that would be administered to their youngest child, again all six attributes influenced the vaccine decision-making significantly (Figure 4.3). Vaccine effectiveness was the key attribute, followed by population coverage, burden of disease and local coverage, with relative importance levels of 50.5%, 42.9% and 24.1% compared to vaccine effectiveness, respectively. Accessibility and frequency of mild VRSE were least valued at 14.8% and 6.6%, respectively. Also, we observed preference heterogeneity through three significant covariate interactions with vaccine attributes.

Table 4.4 shows that the mean utility ranking of the attribute levels of 'burden of disease' is more rational in the child model than in the adult model: in the child model a vaccine protecting against a common & mild disease was generally preferred to a vaccine protecting against a rare & mild disease.

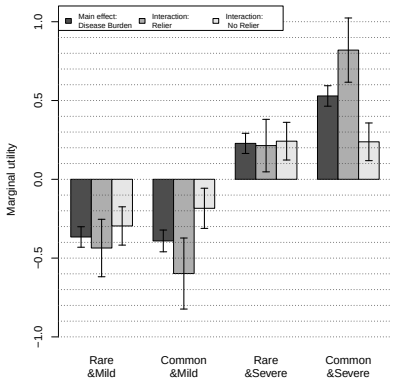
Figure 4.5 shows significant interactions with burden of disease. Single parents attached a higher value to burden of disease: they valued a vaccine protecting against a rare & mild disease and against a common & mild disease less than



(a) Covariate interaction between burden of disease and internet as a source of information.

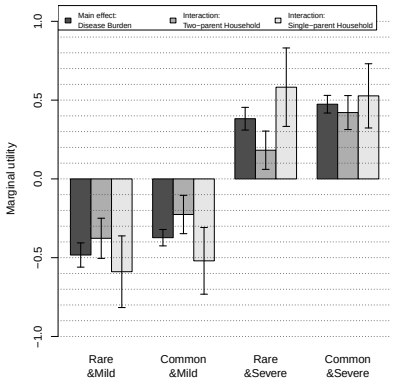


(b) Covariate interaction between Mild VRSE and internet as a source of information.

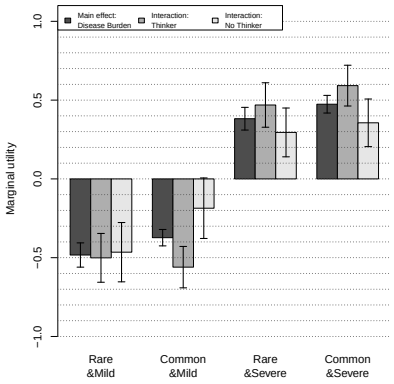


(c) Covariate interaction between burden of disease and agree/disagree with the 'relier' statement.

Figure 4.4: Marginal utilities for the significant covariate interaction terms in the adult model



(a) Covariate interaction between burden of disease and household composition.



(b) Covariate interaction between burden of disease and agree/disagree with the 'rationality' statement.

Figure 4.5: Marginal utilities for the significant covariate interaction terms in the child model

respondents of a two-parent household (Figure 4.5a). Also, single parents attached more value to a vaccine protecting against a rare & severe disease than respondents of a two-parent household.

The significant interaction with being a 'thinker' involves the dichotomized response (agree vs. disagree) on the statement: 'I deliberately weigh the advantages and disadvantages of a vaccine against the disadvantages of the disease, before making a decision' (Figure 4.5b). Individuals agreeing with the 'thinker' statement attached a higher absolute value to the different levels of the burden of disease attribute. However, they valued a vaccine protecting against common & mild disease worse than a vaccine protecting against a rare & mild disease, which seemed somewhat counterintuitive.

Lastly, we discovered preference heterogeneity based on religion and the accessibility attribute. In general, free & available vaccines are preferred, and this preference is more outspoken for Buddhist, Jewish and non-religious people than for Christian and Muslim respondents (Table 4.4).

4.4 Discussion

Four vaccination behavior profiles were recently distinguished by a WHO SAGE Working Group on Vaccine Safety: active demand, passive acceptance, vaccine hesitancy and vaccine refusal. They also defined vaccine hesitancy as a 'delay in acceptance or refusal of vaccination despite availability of vaccination services'. In essence, the vaccine hesitancy continuum is anywhere between those who accept all vaccines on time and those who refuse any vaccine. In order to increase or maintain high vaccination coverage it is therefore pivotal to focus on the population in this hesitancy continuum and develop context, community and vaccine specific strategies [247, 295].

By means of our DCE, we gathered insights in the vaccine decision-making process among a sample of relatively higher educated and slightly younger adults in South Africa. More specifically, we found vaccine effectiveness to be the key element in vaccine-related decision-making. Population coverage, as well as burden of disease, were also highly important, followed by local coverage and accessibility. The frequency of mild VRSE was relatively unimportant. These conclusions hold for both the adult and child group. We did not observe large differences between the two groups except for a few covariate interactions. The attribute importance ranking from the analysis of the ethnicity-adjusted samples tells a similar story. However, accessibility seemed more important in this analysis, which might be due to the fact that Black Africans are more represented in the latter analysis and/or because covariate interactions were not considered.

The marginal utilities of population and local coverage are positive, with the largest utility for population coverage. This means that individuals were more likely to accept a vaccination if more individuals have had already done so. As such, peer effects and social norms dominated vaccine decision-making rather than free-rider motives. This is similar to results from a Belgian [413], an Australian [154], and a US [138] survey.

For policymakers, these results are highly relevant and provide the opportunity to stimulate vaccination coverage. Vaccination campaigns can cause a positive dynamic: a one-time increase in vaccination uptake will have a larger impact through peer influence. However, this dynamic also works in the other direction: a sudden (exogenous) fall in vaccination coverage can also trigger a further decline in vaccine uptake, causing vaccination no longer to be the social norm. Communication about coverage levels on both the population and the local level is however essential for this dynamic to take place. Note

that this social norm effect is opposite to the common hypothesis of free-riding on herd immunity [413]. Behavioral models capturing vaccine decisions in South Africa should consider social norms instead of free-riding behavior. A recent systematic review on vaccine hesitancy confirms social norms to be an important determinant in vaccine decision-making [216].

Timely and accurate information about vaccine effectiveness and burden of disease can contribute to increasing vaccination coverage. Measles vaccines, for instance, are highly efficacious vaccines [405] and it is crucial to emphasize this in vaccine communications by health care workers, health agencies and policymakers. With respect to burden of disease, it is important to stress the severity and susceptibility of vaccine-preventable diseases and co-infections. Especially so in the South African setting where the prevalence of HIV is amongst the highest in the world [476].

Looking at the attribute importance from the analysis of the ethnicity-adjusted samples, we observed relatively high values for the accessibility of the vaccine (Figure 4.2). We found that it is essential to have vaccines available for free and without a prescription. Currently, most vaccines are available at no cost in government health care facilities. Some vaccines, however, are only available in private health care facilities and are not cheap, (e.g., against chickenpox and hepatitis A, and the MMR vaccine). See [277] for more information about the South African public and private immunization schedules. It is essential to keep vaccines conveniently available at an affordable price. Accessibility was also an important attribute in other studies [36, 91, 138, 154, 338], although a different specification of the attribute levels (out-of-pocket cost, cost per visit, etc.) was used in these studies.

We tested covariate interactions with vaccine attributes in a systematic way and found only one significant interaction between religion and vaccine accessibility in the child model. Since measles vaccine is already offered free of charge in South Africa, we think policymakers should look beyond religion to explain low uptake in certain areas and provide accurate and timely information on the attributes that matter most. Moreover, they should target hesitant people, known to be looking for information about vaccines and infectious diseases. If questions remain in hesitant groups, they could receive incorrect or biased information from the internet, social media etc. [194].

The limited importance of perceived VRSE as observed in this study is peculiar, given that VRSE was the most important attribute in a recent DCE about vaccination behavior in Belgium [413]. Nevertheless, the specification of VRSE in the latter study did not control for VRSE severity, i.e. it was only specified

in terms of frequency. In the current study we explicitly specified that all severe VRSE would be exceptional as vaccines for which severe VRSE can occur frequently, will and should not be licensed.

4.5 Study limitations

DCE attributes and attribute levels were selected from a previous DCE [413], whereas DCE guidelines [74, 213] recommend the use of qualitative methods. Even though these attributes were not tailor-made for a specific population, we were able to capture the relative importance our sample attached to six generally accepted vaccine characteristics. This provides the opportunity for policymakers to focus on a select number of vaccine characteristics in information campaigns. Because the aim of our study was to assess the relative importance of the vaccine attributes, we decided not to include an opt-out option. An opt-out option could, nevertheless, be interesting in future research to additionally retrieve trade-offs on vaccinating versus not vaccinating. Our sample was unable to capture the educational attainment level of the South African population. This is due to our decision to collect the data through an online tool and the fact that we did not specify pre-defined quota on educational attainment. Regarding ethnicity, our sample did not fully match the population criteria. However, we investigated the main effects through a bootstrap procedure generating attribute importance rankings with confidence intervals for adjusted samples that matched the census population. With respect to age groups, we matched the population distribution fairly well with the exception of the oldest age group. This could be due to the use of an online panel and our pre-defined sample quota of 50% having at least one child below the age of 18 years. Moreover, the sampling frame, which requires an electronic device with internet access, together with the fact that respondents could only take the survey in English, will most likely have resulted in other, but unobservable, sample imbalances as well. Indeed, the sampling frame is likely to underrepresent people with a low socioeconomic status.

4.6 Conclusion

We performed a discrete choice experiment to gain insights into vaccination behavior in South Africa. We found vaccine effectiveness, vaccination coverage, accessibility and burden of disease to be important attributes. Moreover, we observed positive utility estimates for vaccination coverage, indicating peer influence and social norms to be vital in vaccine decision-making, conditional on people knowing about positive vaccination behavior by others in their circle of acquaintances or in the population at large. Policymakers and health care workers should emphasize the effectiveness of vaccines, stress the burden of vaccine preventable diseases and encourage people to discuss their positive vaccination experiences with their acquaintances. If coverage is sufficiently high, (social) media campaigns reporting coverage are important to further increase and maintain coverage and to reach herd immunity thresholds. These campaigns can also be beneficial if they provide information on the burden of disease (including information on burden of disease in counterfactual scenarios, if coverage were to decline). Such campaigns could also be well-timed around outbreaks (stressing the severity and susceptibility due to low coverage). Moreover, South African policymakers should keep vaccines free of charge and available in all government clinics (as already the case for most vaccines). Cost-effectiveness analyses should determine whether to provide additional vaccines through the public health system.

4.7 Acknowledgements

FV, PB and LW acknowledge support of the Antwerp Study Centre for Infectious Diseases (ASCID) at the University of Antwerp. PB, FV, LW and RK acknowledge support by the Research Foundation Flanders (research project no. G043815N and a postdoctoral fellowship (RK)). Funding for the data collection was provided by the Global Minds initiative at the University of Antwerp. We thank all respondents who participated in the study. We also thank Villyen Motaze for providing background information with respect to the South African immunization programme, and two anonymous referees for providing constructive comments that substantially improved our manuscript. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Conflicts of interest: none.

Table 4.3: Panel mixed logit model estimates of the Adult model: mean and standard deviation (std dev) and significance of the attribute effects obtained from likelihood ratio (LR) tests with a specified number of degrees of freedom (DF).

Term	Mean estimate (std dev; subject std dev)	LR Chi-square	DF	P-value
Vaccine effectiveness				
50%	-0.453 (0.031; 0.121)	141.246	1	< 0.0001
90%	0.453 (0.030; 0.121)			
Population coverage (x10%)	0.113 (0.013; 0.070)	75.302	1	< 0.0001
Burden of disease				
Rare & mild	-0.366 (0.065; 0.096)	82.841	3	< 0.0001
Common & mild	-0.391 (0.069; 0.084)			
Rare & severe	0.228 (0.064; 0.069)			
Common & severe	0.529 (0.065; 0.078)			
Accessibility				
Co-payment & prescription	-0.347 (0.057; 0.090)	34.766	1	< 0.0001
Free & accessible	0.347 (0.041; 0.084)			
Local coverage (x10%)	0.062 (0.012; 0.081)	20.241	1	< 0.0001
Accessibility*Province				
Co-payment & prescription*Eastern Cape	0.385 (0.107; 0.065)	32.510	8	< 0.0001
Co-payment & prescription*Free State	0.044 (0.135; 0.066)			
Co-payment & prescription*Guateng	0.042 (0.069; 0.087)			
Co-payment & prescription*KwaZulu-Natal	0.134 (0.064; 0.060)			
Co-payment & prescription*Limpopo	0.036 (0.255; 0.095)			
Co-payment & prescription*Mpumalanga	0.333 (0.104; 0.069)			
Co-payment & prescription*North West	-0.394 (0.136; 0.081)			
Co-payment & prescription*Northern Cape	-0.303 (0.167; 0.090)			
Co-payment & prescription*Western Cape	-0.277 (0.057; 0.075)			
Free & available*Eastern Cape	-0.385 (0.095; 0.064)			
Free & available*Free State	-0.044 (0.162; 0.070)			
Free & available*Guateng	-0.042 (0.056; 0.083)			
Free & available*KwaZulu-Natal	-0.134 (0.082; 0.071)			
Free & available*Limpopo	-0.036 (0.226; 0.097)			
Free & available*Mpumalanga	-0.333 (0.139; 0.069)			
Free & available*North West	0.394 (0.245; 0.069)			
Free & available*Northern Cape	0.303 (0.192; 0.086)			
Free & available*Western Cape	0.277 (0.079; 0.080)			
Burden of disease*Internet				
Rare & mild*not selected	0.253 (0.054; 0.073)	19.649	3	0.0002
Rare & mild*internet selected	-0.253 (0.046; 0.071)			
Common & mild*not selected	-0.074 (0.056; 0.072)			
Common & mild*internet selected	0.074 (0.055; 0.067)			
Rare & severe*not selected	-0.115 (0.059; 0.058)			
Rare & severe*internet selected	0.115 (0.063; 0.061)			
Common & severe*not selected	-0.064 (0.053; 0.065)			
Common & severe*internet selected	0.064 (0.042; 0.061)			
Burden of disease*Relier				
Rare & mild*disagree	0.070 (0.067; 0.106)	18.929	3	0.0003
Rare & mild*agree	-0.070 (0.055; 0.068)			
Common & mild*disagree	0.207 (0.073; 0.072)			
Common & mild*agree	-0.207 (0.063; 0.078)			
Rare & severe*disagree	0.014 (0.055; 0.071)			
Rare & severe*agree	-0.014 (0.051; 0.073)			
Common & severe*disagree	-0.291 (0.060; 0.067)			
Common & severe*agree	0.291 (0.058; 0.065)			
Population coverage (x10%)*Occupational status				
Population coverage (x10%)*not working	0.042 (0.013; 0.068)	11.703	1	0.0006
Population coverage (x10%)*working	-0.042 (0.012; 0.065)			
Mild VRSE*Internet				
Common*not selected	0.099 (0.022; 0.058)	11.417	1	0.0007
Common*internet selected	-0.099 (0.024; 0.053)			
Rare*not selected	-0.099 (0.024; 0.057)			
Rare*internet selected	0.099 (0.023; 0.055)			
Mild VRSE				
Common	-0.097 (0.026; 0.057)	8.056	1	0.0045
Rare	0.097 (0.027; 0.059)			

Note: Mean estimates corresponding to the last level of an attribute are calculated as minus the sum of the estimates for the other levels of the attribute.

Table 4.4: Panel mixed logit model estimates of the Child model: mean and standard deviation (std dev) and significance of the attribute effects obtained from likelihood ratio (LR) tests with a specified number of degrees of freedom (DF).

Term	Mean estimate (std dev; subject std dev)	LR Chi-square	DF	P-value
Vaccine effectiveness				
50%	-0.583 (0.030; 0.084)	245.794	1	< 0.0001
90%	0.583 (0.030; 0.091)			
Population coverage (x10%)	0.129 (0.010; 0.074)	121.966	1	< 0.0001
Burden of disease				
Rare & mild	-0.483 (0.077; 0.113)	112.268	3	< 0.0001
Common & mild	-0.373 (0.052; 0.094)			
Rare & severe	0.382 (0.072; 0.071)			
Common & severe	0.474 (0.056; 0.075)			
Local coverage (x10%)	0.098 (0.011; 0.070)	56.194	1	< 0.0001
Accessibility				
Co-payment & prescription	-0.681 (0.119; 0.148)	33.361	1	< 0.0001
Free & accessible	0.681 (0.074; 0.148)			
Burden of disease*Household (HH)				
Rare & mild*two parents HH	0.106 (0.071; 0.087)	20.013	3	0.0002
Rare & mild*one parent HH	-0.106 (0.059; 0.085)			
Common & mild*two parents HH	0.147 (0.053; 0.091)			
Common & mild*one parent HH	-0.147 (0.059; 0.098)			
Rare & severe*two parents HH	-0.200 (0.069; 0.066)			
Rare & severe*one parent HH	0.200 (0.065; 0.068)			
Common & severe*two parents HH	-0.053 (0.053; 0.058)			
Common & severe*one parent HH	0.053 (0.059; 0.075)			
Mild VRSE				
Common	-0.116 (0.028; 0.065)	13.548	1	0.0002
Rare	0.116 (0.027; 0.057)			
Accessibility*Religion				
Co-payment & prescription*no answer	0.864 (0.750; 0.071)	26.506	7	0.0004
Co-payment & prescription*not religious	-0.268 (0.196; 0.118)			
Co-payment & prescription*Buddhism	-0.936 (0.756; 0.101)			
Co-payment & prescription*Christian	0.304 (0.125; 0.157)			
Co-payment & prescription*Hindu	0.010 (0.294; 0.088)			
Co-payment & prescription*Judaism	-0.909 (0.478; 0.120)			
Co-payment & prescription*Muslim	0.089 (0.230; 0.074)			
Co-payment & prescription*other	0.846 (0.432; 0.085)			
Free & available*no answer	-0.864 (0.396; 0.075)			
Free & available*not religious	0.268 (0.185; 0.114)			
Free & available*Buddhism	0.936 (0.716; 0.108)			
Free & available*Christian	-0.304 (0.076; 0.149)			
Free & available*Hindu	-0.010 (0.354; 0.081)			
Free & available*Judaism	0.909 (0.486; 0.108)			
Free & available*Muslim	-0.089 (0.254; 0.074)			
Free & available*other	-0.846 (0.417; 0.101)			
Burden of disease*Rational				
Rare & mild*agree	-0.018 (0.058; 0.079)	13.642	3	0.0034
Rare & mild*disagree	0.018 (0.043; 0.079)			
Common & mild*agree	-0.187 (0.050; 0.072)			
Common & mild*disagree	0.187 (0.045; 0.065)			
Rare & severe*agree	0.087 (0.063; 0.058)			
Rare & severe*disagree	-0.087 (0.046; 0.059)			
Common & severe*agree	0.118 (0.046; 0.063)			
Common & severe*disagree	-0.118 (0.040; 0.061)			

Note: Mean estimates corresponding to the last level of an attribute are calculated as minus the sum of the estimates for the other levels of the attribute.

CHAPTER 5

Understanding drivers of childhood and adult vaccination through a multicountry discrete choice experiment

This chapter is based on submitted work "Verelst F, Kessels R, Willem L and Beutels P (2020). No such thing as a free-rider? Understanding drivers of childhood and adult vaccination. Submitted to BMC Public Health" [416].

Summary

Background. Increased vaccine hesitancy and refusal negatively affects vaccine uptake leading to vaccine preventable disease reemergence. We aimed to quantify the relative importance of characteristics people consider when making vaccine decisions for themselves, or for their child, with specific attention for underlying motives arising from context, such as required effort (accessibility) and opportunism (free riding on herd immunity).

Methods. We documented attitudes towards vaccination and performed a discrete choice experiment in 4802 respondents in The United Kingdom, France and Belgium eliciting preferences for six attributes: (1) vaccine effectiveness, (2) vaccine preventable disease burden, (3) vaccine accessibility in terms of co-payment, vaccinator and administrative requirements, (4) frequency of mild vaccine-related side-effects, (5) vaccination coverage in the country's population and (6) local vaccination coverage in personal networks. We distinguished adults deciding on vaccination for themselves ('oneself' group) from parents deciding for their youngest child ('child' group).

Results. While all six attributes were found to be significant, vaccine effectiveness and accessibility stand out in all (sub)samples, followed by vaccine preventable disease burden. We confirmed that people attach more value to severity of disease compared to its frequency and discovered that peer influence dominates free-rider motives, especially for the vaccination of children.

Conclusions. These behavioral data are insightful for policy and are essential to parameterize dynamic vaccination behavior in simulation models. In contrast to what most game theoretical models assume, social norms dominate free-rider incentives. Therefore policy-makers and healthcare workers should actively communicate on high vaccination coverage, and draw attention to the effectiveness of vaccines, while optimizing their practical accessibility.

5.1 Introduction

Vaccination remains a cornerstone of global public health, preventing about 2 to 3 million deaths each year [443]. However, its success is currently undermined by growing vaccine hesitancy and refusal. Sentiments underpinning this have multi-faceted origins, not least distorted perceptions of severe vaccine side-effects, much of which can be traced back to fraudulent research linking measles-mumps-rubella (MMR) vaccination with autism [140, 193], and misconceptions about the use of adjuvants in vaccines [433]. Others include doubts about vaccine effectiveness [193, 217] and about our immune system's coping with the rising number of recommended vaccine antigens [174, 193]. More extreme attitudes are based on government and vaccine industry conspiracy theories [193], religious beliefs (e.g. Protestantism in the Dutch Bible Belt [335]) and "back to nature" motives (i.e. preferring immunity acquired by natural infection to vaccine-induced immunity, under the belief that "divine or natural" risks are smaller and/or more "just" than those imposed by human interventions) [193].

Even though vaccine controversies are not new [311, 369], the internet and a variety of social media have amplified the spread of misinformation and allowed the establishment of new online anti-vaccine communities [214]. According to a 2018 Gallup poll [131], only 40% and 59% of Eastern and Western Europeans, respectively, believe vaccines are safe. In Northern Europe and Northern America, these figures are higher at 73% and 72%, respectively [131].

As a result of these misperceptions, plunging vaccination rates and immunity levels have been observed in recent years. Notably so for measles, which is a highly virulent pathogen for which a safe and effective vaccine was already approved by the Food and Drug Administration (FDA) in 1971 [63]. Indeed, the European Centre for Disease Prevention and Control (ECDC) recently reported the existence of a large pool of people in the EU that are susceptible to measles due to low historical and current vaccination coverage. Only 4 countries achieved two dose measles vaccination coverage of at least 95% in 2017, compared to 14 countries in 2007. Unsurprisingly, measles resurgence has recently been observed, with 44,074 cases in 30 EU member states between 2016 and March 2019 [119]. The same trend has been observed in the US, with 704 cases reported in the first four months of 2019 (even though the US declared elimination of endemic transmission in 2000) [280, 306].

Mathematical and economic models have proven valuable to simulate and evaluate the impact of prevention measures on the spread, burden and economics of infectious diseases. These models inform and guide policy-makers

to prepare for and respond to (re)emerging infectious diseases, particularly when sufficient information from controlled experiments is lacking. However, because of the reasons previously touched upon, the impact of prevention measures and other policy interventions are subject to hosts' compliance and demand. In response, behavioral change models have been developed to incorporate dynamic behavior (i.e. the demand side of prevention measures) into models for infectious disease transmission. As a result of circulating controversies and – usually positive – externalities, vaccination models have become particularly interesting to take dynamic behavior into account. Indeed, vaccination usually results in positive externalities, often referred to as 'herd immunity': successfully vaccinated individuals do not (or hardly) transmit the pathogen to others. As such the marginal utility of vaccination decreases (non-linearly) as coverage increases, and endemic transmission can often be halted without vaccinating the whole population, a phenomenon which is crucial for vulnerable individuals who cannot receive vaccination due to age or medical reasons (e.g. too young or immunocompromised). Where positive externalities exist, game theory applies. Hence, models have been developed in which rational-behaving individuals are assumed to free-ride on 'herd immunity', and therefore increasingly refuse vaccination when they perceive more members of the population to be immunized. However, the majority of behavioral change models in the published literature remains purely theoretical, lacking parameterization with empirical data and a validation process [127, 411]. Consequently, data for parameterization of behavioral change models are highly desirable to construct improved models mimicking realistic vaccination behavior. This is generally recognized as one of the challenges for behavioural change models [128].

Discrete choice experiments (DCEs) have proven successful to elicit preferences and quantify the decision-making process with respect to vaccine characteristics in multiple studies [36, 84, 91, 138, 154, 338, 413, 414]. Moreover, they are well established as an instrument in health economic research in general [85]. A DCE is a quantitative surveying technique in which respondents make a choice between two or more hypothetical profiles in consecutive choice sets. Profiles are represented by attributes with (partially) differing attribute levels [199]. In previous DCEs, vaccines were described using attributes such as vaccine effectiveness [36, 84, 91, 154, 303, 413, 414], vaccine-related side-effects (VRSE) [84, 91, 154, 303, 338, 413, 414] or in terms of vaccine price (whether or not including costs of vaccine administration) [91, 138, 154, 338, 413, 414]. A recent study found that DCEs correctly predicted influenza vaccination choices on an aggregate level when taking scale and preference heterogeneities into account [86].

In this paper, we report on the findings of a DCE quantifying individual preferences for vaccination attributes in Belgium, the United Kingdom (UK) and France. We present these new results together with those of two separately reported DCEs using an identical design, conducted in South Africa and The Netherlands [172, 414]. We aim to: 1) generate and communicate behavioral data with respect to vaccines in order to move from theory to data-driven behavioral change models in infectious disease epidemiology, 2) assess to what extent individual vaccination decisions are driven by social norms or peer pressure as opposed to free-riding motives, 3) identify the vaccine characteristics society values most, and 4) accommodate policy-makers and health care professionals to select focal points in their communication to hesitant individuals.

5.2 Methods

We conducted a survey in France, the UK (both early December 2018) and Belgium (May 2019). We selected these countries for a number of reasons. First of all, no DCE had yet been performed for a general, unnamed vaccine, distinguishing between adults and children in any of these countries. Also, we were interested in between-country differences comparing different backgrounds, cultures and more specifically, a different history with respect to vaccination. France was included in this study because it has been experiencing a lot of vaccine resistance: one in three French inhabitants now believes vaccines are unsafe, which is the highest fraction in the world [131]. More specifically, there is a lot of vaccine resistance in France originating from safety concerns regarding the pandemic A/H1N1 flu vaccine with spillovers to other vaccines (e.g. MMR vaccine) [131, 308]. As a result, the French government expanded the number of compulsory vaccines from 3 to 11 in 2018 [131]. The UK was included because it has a history of vaccine scares with documented impact on vaccine coverage for the whole cell pertussis vaccine in the 1970s and 1980s [11] and MMR vaccine in the 2000s [140]. We also included Belgium, a country with a more neutral vaccination history, achieving generally high and stable vaccine coverage in young children [409]. However, regional disparities have been observed to widen [391], and one in five Belgian citizens believe vaccines are unsafe [131]. In order to facilitate broader between-country comparisons, we report our results alongside those of two more studies using an identical design in South Africa and The Netherlands, conducted in December 2017 and June-July 2018, respectively, and published in detail elsewhere [172, 414].

The majority of the survey questions and the entire DCE design were kept the same as in South Africa and The Netherlands. We adapted the survey questions to reflect country-specific characteristics based on inputs from local experts, for example with respect to the educational system and the organization of the national immunization schedule. As such, we ended up with four versions of the survey for the UK, France, French speaking Belgium, and Dutch speaking Belgium. No physical samples were collected as part of this study and the study protocol was approved by the ethical committee of the Antwerp University Hospital (reference number: 15/2/12). We tested each survey version in a soft launch in which we asked about 10% of the target sample to fill out the survey and evaluate the comprehensibility of the questions. Afterwards, we launched the survey in the sample population. The survey consisted of five sections: 1) background questions probing for age, gender, marital status, occupation, smoking behavior, etc., 2) 21 attitudinal questions on vaccines where responses were recorded on a five-point Likert scale, ranging from completely agree to

completely disagree, 3) a DCE with 10 choice sets based on Verelst et al. [413], including an introduction text with instructions and a sample choice set to familiarize the respondents with the DCE, 4) four questions probing for relative risk perceptions based on a survey by Bults et al. [50], and 5) a health literacy test with three questions from Chew et al. [69]. Based on their background characteristics, we allocated respondents to two distinct surveys: a 'oneself' group (without allocation restrictions) and a 'youngest child' group (only for respondents having at least one child below the age of 18 years), the former filling out the survey with respect to vaccination decisions for themselves, the latter doing so for their youngest child. Preferences elicited in the youngest child group reflect parents' preferences with respect to vaccinations for their youngest child. We opted for a sample size of about 1500 respondents per country, based on previous DCEs with the same design [172, 413, 414]. We gradually built each sample to better match the sample demographics to the population demographics, and thus to obtain a more representative sample. We recruited respondents from an online consumer panel applying an efficient participant allocation algorithm. In total, 9339 respondents started the survey, 4802 of them completed the survey, 1213 chose not to complete it, 59 did not meet the inclusion criteria (e.g., <18 years old), 119 were identified as 'speeders' (who filled out the survey much faster than a reference time) and/or 'straight-liners' (who filled out the same for each question), and 3146 were halted after the first part of the survey with background questions when predefined sample quota were reached. We incentivized participation through credit rewards, transferable into coupons and gift vouchers. Only one member per household could participate in the study. Country and group level sample characteristics are displayed in Table 5.2.

The DCE was characterized by a Bayesian D-efficient design [199] of 50 choice sets with 2 profiles described by 6 attributes with 3 varying and 3 constant levels and optimized for the precise estimation of all main effects as well as all two-way interactions between any of the six attributes and 'vaccine effectiveness', 'VRSE' and 'accessibility'. We divided the design into five surveys of 10 choice sets that we distributed evenly between all participants. We selected the attributes and attribute levels through a literature study, a focus group study and a pilot study in Flanders, the details of which are published in Verelst et al. [413]. We revised the description of VRSE by specifying the severity of side-effects, keeping severe side-effects to be 'highly unlikely' in the two profiles, and only varying the frequency of mild VRSE. This contrasts with the original design in Verelst et al. [413], where we left the severity of side-effects unspecified, but is the same as in Verelst et al. [414] and Hoogink et al. [172]. We opted for this strategy since it prevents the participant from

imagining levels regarding VRSE severity and it mimics real-life VRSE, because vaccines with common severe side-effects should not be licensed. We included population and local coverage as attributes to assess the magnitude of free-riding behavior in the populations under study. Negative utility values for higher coverage levels confirm free-riding behavior, as opposed to positive utility values, in which case peer influence and social norms dominate. All attributes and attribute levels are shown in Table 5.1.

Table 5.1: DCE attributes and levels.

Attribute	Level description
1. Vaccine effectiveness	a) Protects **50%** of vaccinated persons b) Protects **90%** of vaccinated persons
2. Burden of disease	a) The disease, against which the vaccine protects is **rare** and often **mild**: hospitalisation is exceptional and the disease is not life-threatening b) The disease, against which the vaccine protects is **rare** and often **severe**: often with hospitalisation and the disease is life-threatening c) The disease, against which the vaccine protects is **common** and often **mild**: hospitalisation is exceptional and the disease is not life-threatening d) The disease, against which the vaccine protects is **common** and often **severe**: often with hospitalisation and the disease is life-threatening
3. VRSE	a) Mild side-effects **commonly** occur and severe side-effects are highly unlikely b) Mild side-effects **rarely** occur and severe side-effects are highly unlikely
4. Accessibility	a) The vaccine is provided for **free** and **is directly available at the vaccinator** (GP, well-baby clinic, school- or occupational physician) b) The vaccine is **not reimbursed** and is **only available with a prescription**
5. Local coverage	a) **30%** of your acquaintances (friends and family) is vaccinated b) **60%** of your acquaintances (friends and family) is vaccinated c) **90%** of your acquaintances (friends and family) is vaccinated
6. Population coverage	a) **30%** of the population in general is vaccinated b) **60%** of the population in general is vaccinated c) **90%** of the population in general is vaccinated

We analysed the DCE using the JMP Pro 14 Choice Platform [179] and applied a Panel Mixed Logit (PML) modeling approach with 10,000 Bayesian iterations, with the last 5,000 used for estimation. We distinguished between models estimating the attribute effects – allowing for model comparison between study populations – and models including interaction effects between the attributes and respondent covariates – allowing for identifiable preference heterogeneity within study populations. In the latter, we systematically estimated covariate interactions one-by-one, keeping record of all the statistically significant model

terms including the main effects. Afterwards, we estimated a joint model combining all main effects and individually significant interactions. We dropped insignificant interactions in an iterative process until we reached a model with the most important covariates. We ranked the significant model terms by importance using the normalized LogWorth statistic, i.e. -$\log_{10}$(p-value of the LR-test), where the LR-test is short for the likelihood ratio test for significance of a given model term. We used R [320] for cleaning the raw survey data and creating the bar charts.

5.3 Results

We managed to retrieve a quasi-representative sample of about 1600 survey respondents in each country, as shown in Table 5.2. Women are slightly over-represented in the samples from the UK and France. We found a representative population with respect to age to be incompatible with having at least 750 respondents with children below the age of 18. Moreover, concerning educational attainment, the samples are also somewhat biased towards the higher educated, especially so in France. This is likely because older French respondents, who tend to be lower educated, are underrepresented in our sample. Note however, that the youngest age groups are by definition lower educated since the census data also include school-age teenagers (15-18 years). We investigated the impact of mismatching sample characteristics by estimating covariate interactions between the attributes and gender, educational attainment and region, and found none of them to significantly influence our findings. Significant covariate interactions with respondents' age group are included and reported in Appendix B.1.

Vaccine attitudes tended to be positive in general as represented in Figures 5.1 and 5.2 for a selection of general vaccine statements. We observed French respondents in the 'adult' group to be relatively neutral towards the statements "The people who are important to me think that I must get vaccinated" and "I have confidence in the information about vaccinations that I receive from the Government". These sentiments appeared to be more negative in the 'adult' group than for the 'child group'. In contrast, the respondents from the UK were in general more agreeing on this selection of statements. The median UK respondent strongly agreed with the statements "I think that getting vaccinated against infectious diseases is wise" and "I think that getting vaccinated against infectious diseases is important" in the 'adult' group, whereas in the 'child' group the median UK respondent strongly agreed with the statements "The diseases that are vaccinated against can be very serious" and "I think that vaccinating my child according to the National Vaccination Program is important". Other 'child' group samples, on average, agree on all statements, though there is a lot of variability within the samples. Attitudes from Belgian and Dutch respondents were usually found in between the UK and the French sample means. Details on all 21 attitudinal questions are presented in Appendix B.2.

All six attributes were found to be statistically significant in all five countries. The normalized LogWorth values represent the relative importance of the attributes in each country and subgroup, and are visualized in Figure 5.3. Two attributes stand out: vaccine effectiveness and accessibility. Vaccine effective-

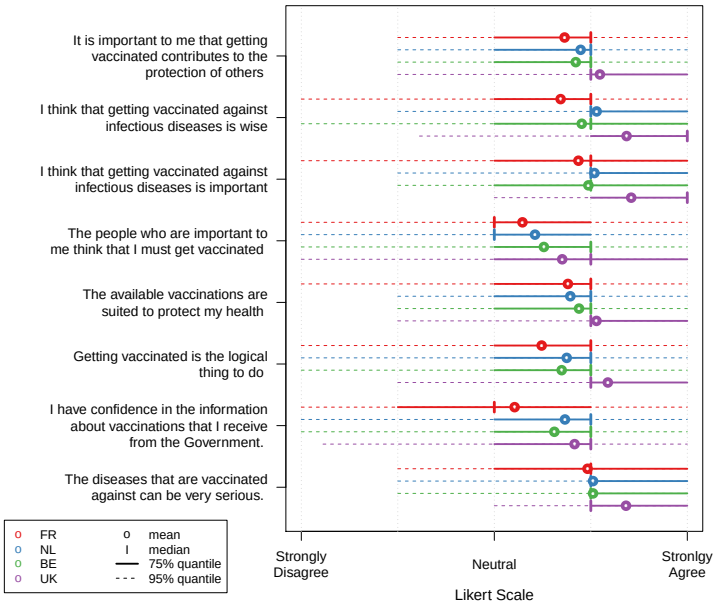


Figure 5.1: Likert scale responses for a selection of vaccination attitude statements in the 'adult' group in France, The Netherlands, Belgium and the United Kingdom.

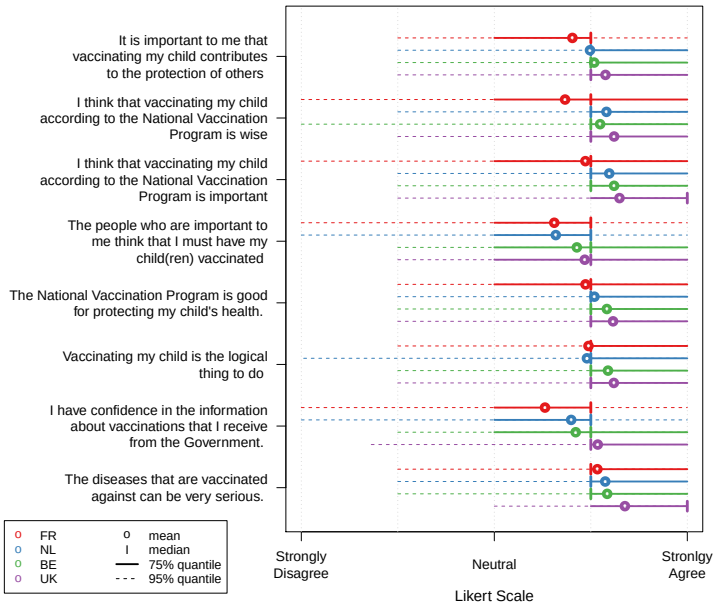


Figure 5.2: Likert scale responses for a selection of vaccination attitude statements in the 'child' group in France, The Netherlands, Belgium and the United Kingdom.

Table 5.2: Sample characteristics and national statistics for Belgium, France & The UK (*age groups from the survey are compared to age groups [15-29], [30-49], [50-64] and [65-84] as reported in the 2011 census database [383].)

Characteristic	Belgium		United Kingdom		France	
	Sample (%)	**Population (%)**	**Sample (%)**	**Population (%)**	**Sample (%)**	**Population (%)**
Gender						
Male	50.2	49.1	45.8	49.1	40.7	48.4
Female	49.8	50.9	54.2	50.9	59.3	51.6
Age group (*)						
18-34	26.6	22.9	24.8	24.9	27.1	23.5
35-49	26.4	34.7	36.4	34.7	39.6	34.2
50-65	25.4	24.0	26.9	22.7	24.6	24.2
66-85	21.6	18.4	12.0	17.7	8.8	18.1
Educational attainment						
Primary education (ISCED 1) or lower	8.3	14.6	<1	<1	1.1	17.5
Secondary education (ISCED 2+3)	55.6	49.6	58.4	70.0	72.2	58.3
Post-secondary or (post-)university education (ISCED 4 or higher)	33.7	26.3	39.3	30.0	25.8	24.2
Other	2.4	9.5	1.8	<1	<1	<1
NUTS 1 region						
Belgium						
Flanders	57.4	57.5				
Walloon Region	30.2	32.2				
Brussels Capital Region	12.3	10.3				
UK						
North East			5.4	4.1		
North West			10.0	11.2		
Yorkshire and the Humber			8.6	8.4		
East Midlands			6.6	7.2		
West Midlands			9.7	8.9		
East of England			8.9	9.3		
London			11.2	12.9		
South East			12.6	13.7		
South West			8.3	8.4		
Wales			6.3	4.8		
Scotland			8.6	8.4		
Northern Ireland			3.9	2.9		
France						
Région parisienne					16.3	18.3
Bassin parisien					22.1	16.6
Nord					5.6	6.2
Est					10.8	8.3
Ouest					12.9	13.2
Sud-Ouest					11.3	10.6
Centre-Est					10.0	11.8
Méditerranée					10.8	12.2
Départements d'Outre Mer					0.2	2.9
Sample size	**N=1602**		**N=1600**		**N=1600**	
'Oneself'	N=1001		N=850		N=850	
'Youngest child'	N=601		N=750		N=750	

ness is the key characteristic for all survey respondents in the UK and South Africa, but also for the 'child' group in The Netherlands. For the Belgian population as well as the French 'oneself' group, accessibility was found to be most important. The French 'child' group attached most importance to burden of disease, whereas this was considered much less important by the same subpopulation in the UK. We found local coverage and mild VRSE to be also statistically significant but of limited importance in most study samples, with a relative importance of 30% or less. Population coverage was found to have more influence, especially so in the case of 'child' models, with the Netherlands being an exception. Note that among all five countries mild VRSE had the highest impact in vaccine decision-making in France and Belgium.

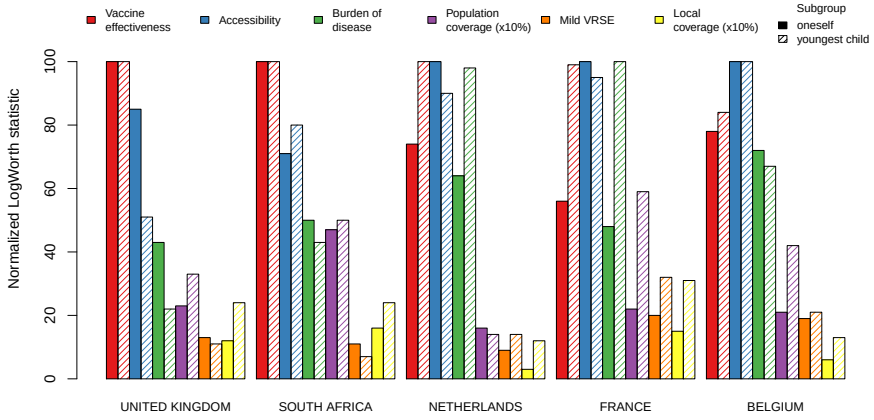


Figure 5.3: Importance of all statistically significant (p-value $<$0.05) main effects relative to the most important attribute. All five countries. Estimates for the Netherlands and South Africa are derived from Hoogink et al. [172] and Verelst et al. [414].

For both population and local coverage, estimates were found to be positive for all subsamples in all study countries (see Tables 5.3 to 5.5). Hence, respondents were more inclined to choose a vaccine if it already had a high coverage in their network of contacts and in the population at large. For example, for the 'child' group in France, a 10% increase in the population's vaccination coverage increases vaccine utility by 0.108 on average (see Table 5.5).

Vaccine effectiveness stands out as the most important attribute in the UK, South Africa and in the 'child' group in the Netherlands. In Belgium and France, we found vaccine effectiveness to be a crucial element as well, at a relative importance of about 80% and 60% respectively. In all countries, vaccine effectiveness was ranked more important, or equally important, in the 'child' group compared to the 'oneself' group.

In contrast, vaccine accessibility was valued higher, or equally, in the 'oneself' group compared to the 'child' group in all countries, except for South Africa. In addition, accessibility was the most important attribute in Belgium, and in the 'oneself' group in France and the Netherlands.

The 'child' group in France cared most about the burden of the disease. This attribute was also of considerable importance in the same group in the Netherlands. There are notable differences in valuation of this attribute between all subgroups involved. Indeed, in the UK sample, the burden of disease was valued at a relative importance of about 40% in the 'oneself' group and about 20% in the 'child' group. Whereas in the Netherlands, France and Belgium, this attribute was valued at a relative importance of about 50% or more.

We observed a clear distinction between the 'oneself' group and the 'child' group with respect to population coverage. Indeed, both these indicators of vaccination coverage were considered relatively more important for children than for adults in all countries except the Netherlands. This implies that when parents decide about vaccinating their child, they are more prone to peer influence, than when adults (including parents) make these decisions for themselves. Overall, both population and local coverage were considered most important in France and South Africa and least important in the Netherlands and the UK.

Mild VRSE and local coverage were, although statistically significant for all subgroups, found to be of the relative lowest importance in most countries and subgroups.

Attribute-level utility estimates are listed in Tables 5.3 to 5.5. As could be expected, respondents in all study populations preferred the most a vaccine with 90% effectiveness, that is free & accessible, protects against a common & severe disease, rarely exhibits mild VRSE and for which vaccination coverage is high. In addition, we consistently found disease severity to dominate frequency of disease in all study samples.

The models including the attributes' main effects as well as the most important covariate interactions are provided in Appendix B.1. Vaccine-related attitude statements were able to explain most preference heterogeneity. For example for Belgium, in the 'oneself' model we discovered respondents agreeing (disagreeing) with the statement "The available vaccinations are suited to protect my health" attached more (less) value to a vaccine with an efficacy of 90% (50%), compared to the average (see Figure B.1 below). Moreover, we also found that in the 'oneself' model for the UK, respondents indicating that they were at

low risk of contracting measles, cared more about the vaccine being free & accessible (see Figure B.3 above). The same is true for individuals agreeing with "vaccinating my child is the logical thing to do" in the 'child' model for the UK (see Figure B.4 above). For details on additional covariate interactions, we refer to Appendix B.1.

5.4 Discussion

The need for behavioral data in relation to infectious disease epidemiology and prevention has been raised repeatedly over the past decade [127, 128, 411]. Our multi-country series of DCEs generated highly valuable data for parameterization and validation of epidemiological models. This is because data-driven hosts' behavior derived from DCEs can be added to models mimicking the spread of infectious diseases. For example, dynamic behavior can be modelled through a utility function using prevalence utility estimates from the burden of disease attribute. As such, the utility of a vaccine increases when a disease becomes more prevalent. Similar dynamics can be modelled using the utility estimates of population or local coverage. Moreover, exogenous shocks, such as changing risk perceptions, can be introduced in such integrated models. Utility estimates on vaccine effectiveness, accessibility, disease severity and mild VRSE can facilitate data-driven introductions of exogenous shocks. Furthermore, the multi-country character of our study allows modelling vaccination behavior in five countries. However, an integrated model combining data-driven vaccination behavior with infectious disease transmission dynamics, requires the specification of a dichotomous vaccine outcome (to be vaccinated or not) based on individual utilities derived from vaccine attributes. That is, a function that derives vaccine uptake from utility associated with vaccination. Future research will explore the specification of such vaccine uptake functions.

The positive estimates for both coverage attributes in all (sub)samples imply social norms or peer influence are more important than free-rider incentives. These findings confirm the positive coverage estimates reported in vaccination DCEs in Australia [154] and in the US [138]. Overall, it seems unlikely that respondents take externalities – such as herd immunity – into account when making vaccine decisions. As such, game theoretical models characterizing vaccine decisions as a strategic interaction between rational individuals, seem inappropriate to capture real-life vaccination dynamics. If individuals do include herd immunity effects in their decisions, it might very well be the case that they behave altruistically and opt for vaccination, contributing to the protection of vulnerable individuals. This was observed in several empirical studies, such as the study by Skea et al. [364] reporting on 'avoiding harm to others' incentives in the context of MMR vaccination in the UK. They found parents on a chat forum to be critical towards parents not vaccinating their healthy children, thereby putting vulnerable ones at risk. Altruistic motives were also described in the papers by Hakim et al. [153] and Shim et al. [362] in the context of influenza vaccination, and by Vietri et al. [421] about assessing the extent of altruism with respect to HPV and influenza vaccination. Policy-

makers and healthcare workers can influence vaccine hesitant individuals by communicating high coverage levels, i.e. describing that "accepting the vaccine is the mainstream thing to do", in addition to other strategies (see Leask et al. [220] for a framework on "communicating with parents about vaccination").

Vaccine accessibility has proven highly significant in our study, as well as in other studies [36, 91, 138, 154, 414], where it was, however, mostly described in terms of out-of-pocket or total costs. For example, Wong et al. [452] performed a DCE on mothers' preferences for HPV vaccination in Hong Kong and found a significant impact of out-of-pocket cost on the decision to receive the vaccine. Poulos et al. [314] reported similar results with respect to traveler vaccines. This has also been confirmed by observational studies. For instance, in a retrospective cohort study, Lefevere et al. [222] found both personal information letters and removing out-of-pocket costs had a significant positive effect on HPV vaccination initiation in Belgium.

Given the importance of vaccine accessibility, policy-makers can increase vaccine coverage by making vaccines easily available at an affordable price. There is still significant room for improvement concerning adults (cfr. the 'oneself group') who are often confronted with an expensive, complicated and time consuming process of vaccination. Take for instance influenza vaccination in Belgium, where individuals typically visit a GP for a prescription, then buy the vaccine (often without reimbursement) at a pharmacy and lastly have to go back to the GP to be vaccinated. Not surprisingly, influenza vaccine coverage has usually been below 25% [386]. Adults cannot rely on the routine vaccination services available for children (e.g. well-baby clinics, child health clinics or school health centres). In this respect, (expansion of) workplace vaccination can play a vital role in facilitating vaccination for working-age adults. Policy-makers should consider incentivizing employers to offer certain vaccines to their employees at the workplace, e.g. influenza, and tetanus, diphtheria and pertussis (Tdap) vaccination, or hepatitis A for employees working in the food industry. Workplace vaccination may also prove useful in catch-up campaigns which would, for example, be required to maintain measles elimination targets [129, 210, 393]. Note that for the 'child' group, accessibility was found to be very important as well. Policy-makers should remain focused on making vaccines as accessible as possible for both groups.

In line with previous studies [91, 414, 452], vaccine effectiveness was observed to be of great importance in all models. Therefore its is essential that the public should remain fully aware of the positive impact vaccines are having on population health. According to a 2018 Gallup poll, the effectiveness of

vaccines is perceived to be significantly more reliable than their safety. Of the five countries included in our study, France scored worst with about 20% of the population disagreeing that vaccines are effective, followed by The Netherlands and South Africa both at 11% [131].

In a previous study in Flanders [413], we applied the same DCE design but did not specify the severity of VRSE. The updated description in this study, varying only mild VRSE and describing severe VRSE as being 'highly unlikely', shifted the attribute's importance from the highest rank in the earlier study, to one of the lowest ranks in the current. Safety concerns with respect to vaccinations remain crucial in vaccine misperceptions. VRSE may indeed occur, but are mostly mild and clear up quickly [446]. In this study it became clear that when respondents used realistic information on vaccine side-effects they cared less about them while making vaccination decisions. Acknowledging the existence of VRSE and providing risk and benefit information is recommended when discussing safety concerns with potential vaccine recipients (or their parents) [220]. The relative importance of burden of disease is more volatile and appears to be country-specific. In the 'child' model for the UK, we found it to be relatively unimportant, whereas for the same subpopulation in France, burden of disease was most important. The severity of the infectious disease was found to be more important than the frequency of the disease. This is in line with Sadique et al. [338], who showed severity of both vaccine-preventable disease and VRSE to be more important than their frequency. To address concerns about the burden of disease and VRSE, healthcare workers as key informants, should be well-versed in the general topic of vaccination and should use standard guidelines for each vaccine and disease so that potential vaccine recipients are consistently and well-informed. See also Leask et al. [220], who provide a vaccine communication framework.

5.5 Conclusion

In conclusion, we found slightly variable preferences for vaccine attributes between countries. Nonetheless, there are communalities in that people's vaccine decisions seem to depend in the first place on how they perceive the effectiveness and risks of severe VRSE, as well as the burden of vaccine preventable disease. Their decisions are also influenced significantly by how easy it is to be vaccinated, in terms of effort and costs, by the possibility of mild VRSE and by how many other people are being vaccinated. Especially vaccination of the population in general is an important element when having a child vaccinated. Therefore communication strategies on vaccination should not forget to include information on vaccination rates, reflecting that vaccination is still the norm, and non-vaccination remains exceptional. Contrary to what most game theoretical models assume, this information would be an incentive to receive vaccination, rather than to forego it intending to take a free ride.

5.6 Acknowledgments

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Table 5.3: Panel mixed logit model estimates (means and standard deviations) and significances of the attribute effects obtained from likelihood ratio (LR) tests. Belgium

Term	Mean estimate (std dev; subject std dev)	LR Chi-square	DF	P-value
'Oneself' model				
Accessibility				
Co-payment & prescription	-0.403 (0.020; 0.334)	326.606	1	< 0.0001
Free & accessible	0.403 (0.020; 0.316)			
Vaccine effectiveness				
50%	-0.465 (0.024; 0.244)	252.171	1	< 0.0001
90%	0.465 (0.025; 0.210)			
Burden of disease				
Rare & mild	-0.436 (0.045; 0.615)	243.682	3	< 0.0001
Common & mild	-0.481 (0.047; 0.361)			
Rare & severe	0.324 (0.037; 0.128)			
Common & severe	0.593 (0.043; 0.174)			
Population coverage (x10%)	0.081 (0.008; 0.099)	65.749	1	< 0.0001
Mild VRSE				
Common	-0.184 (0.019; 0.098)	57.931	1	< 0.0001
Rare	0.184 (0.020; 0.091)			
Local coverage (x10%)	0.043 (0.008; 0.079)	17.977	1	< 0.0001
'Youngest child' model				
Accessibility				
Co-payment & prescription	-0.472 (0.031; 0.346)	228.127	1	< 0.0001
Free & accessible	0.472 (0.029; 0.337)			
Vaccine effectiveness				
50%	-0.571 (0.037; 0.245)	191.508	1	< 0.0001
90%	0.571 (0.039; 0.226)			
Burden of disease				
Rare & mild	-0.370 (0.058; 0.463)	161.860	3	< 0.0001
Common & mild	-0.613 (0.062; 0.418)			
Rare & severe	0.307 (0.056; 0.284)			
Common & severe	0.676 (0.061; 0.348)			
Population coverage (x10%)	0.128 (0.012; 0.126)	93.449	1	< 0.0001
Mild VRSE				
Common	-0.234 (0.028; 0.137)	45.280	1	< 0.0001
Rare	0.234 (0.031; 0.129)			
Local coverage (x10%)	0.071 (0.013; 0.123)	27.429	1	< 0.0001

Note: Mean estimates corresponding to the last level of an attribute are calculated as minus the sum of the estimates for the other levels of the attribute.

Table 5.4: Panel mixed logit model estimates (means and standard deviations) and significances of the attribute effects obtained from likelihood ratio (LR) tests. United Kingdom

Term	Mean estimate (std dev; subject std dev)	LR Chi-square	DF	P-value
'Oneself' model				
Vaccine effectiveness				
50%	-0.683 (0.035; 0.275)	425.353	1	< 0.0001
90%	0.683 (0.031; 0.277)			
Accessibility				
Co-payment & prescription	-0.486 (0.023; 0.316)	360.260	1	< 0.0001
Free & accessible	0.486 (0.027; 0.292)			
Burden of disease				
Rare & mild	-0.517 (0.049; 0.277)	189.172	3	< 0.0001
Common & mild	-0.351 (0.051; 0.430)			
Rare & severe	0.307 (0.045; 0.206)			
Common & severe	0.561 (0.051; 0.239)			
Population coverage (x10%)	0.096 (0.010; 0.118)	94.330	1	< 0.0001
Mild VRSE				
Common	-0.180 (0.024; 0.124)	50.290	1	< 0.0001
Rare	0.180 (0.025; 0.123)			
Local coverage (x10%)	0.080 (0.010; 0.078)	47.291	1	< 0.0001
'Youngest child' model				
Vaccine effectiveness				
50%	-0.591 (0.033; 0.243)	297.130	1	< 0.0001
90%	0.591 (0.033; 0.246)			
Accessibility				
Co-payment & prescription	-0.309 (0.024; 0.233)	149.559	1	< 0.0001
Free & accessible	0.309 (0.024; 0.218)			
Population coverage (x10%)	0.107 (0.009; 0.101)	94.979	1	< 0.0001
Local coverage (x10%)	0.097 (0.010; 0.094)	67.461	1	< 0.0001
Burden of disease				
Rare & mild	-0.198 (0.055; 0.266)	70.146	3	< 0.0001
Common & mild	-0.344 (0.042; 0.305)			
Rare & severe	0.187 (0.045; 0.178)			
Common & severe	0.355 (0.053; 0.216)			
Mild VRSE				
Common	-0.143 (0.026; 0.087)	30.732	1	< 0.0001
Rare	0.143 (0.026; 0.085)			

Note: Mean estimates corresponding to the last level of an attribute are calculated as minus the sum of the estimates for the other levels of the attribute.

Table 5.5: Panel mixed logit model estimates (means and standard deviations) and significances of the attribute effects obtained from likelihood ratio (LR) tests. France

Term	Mean estimate (std dev; subject std dev)	LR Chi-square	DF	P-value
'Oneself' model				
Accessibility				
Co-payment & prescription	-0.389 (0.026; 0.410)	238.254	1	< 0.0001
Free & accessible	0.389 (0.025; 0.383)			
Vaccine effectiveness				
50%	-0.375 (0.030; 0.222)	131.380	1	< 0.0001
90%	0.375 (0.032; 0.218)			
Burden of disease				
Rare & mild	-0.364 (0.052; 0.318)	122.873	3	< 0.0001
Common & mild	-0.358 (0.042; 0.416)			
Rare & severe	0.273 (0.048; 0.224)			
Common & severe	0.449 (0.053; 0.187)			
Population coverage (x10%)	0.079 (0.010; 0.131)	48.157	1	< 0.0001
Mild VRSE				
Common	-0.164 (0.027; 0.092)	44.450	1	< 0.0001
Rare	0.164 (0.025; 0.093)			
Local coverage (x10%)	0.064 (0.010; 0.093)	33.480	1	< 0.0001
'Youngest child' model				
Burden of disease				
Rare & mild	-0.369 (0.048; 0.300)	163.809	3	< 0.0001
Common & mild	-0.474 (0.051; 0.323)			
Rare & severe	0.331 (0.049; 0.202)			
Common & severe	0.512 (0.048; 0.190)			
Vaccine effectiveness				
50%	-0.430 (0.029; 0.231)	152.182	1	< 0.0001
90%	0.430 (0.034; 0.237)			
Accessibility				
Co-payment & prescription	-0.314 (0.023; 0.278)	144.967	1	< 0.0001
Free & accessible	0.314 (0.025; 0.260)			
Population coverage (x10%)	0.108 (0.010; 0.135)	88.489	1	< 0.0001
Mild VRSE				
Common	-0.180 (0.026; 0.098)	46.913	1	< 0.0001
Rare	0.180 (0.022; 0.095)			
Local coverage (x10%)	0.078 (0.010; 0.086)	44.981	1	< 0.0001

Note: Mean estimates corresponding to the last level of an attribute are calculated as minus the sum of the estimates for the other levels of the attribute.

CHAPTER 6

Integrating data from Discrete Choice Experiments

This chapter is based on unpublished research.

Summary

Introduction. Behavioral change models (BCM) are increasingly incorporated in models for the transmission of infectious diseases. However, most of these models remain theoretical and lack representative data for parameterization and validation. Measles vaccination is topical to include in such models as it was confronted with a vaccine scare and the high transmissibility requires a vaccination coverage of 95% or higher to halt transmission in the population.

Methods. We presented a proof of concept study on how data from discrete-choice experiments can be integrated to parameterize BCMs. More specifically, we simulated the dynamic uptake of measles vaccine, in parallel to a dynamic transmission model for the spread of measles in Flanders, Belgium. We fitted vaccine utility data to a vaccine coverage function that determines the uptake of measles vaccine in children at one year of age. Measles disease dynamics are modelled using a deterministic ordinary differential equation SIRV model including births and deaths. We investigate the impact of 7 different behavioral scenarios on vaccine utility, vaccine coverage and disease dynamics.

Results. The addition of a default BCM has no significant impact on disease transmission and increases vaccine coverage slightly. Introducing shocks, such as a permanent vaccine scare or suspending the vaccine from the immunization schedule, causes recurring measles outbreaks in the Flemish population. On the other hand, a temporary vaccine scare of 5 years and a lower risk perception of measles severity did not alter disease transmission compared to the default simulation. A permanent vaccine scare followed by a suspension from the schedule triggers volatility in vaccine coverage ranging between 25% and 85%, with large outbreaks reoccurring every few years.

Discussion. Even though the DCE estimates are helpful in the BCM parameterization, quite some theoretical assumptions still needed to be made. Additional and recent behavioral surveillance data is needed to determine the population's perception on each vaccine attribute. When such data becomes available, future work should include probabilistic sensitivity analyses.

6.1 Introduction

In 2018, 140,000 people died from Measles, with the majority of the fatalities in low- and middle-income countries [444]. Measles is a highly virulent and severe disease with a basic reproduction number of around 15-17 [12]. A vaccine has been in use since the 1960's. The vaccine is safe, effective and inexpensive [444]. A vaccine coverage of 95% in the population at large is required to halt the spread of the virus [171]. In addition, it is important that unvaccinated individuals do not concentrate in so called susceptible clusters [209], since they pose a risk for local outbreaks. Such outbreaks were observed in an anthroposophic school in 2011 and in a prison in 2017 – both in Ghent (Belgium) [40, 156]. Even though measles vaccine coverage was found to be high and stable in Flanders, at 96.2% for MMR1 in 2016 [409], small outbreaks have occurred in the past years [40, 156, 337]. However, it is uncertain to which extent people still understand the clinical features of measles, compared to the times when the virus was circulating (in a pre-vaccination era).

Measles vaccines are live-attenuated and cannot be administered to certain individuals as a result of their health status (e.g. immunodeficient, pregnant women etc.) or age (e.g. too young). As such, a high vaccination coverage, inducing a strong herd immunity in the population, is of vital importance to protect those who cannot be vaccinated. Unfortunately, even in Europe a large pool of people remain susceptible to measles due to low historical and current vaccination coverage [119].

As such, measles eradication remains challenging and requires more than the availability of a safe and effective vaccine [171]. Indeed, outbreaks in Europe in recent years still occurred due to immunity gaps [119]. Future outbreaks and potential measles elimination or eradication therefore depend on whether a sufficiently high vaccine coverage for the two doses of measles vaccine can be reached [119]. Hence, the responsibility for measles control and elimination lies to a large extent with the decisions parents make with respect to vaccination for their children.

Prevention behavior – including, but not limited to vaccination decisions – has increasingly been included in models for the transmission of infectious diseases [411]. Measles vaccination has been included in such models, e.g. by applying game-theory to measles vaccine decisions (e.g. [23, 31, 363]) or by modelling the spread of information circulating among parents that need to decide about measles vaccination for their children [99]. Many of these models lack data-driven parameters and remain mostly theoretical – a concern that has been echoed in the BCM literature in the last decade [127, 128, 411]

In this chapter, we illustrate how discrete choice experiments can be used in the parameterization of behavioral change models. We develop a BCM in parallel to a compartmental deterministic model for the transmission of measles in Flanders, Belgium. We elaborate on the coupled dynamics of MMR vaccine uptake and the spread of measles in the Flemish population. Even though the DCE data are useful to parameterize BCMs, some theoretical assumptions remain. Please note that this chapter is included in this thesis with as a main objective to illustrate the use of DCE data in behavioral change models. As such, we do not aim to accurately predict measles outbreaks and vaccine uptake in the Flemish population. A more complex transmission model with stochastic features, age-classes and adaptive behavior is needed to more accurately predict measles transmission. Moreover, additional detailed data on risk perception is required to parameterize measles vaccine uptake and to determine initial utility levels.

6.2 Materials and methods

Modelling the spread of measles

We use a compartmental, deterministic model in order to simulate the spread of measles in the population of Flanders. The schematic description of the model is given in Figure 6.1. Newborns enter the population at a rate μ into the susceptible compartment (S_1). For all individuals that are x weeks of age, a proportion η gets vaccinated and moves to the V compartment. The remaining proportion (1-η) decides against measles vaccination and moves to the S_2 compartment in which they remain susceptible to the virus. In this application, we set x to 52 weeks (or one year), which is the recommended age for children to receive the MMR vaccine [27]. The proportion that decides to get vaccinated (η) is guided by the behavioral change model, on which we elaborate in further paragraphs. Infection occurs at a rate βI moving individuals from the susceptible compartments (S_1 and S_2) into the infectious compartment. People recover from measles at a rate σ. Regardless of the health condition, in all compartments, individuals die at a rate μ, which is equal to the birth rate, such that the population size remains constant over time.

The system of ordinary differential equations is given by:

$$\begin{cases} \frac{dS_1}{dt} = \mu - \beta I S_1 - \mu S_1 - \eta \frac{S_1}{x} - (1-\eta)\frac{S_1}{x} \\ \frac{dS_2}{dt} = (1-\eta)\frac{S_1}{x} - \mu S_2 - \beta I S_2 \\ \frac{dI}{dt} = \beta I S_1 + \beta I S_2 - \mu I - \sigma I \\ \frac{dR}{dt} = \sigma I - \mu R \\ \frac{dV}{dt} = \frac{\eta}{x} S_1 - \mu V \end{cases}$$

Modelling vaccination behavior

The BCM described in this chapter is an integrated model that includes a feedback mechanism between vaccine utility – which in turn determines vaccination coverage in toddlers at 52 weeks of age (η) – on the one hand, and a disease transmission model on the other hand. We assume that in the absence of a BCM, there is no feedback mechanism, so that vaccine utility, and hence coverage in toddlers, remains equal at current levels (96.2%). Vaccine utility presents the value people attach to a vaccine, which is determined by preferences (collected by means of a DCE described in Verelst et al. [413] and Chapter 3) on the one hand, and (perceived) vaccine characteristics on the other hand. Some vaccine characteristics in the BCM are assumed to be constant (exogenous vaccine utility) whereas other characteristics are assumed

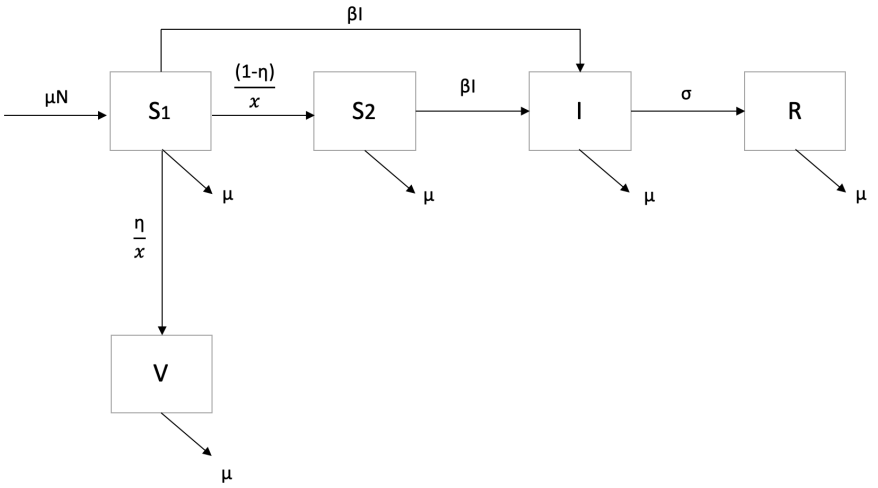


Figure 6.1: Compartmental model used to simulate the transmission of measles. Individuals are either susceptible (S_1 or S_2), successfully vaccinated (V), infected (I) or recovered (R). Newborns are introduced to the population at a rate μ. People die at the same rate μ such that the population remains constant over time.

to change in response to disease dynamics (endogenous vaccine utility). The latter characteristics are determined by the measles transmission model. We will first elaborate on the assumptions of the vaccine utility function.

In a first step we selected respondents from Flanders in the "child" group, i.e. individuals that made hypothetical decisions about vaccinating their youngest child. Afterwards, we identified survey respondents that fully disagreed with the statement "Vaccination is mostly a good way to protect individuals against a disease, when a vaccine is available against this disease". We found 16 out of 828 (1.9%) to be such respondents. It is assumed in our model that this proportion will never opt for vaccination as they indicate to be strongly against. In addition, there are toddlers that cannot be vaccinated for medical reasons (e.g. immunodeficiency), which we did not explicitly account for [27]. As such, the maximal achievable vaccine coverage in our BCM equals 98.1%. We estimated a Panel Mixed Logit (PML) model using the Hierarchical Bayes technique in the JMP 14 Pro Choice platform [179] (10,000 Bayesian iterations, with the last 5000 used for estimation) for all model main effects, using the remaining survey responses (N=812). We assumed normally distributed preference parameters

Table 6.1: Transmission model parameters

Symbol	Parameter	Value	Source
N	Population size Flanders	6,552,967	[375]
	Newborns in Flanders per year	64,336	[376]
μ	Weekly birth/mortality rate	0.0001888047	Calculated from [375, 376]
X	Age at vaccination (in weeks)	52	[27]
R_0	Basic reproduction number	16	[12]
σ	Recovery rate	$1/(8/7) = 0.875^*$	[155]
β	Effective contact rate	$(\sigma + \mu) * R_0 = 14$	Calculated from [12, 155, 375, 376]
Initial values at t=o			
$S_1^{t=0}$	Susceptible ($\leq$52 weeks of age)	0.0098	[375, 376]
$S_2^{t=0}$	Susceptible (>52 weeks of age)	0.0703	$1 - S_1^{t=0} - I^{t=0} - R^{t=0} - V^{t=0}$
$I^{t=0}$	Infected	$1.5260 * 10^{-7}$	Assumption†
$R^{t=0}$	Recovered	0.5618	Calculated from [166, 371]
$V^{t=0}$	Vaccinated	0.3581	Calculated from [166, 371]

Note: All time steps and rates are calculated per week. All disease states are expressed as a fraction of the total Flemish population. *Mean infectious period of 8 days. †Corresponds to one infected case in the Flemish population.

without correlation between the attributes. Random parameters control for unobserved heterogeneity in the respondents' preferences. The results of the PML model can be found in Table 6.2.

In a next step, we constructed the behavioral change model, based on DCE derived utilities. We distinguished between endogenous behavioral parameters

Table 6.2: Panel mixed logit model estimates (means and standard deviations) and significances of the attribute effects obtained from likelihood ratio (LR) tests.

Term	Mean estimate (std dev; subject std dev)	LR Chi-square	DF	P-value
Vaccine effectiveness				
50%	-0.659 (0.036; 0.292)	320.225	1	< 0.0001
90%	0.659			
VRSE				
Common	-0.637 (0.031; 0.261)	439.770	1	< 0.0001
Rare	0.637			
Accessibility				
Co-payment & prescription	-0.564 (0.029; 0.315)	382.846	1	< 0.0001
Free & available	0.564			
Burden of disease: frequency				
Frequent	0.221 (0.034; 0.197)	43.427	1	< 0.0001
Rare	-0.221			
Burden of disease: severity				
Severe	0.619 (0.035; 0.738)	275.839	1	< 0.0001
Not severe	-0.619			
Global coverage (x10%)	0.099 (0.010; 0.093)	71.866	1	< 0.0001

Note: Mean estimates corresponding to the last level of an attribute are calculated as minus the sum of the estimates for the other levels of the attribute.

and exogenous behavioral parameters. Endogenous parameters have a link with the transmission model, whereas exogenous parameters are parameterized independently from the transmission model and can be used to introduce exogenous shocks to the public's behavior.

Exogenous vaccine utility

1. Vaccine effectiveness. In a recent Gallup poll about attitudes to vaccines, 5% of the Belgian respondents disagreed that vaccines are effective [131]. In addition, using data from a large outbreak in Germany, measles vaccine was indeed found to be very effective [405]. As such, we set the utility level for vaccine effectiveness as follows:

$$U_{VE}^{total} = 0.95 * U_{VE}^{90\%} + 0.05 * U_{VE}^{50\%}$$
$$U_{VE}^{total} = 0.95 * 0.659 + 0.05 * (-0.659)$$
$$U_{VE}^{total} = 0.5934$$

The perception of measles vaccine effectiveness can be changed as a result of an exogenous shock leading to a change in vaccine utility within the range: $-0.659 < U_{VE}^{total} < 0.659$.

2. Vaccine related side-effects (VRSE). In the same Gallup poll, 21% of Belgians disagreed with the fact that vaccines are safe [131]. The specification of VRSE in the DCE in Flanders was limited to the frequency of the side-effects. As such, in the absence of utility values of the severity of VRSE, it is assumed that vaccine safety relates only to the frequency (or probability) of VRSE. Hence, we follow a similar process to derive the current utility value for VRSE:

$$U_{VRSE}^{total} = 0.79 * U_{VRSE}^{rare} + 0.21 * U_{VRSE}^{frequent}$$
$$U_{VRSE}^{total} = 0.79 * 0.637 + 0.21 * (-0.637)$$
$$U_{VRSE}^{total} = 0.3697$$

In case of a vaccine scare, for example, the utility value can decrease as an exogenous shock up to a minimum value of -0.637, in which all individuals would perceive VRSE to be frequent.

3. Vaccine accessibility. MMR vaccination is included in the Flemish immunization schedule and offered at no cost at the well-baby clinic (at age 52 weeks) and through a system of school doctors and nurses (currently at 11 years of age) [27]. As such, the MMR vaccine is free & available for all Flemish individuals, and is likely to stay in the basic immunization schedule for the foreseeable future, unless measles eradication could be reached. Hence, the utility value of accessibility is set as:

$U^{total}_{ACCESS} = U^{free\&available}_{ACCESS}$, such that: $U^{total}_{ACCESS} = 0.564$

If need be, an exogenous shock can be introduced when measles vaccine would require a prescription or when a co-payment is introduced.

Endogenous vaccine utility

4. Burden of disease: frequency. The DCE estimates suggest that when the prevalence of a disease increases, so does the utility of the vaccine preventing this disease. A paper by Bauch & Bhattacharyya [23], reports on such a feedback mechanism. As such, we coupled this endogenous parameter to the number of measles infections in the disease transmission model. Naturally, the perceived likelihood of contracting measles is depending on a persons' own vaccination status. We assume here that individuals have some memory about infectious disease outbreaks. In the absence of a clear relation between actual prevalence and perceived prevalence, we modelled the proportion that perceived measles as a frequent disease (i.e. increased susceptibility), as the proportion of the past 52 weeks that had more than 2 measles cases reported.

$$P^t_{common} = \frac{no\ of\ weeks\ in\ [t-52;t]\ for\ which\ I \geq 2}{52}$$

$$U^t_{PREV} = P^t_{common} U^{common}_{PREV} + (1 - P^t_{common}) U^{rare}_{PREV}$$

In the first time steps of the simulation, the value of P^t_{common} is derived by the number of weeks that were already simulated.

5. Burden of disease: severity. In our survey in May 2019, 52.74% of the respondents perceived measles as a 'severe' or 'very severe' disease [416]. Perry & Halsey found that measles case-fatality rate (CFR) in developing countries has decreased to a value below 1% [310]. However, when a high number individuals get infected – e.g. because of clusters of susceptible individuals in schools or households [40, 209] – fatal cases may occur. In the BCM – roughly approximating the findings by Perry & Halsey – this translates to a jump in the perception of measles severity up to 'severe' for every individual in the population, for weeks with 1,000 cases or more. We assume an exponential decay of this perception over 5 years up to a proportion of 52% that always perceives measles as a severe disease. This proportion was set at 52% since this is the only data we have available on measles perception in Flanders. Moreover, setting this proportion around a value of 50% results in a neutral impact of the severity attribute to the utility function. More data about measles severity perception is required to accurately parameterize our model.

$P^t_{severe} = 0.5274$

When there are 1 000 or more infected cases in one week, P^t_{severe} takes a value derived from an exponential function up to the point (t) where it reaches $P^t_{severe} = 0.5274$:

$$P^t_{severe} = e^{-\gamma t} \qquad \text{with} \qquad \gamma = \frac{-ln(0.5274)}{5*52}$$

Note that when the threshold of 1 000 cases is exceeded within 5 years of the previous exceedance, the proportion that perceives measles as severe is again set at 100% and the exponential decay is reset to $t = 1$. $U^t_{SEVERITY}$ is derived as follows:

$$U^t_{SEVERITY} = P^t_{severe} U^{severe}_{SEVERITY} + (1 - P^t_{SEVERITY}) U^{not\ severe}_{SEVERITY}$$

$$U^t_{SEVERITY} = P^t_{severe} 0.619 + (1 - P^t_{severe}) - 0.619$$

$$U^{t=0}_{SEVERITY} = 0.0339$$

6. Population coverage. Verelst et al. [413] found social norms to dominate free-rider considerations such that when coverage in the population at large increases, the likelihood of vaccinating oneself or one's children increases as well. Therefore, we included the global coverage attribute into vaccination behavior as a lagged cumulative effect of what others did in the past (i.e. based on η in previous weeks). We assumed people would base their decision on how other parents decided about measles vaccination in the past year. As such, we calculated the 'coverage utility' as follows:

$$\overline{\eta^t} = \frac{\eta_{t-53} + \eta_{t-52} + ... \eta_{t-1}}{52}$$

$$U^t_{COVERAGE} = \overline{\eta^t} * 0.99, \qquad \text{such that} \qquad 0 \geq U^t_{COVERAGE} \geq 0.99$$

At the start of the simulation, we set the coverage to 96.2% (η at t=0),which corresponds to the observed MMR1 coverage in Flanders in 2016 [409]. For $1 \geq t \geq 52$, $\overline{\eta^t}$ is calculated as the average coverage over time t.

Total vaccine utility

Adding up the utility of all vaccine attributes, both exogenous and endogenous, we come up with a population level utility for measles vaccine in time t.

$$U^t = \underbrace{U^{total}_{VE} + U^{total}_{VRSE} + U^{total}_{ACCESS}}_{\text{exogenous}} + \underbrace{U^t_{PREV} + U^t_{SEVERITY} + U^t_{COVERAGE}}_{\text{endogenous}}$$

We fitted the current utility level (2.3079), maximum utility level (3.69) and minimum utility level (-2.70) to a coverage of 98.06%, 100% and 0% respectively

for 98.1% the Flemish population, excluding the proportion that we excluded and assumed would never vaccinate (1.9%).

We fitted an exponential function to three data points under the following assumptions (1) at the maximal possible utility level (3.69), we assume that everyone in the general population will let their child become vaccinated, (2) at the minimum possible utility level (-2.70), we assume no-one will become vaccinated, (3) in the current utility situation (2.3079), 96.2% of the population at large is vaccinated, which corresponds to a 98% coverage in the population excluding the 'refusers' (1.9%).

The relation between total vaccine utility and coverage in the non-refusing population $(-r)$ was found to be as follows:

$$Cov^t_{-r}(U^t) = \frac{1}{1+e^{\frac{-U^t}{0.5347434}}} - 0.00372971$$

Such that the coverage in the total population is:

$$\eta^t = Cov^t_{-r}(U^t) * 0.981$$

Modelling scenarios

We investigated the impact of different behavioral scenarios on the disease spread, the utility levels (U^t) and the vaccination coverage in the target population (η^t). More specifically, we analyzed the following scenarios:

1. BCM from the start. In this default scenario we run the BCM in parallel with the transmission model for measles from the start of the simulation. The vaccine coverage is set to 96.02% at the start of the simulation, and is determined by the BCM (i.e. the vaccine's utility) in further time steps.

2. No BCM. In the absence of a BCM, the proportion that vaccinates their youngest child remains equal to the current observed vaccination coverage: $\eta^t = 0.962$. This scenario was included in order to assess the impact of adding a BCM to the measles transmission model, compared to a traditional approach of keeping vaccine utility and coverage constant over time.

3. Vaccine scare from the start. This scenario is similar to the first scenario except that the exogenous utility value of VRSE is set to the value in which everyone perceives VRSE to be frequent. This induces an exogenous shock, with VRSE utility reducing to -0.637 throughout the entire simulation. All endogenous behavior changes, are determined by the BCM.

4. A temporary vaccine scare. While in the latter scenario the vaccine scare remains equal throughout the entire simulation, this scenario assessed the impact of a temporary vaccine scare which reduces the VRSE utility to -0.637 for a limited time throughout the simulation. We aimed to see how vaccine coverage gets restored once the vaccine confidence is set back to its initial levels. More specifically, we imposed a vaccine scare 5 years after the start of the simulations (t=260), that lasts for 5 years.

5. Suspension from basic immunization schedule. In this scenario we looked at the implications of taking the MMR vaccine out of the basic immunization schedule. In that case, parents would be confronted with a rather wearisome process of: i) visiting a physician in order to get a prescription, ii) visit the pharmacy and pay for the vaccine themselves, iii) visit a physician to administer the vaccine to their child. This scenario is implemented through an exogenous shock in the BCM by setting the U_{ACCESS} equal to the level "co-payment & prescription", such that the utility decreases to $U^{total}_{ACCESS} = -0.564$. This exogenous shock is implemented at the start of the simulations $(t = 0)$.

6. Severity decay to 5%. In this scenario, we deviated from the BCM description with respect to disease severity. Instead of returning to a level of 52% that perceives measles as a severe disease, after a 5 year exponential decay, in this scenario, we assumed an exponential decay up to 5% after 5 years of less than 1,000 cases per week. Since we alter an endogenous utility variable, we keep this value equal during the entire course of the simulation. At the start of the simulation, $P^t_{severe} = 0.52$ up to a point that the threshold of 1,000 cases per week is reached. Afterwards, the proportion that perceives measles as a severe disease is derived as follows:

$$P^t_{severe} = e^{-\gamma t} \qquad \text{with} \qquad \gamma = \frac{-ln(0.05)}{5*52}$$

After the 5 year decay, P^t_{severe} was held constant at 0.05 up to the point where the threshold was reached again and the behavioral process was repeated.

7. Vaccine scare & suspension. In this scenario we combined a vaccine scare from the start of the simulation followed by a suspension of the vaccine from the basic immunization schedule. It is assumed here that the public influence on the misperception of the frequency of VRSE is at such high levels that the policymakers suspend the vaccine program and that it is only available at the pharamacy at the full expense of the patient. Whereas the vaccine scare is implemented from the start of the simulation, the suspension is implemented from week 156 (3 years) and stays in place until the end of the simulation.

The simulations were performed in Python 3 [407]. The utility values were estimated in JMPPro 14 [179].

6.3 Results

In Figure 6.2, the utility dynamics are depicted for all scenarios. The charts are split to clearly visualize the different utility levels. First of all, in the default simulation (scenario 1: a BCM from the start), the utility levels were found to be higher, compared to the "No BCM" scenario (scenario 2), the latter in which the vaccine's utility – and thus vaccination uptake – remains constant. In all scenarios, we observe a large outbreak at about one year in the simulation (Figure 6.4). This drives the vaccine's utility in the default scenario up to a level above three (see Figure 6.2a, where the utility levels overlap for the default situation (scenario 1) and the temporary scare (scenario 4)). This peak in utility is driven by the endogenous parameters: prevalence, severity and coverage, that all increase the vaccine's utility. When the outbreak is over, the utility level in scenario 1 stabilizes to about 2.3 – which is higher than the constant utility in scenario 2 – due to the population coverage dynamics taking into account what others have done in the past. In the absence of any new outbreaks, the utility remains equal at this level. The implications on vaccine coverage are however minimal. In Figure 6.3a, we observed the coverage under the default BCM (1) to be only slightly higher than in a scenario without a BCM (2): 96.4% versus 96.2%, respectively. As such, there are no notable differences in the transmission of measles, which can be seen in Figures 6.4a and 6.4b.

A permanent vaccine scare (scenario 3) reduces the vaccine utility significantly (6.2a) in the absence of large measles outbreaks. This in turn causes vaccine coverage to decrease to levels below 90% as can be seen in Figure 6.3a. Since a sufficiently high coverage is required to halt the spread of measles, large outbreaks are simulated in the years following low coverage in the target population, which is shown in Figure 6.4c. As a result of such outbreaks, vaccine utility and subsequently coverage, quickly increase again to default (scenario 1) levels through the endogenous utility parameters. When the outbreak is over, the coupled behavior-transmission cycle is repaeted.

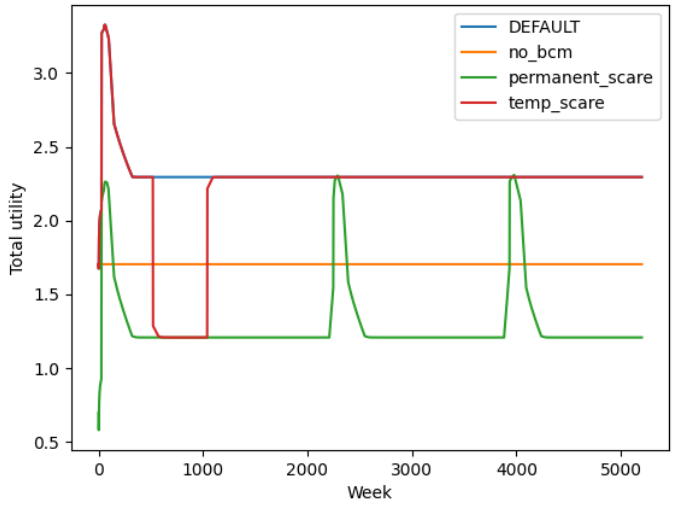
The temporary vaccine scare of 5 years (scenario 4) remains insufficient to trigger a long term impact on utility (Figure 6.2a). The vaccine coverage is lower for a 5-year cohort and rises back when the vaccine scare is over – as can be seen in Figure 6.3a – but remains insufficient to cause further outbreaks in the simulation (Figure 6.4d). The latter is probably due to the homogeneous mixing hypothesis which is implicitly assumed in the compartmental model we applied in this study.

Suspension of the measles vaccine from the immunization schedule (scenario 5) has a strong impact on the vaccine's utility levels over time as can be seen in

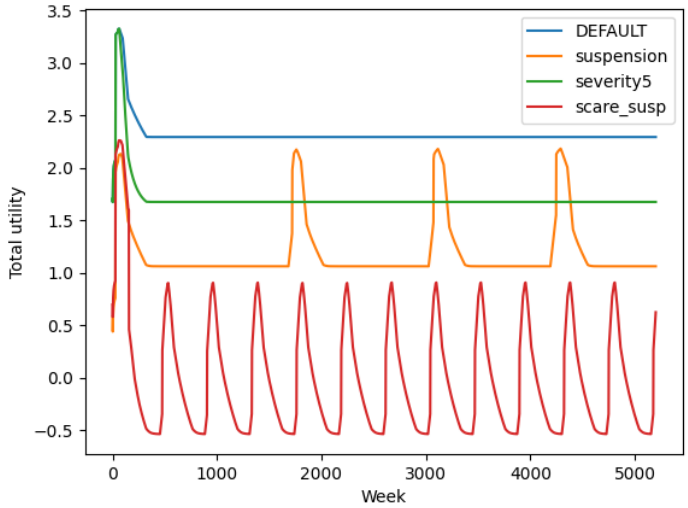
Figure 6.2b. As a result, the vaccine coverage in the target population drops below 90% in the absence of recent outbreaks (Figure 6.3b). Unsurprisingly outbreaks occur every few years as can be seen in Figure 6.4e. Additionally, we observed that the time between outbreaks reduces with every new outbreak.

In scenario 6, we assumed the proportion that perceives measles as a severe disease to reduce to 5% after the first outbreak, compared to 52% in the default situation (scenario 1). In Figure 6.2b, we see the impact on measles vaccine utility, which reduces to about 1.7, compared to 2.4 in the default BCM scenario. The impact on vaccine coverage is rather limited with a vaccine coverage converging to about 94%, compared to 96% in the baseline situation (Figure 6.3b). This reduction in vaccine coverage seems to be insufficient to trigger further outbreaks in the transmission model (Figure 6.4f), except for the initial one that we observed in all scenarios.

We observed persistent outbreaks in scenario 7, in which the vaccine scare followed by a suspension drives utility below zero after the initial outbreak (Figure 6.2b). This fall in utility, is followed by recurrent ups and downs in vaccine utility as a result of persistent measles outbreaks (Figure 6.4g). This is because vaccine coverage in the target population is volatile as well – ranging between 80% and 25% (Figure 6.3b) – which in turn is driven by the vaccine's utility. As such the BCM – with a very low coverage in the absence of measles cases – induces large measles outbreaks every 10-12 years.

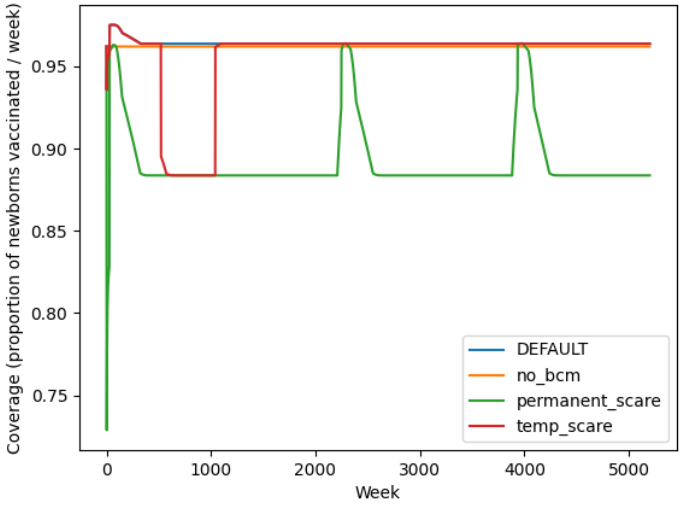


(a) Measles vaccine utility for scenarios 1 to 4. DEFAULT represents a BCM from the start (scenario 1).

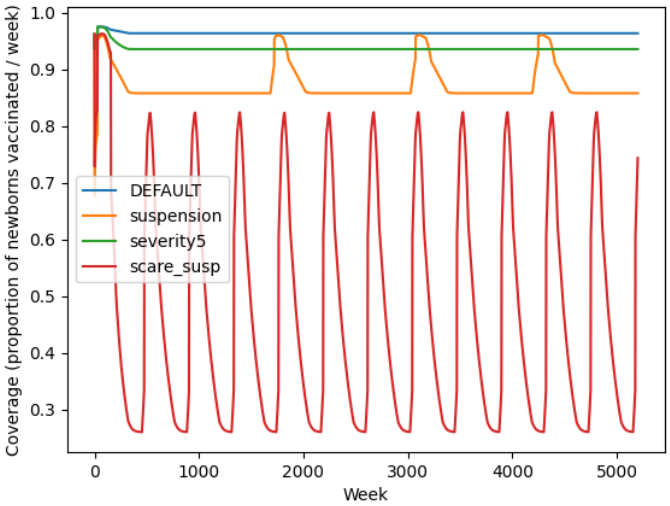


(b) Measles vaccine utility for scenarios 1 and 5 to 7. DEFAULT represents a BCM from the start (scenario 1).

Figure 6.2: Utility levels through time for all scenarios, compared to a DEFAULT, which is defined as a BCM from the start (scenario 1).



(a) Measles vaccine coverage for scenarios 1 to 4. DEFAULT represents a BCM from the start.



(b) Measles vaccine coverage for scenarios 1 and 5 to 7. DEFAULT represents a BCM from the start.

Figure 6.3: Coverage levels in the target population through time for all scenarios, compared to a DEFAULT, which is defined as a BCM from the start (Scenario 1)

6.4 Discussion

We demonstrated the usefulness of DCE data to parameterize vaccination BCMs in parallel to a disease transmission model. Even though this study primarily demonstrates a proof of concept, it provides insights in the dynamics of vaccine uptake and measles outbreaks under a transparent set of assumptions. Note that this type of BCM can be applied to a variety of transmission models and pathogens for which a vaccine is available, i.e. its use is not limited to compartmental deterministic models for the spread and vaccination of measles.

High and stable vaccine coverages have been observed in Flanders since 2005 [409]. Hence, in this study we observed that the addition of a default BCM (scenario 1) has similar consequences on the spread of measles in Flanders, compared to a situation without BCM (scenario 2). Note however, that the transmission model we used has quite some limitations, e.g. the susceptible population (S_1 & S_2) gets infected very early in the simulation in a large outbreak – with about 13,000 infected cases per week at the peak of the infection. As such, a very large fraction becomes immune in the early stages of the simulation, even though this immunity comes at the expense of significant morbidity and likely a dozen fatalities.

Nevertheless, when introducing exogenous shocks to the BCM, recurrent outbreaks were observed. When a vaccine scare was implemented from the start of the simulation (scenario 3), or when the measles vaccine got suspended from the immunization schedule (scenario 4), outbreaks appeared to reoccur as a result of coupled behavior-transmission dynamics. A vaccine scare followed by a suspension of the vaccine from the immunization schedule (scenario 7) would impose significant pressure on healthcare systems, with 23,000 infected cases per week at the peaks, every few years.

Orenstein et al. found in 2000 that measles eradication is possible and is within our future [294]. They identified 6 potential impediments to eradiction: "(1) lack of political will in some industrialized countries, (2) transmission among adults, (3) increasing urbanization and population density, (4) the HIV epidemic, (5) waning immunity and the possibility of transmission from subclinical cases, and (6) risk of unsafe injections" [294]. However, by now it has become clear that other impediments remain. Among other factors – such as logistical challenges [42] or early maternal antibody waning [224] – suboptimal vaccine uptake has been one of the major contributors to sustained outbreaks in Europe [119].

Infectious disease modellers need to incorporate dynamic vaccine uptake in

order to accurately predict infectious disease dynamics. Naturally, eradication of an infectious disease ultimately depends on whether a sufficiently high vaccine coverage can be reached and future outbreaks or resurgence can be halted. As such, assessing the feasibility of eradicating an infectious disease by vaccination, requires to take behavioral changes into account as well. Health economic analyses rely heavily on such transmission models in order to assess the cost-effectiveness of vaccination programs. When assuming a constant vaccination coverage or setting the coverage to the most optimal value – thereby neglecting individuals' behavioral changes – health economic evaluation is prone to estimation errors.

Indeed, the cost-effectiveness of measles vaccination is highly sensitive to sub-optimal vaccine coverage, even when this coverage is just below the target. When herd immunity fails, even at a district level, sustained outbreaks jeopardise immunization efforts of the past and necessitate measles vaccination to continue over the next years. The health economic consequences in such outbreaks are significant encompassing, among others, increased mortality, increased healthcare costs to treat infected cases and the costs of continued immunization efforts to prevent future outbreaks. These costs would be averted if global measles eradication can be reached.

A paper from 2010 reported that global measles eradication has the potential to save about $1.5bn in treatment and prevention costs in addition to 1 million deaths averted each year [294]. Moreover, a 2011 study found measles eradication by 2020 to be most cost-effective, compared to mortality reduction goals set by the WHO [225]. In both studies, vaccination behavior was not taken into account. Yet, given the voluntary nature of measles vaccination in many countries, policymakers have limited control over the ultimate feasibility of measles elimination or eradication.

DCE estimates were already applied to parameterise HIV prevention uptake in South Africa in a 2016 study by Terris-Prestholt et al. [388]. They found that DCE-based uptake provided more nuanced projections for HIV interventions (TPrEP and condom use) and thus should be used to inform model based cost-effectiveness analyses. A bias of up to 50% was found when DCE-based uptake and substitution estimates were not included in economic analyses [388]. A similar methodology was applied in another study estimating the cost-effectiveness of HIV and pregnancy prevention technologies in South-Africa [319]. Both studies used a static transmission model.

Study limitations

Data is still scarce and we still need to rely on a set of assumptions. We retrieved data about which vaccine attributes people attach more/less value to, but we have limited information about risk perceptions and how these perceptions are altered as a result of infectious disease outbreaks. As such, risk perception surveillance data is needed in order to fully parameterize the BCM we introduced in this chapter. Additionally, a reliable relation between vaccine utility and coverage in the target population requires additional research.

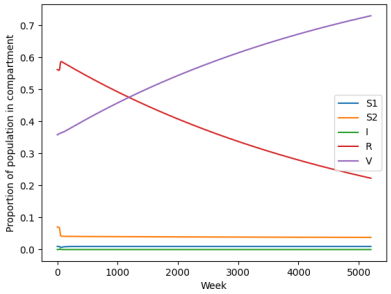
An updated DCE should explicitly query for variations in the vaccine's severity of VRSE as it was found to be of crucial importance in a DCE study on vaccination by Sadique et al. [338]. This attribute would clearly be of interest to model measles vaccine uptake as it was – and to some extent still is – confronted with the perception that MMR vaccine would cause autism, as a result of a fraudulent paper published in 1998 [140]. A vaccine scare could be more easily integrated in a BCM if VRSE severity estimates were available. For some people, there are other motivations that drive their vaccination decision. When these vaccine related aspects are not included as DCE attributes or levels, we cannot control for these aspects in the BCM.

We only looked at immunity derived from natural infection and from a first dose of MMR vaccine. A more realistic measles model should also include immunity derived from maternal antibodies and from a second dose of MMR vaccine – which in Flanders is administered at the age of 10 years [27] – especially when such a model would be fitted to historical data.

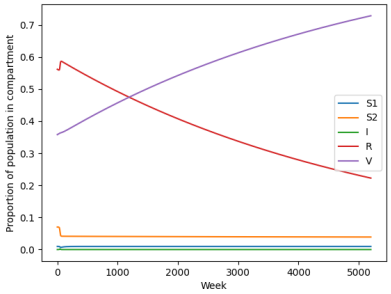
A thorough probabilistic sensitivity analysis is necessary to incorporate uncertainty in the analysis. A confidence interval around the utility estimates could, for example, be instrumental in such a sensitivity analysis. These are provided by default in a PML model. Additionally, a stochastic transmission model with much more detail is needed to accurately simulate measles transmission in highly immunized populations.

6.5 Acknowledgments

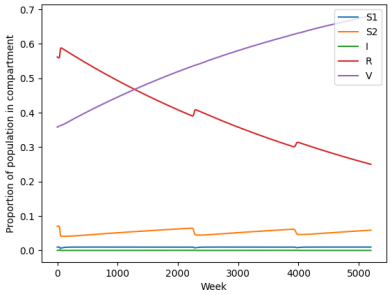
I would like to thank Elise Kuylen and Sereina Herzog at the University of Antwerp for their valuable guidance in constructing the models in this chapter.



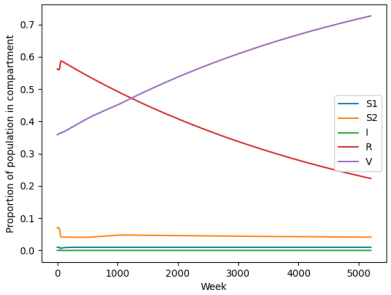
(a) Measles transmission for scenario 1: BCM from the start



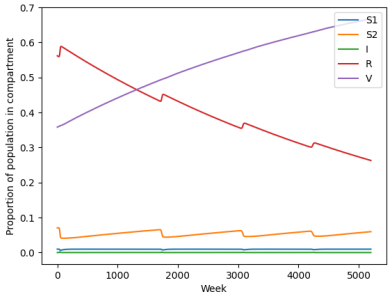
(b) Measles transmission for scenario 2: No BCM



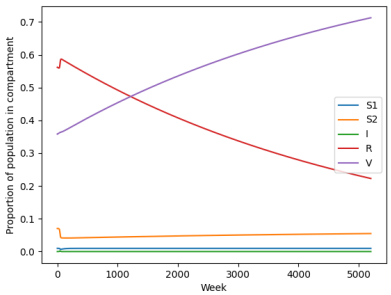
(c) Measles transmission for scenario 3: Vaccine scare from the start



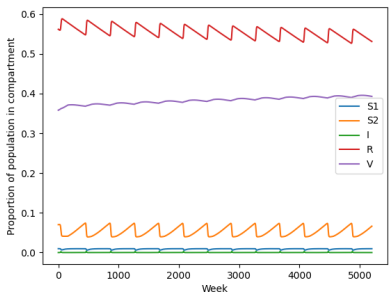
(d) Measles transmission for scenario 4: Temporary vaccine scare



(e) Measles transmission for scenario 5: Suspension from immunization schedule



(f) Measles transmission for scenario 6: Severity decay to 5%



(g) Measles transmission for scenario 7: Vaccine scare followed by suspension

Figure 6.4: Transmission models for all scenarios.

CHAPTER 7

Workplace influenza vaccination to reduce employee absenteeism: An economic analysis from the employers' perspective

This chapter is based on submitted work "Verelst F, Beutels P, Hens N and Willem L (2020). Workplace influenza vaccination to reduce employee absenteeism: An economic analysis from the employers' perspective. Submitted to Vaccine" [415].

Summary

Background. Each year, about 10% of unvaccinated adults contract seasonal influenza, with half of this proportion developing symptoms. As a result, employers experience significant economic losses in terms of employee absenteeism. Influenza vaccines can be instrumental in reducing this burden. Workplace vaccination is expected to reduce employee absenteeism more than linearly as a result of positive externalities. It remains unclear whether workplace influenza vaccination yields a positive return on investment.

Methods. We simulated the spread of influenza in the seasons 2011-12 up to 2017-18 in Belgium by means of a compartmental transmission model. We accounted for age-specific social contact patterns and included reduced contact behavior when symptomatically infected. We simulated the impact of employer-funded influenza vaccination at the workplace and performed a cost-benefit analysis to assess the employers' return on workplace vaccination. Furthermore, we look into the cost-benefit of rewarding vaccinated employees by offering an additional day off.

Results. Workplace vaccination reduced the burden of influenza both on the workplace and in the population at large. Compared to the current vaccine coverage – 21% in the population at large – an employee vaccine coverage of 90% could avert an additional 355 000 cases, of which about 150 000 in the employed population and 205 000 in the unemployed population. While seasonal influenza vaccination has been cost-saving on average at about €10 per vaccinated employee, the cost-benefit analysis was prone to significant between-season variability.

Conclusions. Vaccinated employees can serve as a barrier to limit the spread of influenza in the population, reducing the attack rate by 78% at an employee coverage of 90%. While workplace vaccination is relatively inexpensive (due to economies of scale) and convenient, the return on investment is volatile. Government subsidies can be pivotal to encourage employers to provide vaccination at the workplace with positive externalities to society as a whole.

7.1 Introduction

Absenteeism from work causes a large economic burden to society. Seasonal influenza accounts for a significant share of this burden [351]. Indeed, in unvaccinated adults the attack rate for seasonal influenza is estimated to be around 10%, with about half of the cases experiencing symptoms [368]. Furthermore, the timing and intensity of influenza epidemics have been successfully linked to patterns in employee absenteeism [418]. More importantly, seasonal influenza causes considerable mortality and morbidity to society as a whole, in particular to vulnerable subgroups in the population (e.g. older age groups and pregnant women). Prevention measures such as vaccination and antivirals can limit the burden of influenza in the population. Nevertheless, yearly influenza vaccine effectiveness is uncertain due to, among others, the potential mismatch between vaccine and circulating strains [394].

In most developed countries, influenza vaccination is currently recommended for individuals aged 60-65 and older [178]. However, in the United States of America (US) all individuals older than 6 months are targeted to receive vaccination [64] and in the United Kingdom (UK) children were recently included in routine flu vaccination as well [282]. In Belgium, next to health care workers and risk groups (e.g. chronically ill and people older than 65 years of age), health authorities recommended to vaccinate everyone between 50 and 65 years of age [135]. Despite the economic impact of employee absenteeism, influenza vaccine is usually not reimbursed, nor conveniently available for healthy employees. Unsurprisingly, uptake of influenza vaccine in Belgium remains relatively low. Each year, only about 20% of the population at large is vaccinated and about 60% of the elderly [386].

The benefits of employee vaccination translate in a reduction of disease, directly in vaccinated persons, but indirectly also in the work and other social contacts of vaccinated persons. Indeed, successfully vaccinated individuals contribute to herd immunity as they are unable to transmit the pathogen to their social contacts (see Fine et al. [114]). Therefore, absenteeism is expected to reduce more than linearly. Workplace vaccination can be instrumental in reaching a higher influenza vaccination coverage for several reasons, among which: convenience for vaccinnees (e.g. no GP visit and no out-of-pocket cost), economies of scale and a potential return on investment for employers. However, this return on investment is not fully explored yet.

Economic analyses are typically limited to risk groups and focus on societal or health care payer perspectives. Influenza immunization programs in such

risk groups are often found to be cost-effective [390]. However, with respect to employer funded vaccination, employees usually do not belong to a risk group. In addition, the majority of the costs related to influenza absenteeism and workplace vaccination are borne by the employer. Research focussing on the perspective of the employer is relatively scarce and is often limited to healthcare settings.

Few analyses have been performed on the economics of workplace influenza vaccination. Lee et al. [221] performed an economic analysis of employer-sponsored workplace vaccination for the prevention of seasonal and pandemic influenza in the US. Others compared the absenteeism of vaccinated and non-vaccinated employees in single companies [54, 223, 290, 345]. Bridges et al. [44] describe a double-blind, randomized, placebo-controlled trial on the effectiveness and cost-benefit of influenza vaccination of healthy workers. However, studies that apply a dynamic transmission model are lacking.

Nevertheless, because of herd immunity induced at the workplace and in the community, the use of a dynamic transmission model is most appropriate to capture all the benefits of workplace vaccination [297]. Dynamic transmission models account for the positive externalities of herd immunity by accounting for the infectious cases, vaccination and force of infection varying over time. The latter is linked to social contact behavior [425], which depends on age and temporal factors [448]. In addition, health state also plays an important role on social contact behavior [406]. Eames et al. found significant reductions in social contact behavior of symptomatic cases in the UK during the 2009 influenza pandemic [109]. The impact of this adaptive social contact behavior on transmission dynamics was found to be of high importance [349].

In this study, we estimated the cost-benefit of employer-funded influenza vaccination in Belgium with a dynamic transmission model. We accounted for reduced social contact behavior when cases are symptomatically infected. The model is fitted to incidence data from 2011-12 up to 2017-18. The predicted burden of disease under different scenarios (e.g. vaccine coverage) is used to assess the employers' return on investment. Finally, we calculated the cost-benefit of rewarding vaccinated employees by offering an additional day off.

7.2 Materials and methods

Transmission model

We built on a compartmental transmission model developed by Santermans et al. [349] to simulate the spread of influenza in the Belgian population for flu seasons 2011-12 up to 2017-18. The model structure is presented in Figure 7.1 and each compartment is subdivided by age and employment status (employed versus unemployed), which is based on data obtained from StatBel [374]. We used five age groups: [0-4], [5-19], [20-44], [45-64] and 65+ years of age. At the beginning of the simulation, a proportion μ gets vaccinated (V) with an inactivated influenza vaccine, which we assumed to be an all-or-none vaccine with an efficacy of ϵ, $(0 \leq \epsilon \leq 1)$. The force of infection, λ, represents the rate at which individuals are infected at time t, moving a proportion of the susceptible population to the exposed compartment (E). All exposed individuals (E) are initially asymptomatically infected (I_1^a) at a rate γ. In a next step, a proportion ϕ becomes symptomatic (I^s) at a rate θ, while the remaining proportion stays asymptomatic (I_2^a). In line with the work of Santermans et al. [349], we applied a different degree of infectiousness to symptomatic versus asymptomatic infection. Likewise, the recovery rate distinguishes symptomatic (σ^s) from asymptomatic (σ^a) cases, moving people to the recovered (R) compartment. An overview of the model parameters is presented in Table 7.1 with corresponding references.

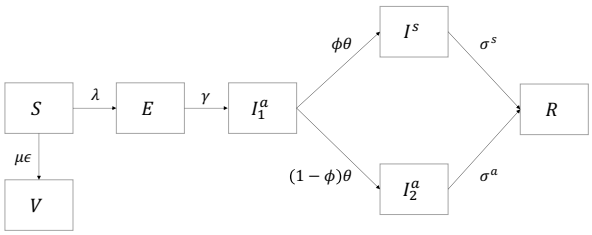


Figure 7.1: Model structure to simulate the transmission of influenza. Individuals are either susceptible (S), successfully vaccinated (V), exposed to influenza (E), infectious (I) or recovered (R). Superscripts distinguish between symptomatic (s) or asymptomatic (a) infection. Each compartment is split into age- and work-specific sub-compartments. Parameter values and model features are provided in the main text and table 7.1.

We estimated the transmission probability using the social contact hypothesis

by Wallinga et al. [425] with proportionality factors q^a and q^s for asymptomatically and symptomatically infected individuals, respectively. In order to include seasonal transmission dynamics, we applied a sinusoidal function to the model's force of infection as described in Goeyvaerts et al. [141]. The force of infection is specified as:

$$\begin{aligned}\lambda &= \beta^s * I^s + \beta^a * (I_1^a + I_2^a) * z(t),\\ \beta^s &= q^s * M^s / N * z(t)\\ \beta^a &= q^a * M^a / N * z(t)\\ z(t) &= 1 + \delta sin((2\pi(t - t_0))/365)\end{aligned}$$

with the social contact matrix M^s representing the contact behavior of symptomatically infected individuals and M^a the contact behavior for individuals in any other health state. We derived the social contact matrices from Belgian social contact survey data [276] using the socialmixr package in R [130] and distinguished between social contact behavior during holidays and regular (i.e. non-holiday) periods. In order to incorporate adaptive social contact behavior when people are symptomatically infected (e.g. staying home from work or school), we applied location-specific reduction rates from a UK survey during the 2009 influenza pandemic [109]. The observed reductions are mostly driven by individuals staying at home, thereby limiting their social contact behavior elsewhere. Based on the social contact matrix for healthy and asymptomatic individuals (M^a), we calculated M^s as follows:

$$\begin{aligned}M^a &= M^{home} + M^{school\ \&\ work} + M^{transport} + M^{leisure} + M^{other},\\ M^s &= M^{home} + 0.09M^{school\ \&\ work} + 0.13M^{transport} + 0.06M^{leisure} + 0.25M^{other}\end{aligned}$$

Social contact matrices for regular and holiday periods and the corresponding age-specific reduction due to illness are presented in Figure 7.2. For example, individuals between 5 and 19 years of age have more contacts with each other during regular periods compared to holidays (left vs. right) Moreover, during regular periods, these contacts are reduced by 82% when individuals contract symptomatic influenza. The reduction is lower during holiday periods.

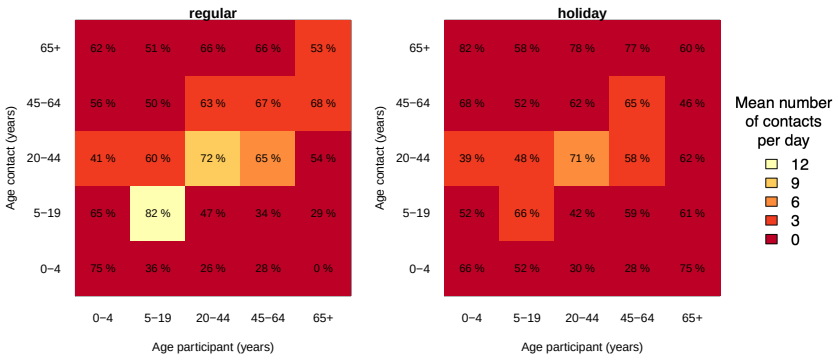


Figure 7.2: Social contact behavior by age during regular (left) and holiday (right) periods. The colors represent the daily average number of contacts M_{ij} between an individual of age i (horizontal axis) with an individual of age j (vertical axis). The percentages represent the reduction in social contacts when symptomatically infected.

Incidence and vaccine effectiveness data

The transmission model was first calibrated to reproduce the observed influenza incidence in Belgium from 2011-2018. Data were obtained from the National Reference Centre for Influenza in terms of reported influenza-like-illness (ILI) cases per 100 000 individuals, the number of cases tested for influenza and number of positive influenza cases per week. We aggregated the ILI data into the selected age groups and calculated a weekly proportion of positive cases for each flu season (from week 40 until week 39 the year after). Due to data-sparseness, we could not calculate the proportion of positive cases by age. Season-specific vaccine effectiveness estimates were based on primary care data from the I-MOVE multi-center case-control study [204]. We used the point estimates for the age-specific vaccine effectiveness against any influenza for our analysis and substituted the negative values by zero (i.e. no effect). All vaccine effectiveness estimates are provided in Table 7.2. Vaccine coverage for influenza in Belgium was retrieved from [386] to calibrate our transmission model.

Parameter estimation

We estimated five model parameters (see Table 7.1) for each season via an active learning approach with 3 iterations [141, 449]. To start, we sampled 50 000 values for each parameter according to a Latin Hypercube design. For each parameter set, we scored the predicted age-specific incidence with the reference data by shape of the curve (using weighted least-squares (WLS)) and

the relative difference in total incidence (i.e. the difference in the area under the curve). We selected parameter sets in this two-objective optimization based on the Pareto front according to both scores. We aggregated the parameter ranges from the Pareto front subset per season, extended this range by $\pm 10\%$, and used this to sample parameter values in the next iteration. We applied a maximum least-square score of 10^6 to remove the simulations with a matching total incidence but totally different timing (shape). After 3 iterations, we selected the parameter set from the pareto front with the lowest WLS score and a relative difference in incidence of maximum 5%.

Cost-benefit analysis

The employers' cost of vaccinating employees consists of both direct and indirect costs related to vaccination: cost of the vaccine, cost of administration and a productivity cost for employees spending time to receive the vaccine, which we assumed to be 30 minutes (Table 7.1). In total, the cost per vaccinated employee was less than €40. We extracted Belgian employment statistics such as the year-specific mean gross wage and the employed population by age from Statbel [372]. We corrected for part-time employees, public holidays, weekends and 27 additional holidays (average obtained from [401]) to obtain a working day probability of 55.8%. The direct cost of absenteeism per day per employee was estimated to be 8.6% of the gross monthly income as reported by Securex, a Belgian HR services agency [418]. As such, the cost per day of absenteeism depends on the year-specific wage and ranged between €274 and €306. We opted for a conservative approach in which the total cost of absenteeism only accounted for direct costs. This is in line with the marginal productivity theory of wage determination in which the market for labor is in equilibrium when the marginal cost of labor (i.e. wage cost) equals the marginal product of labor. The impact of adding an indirect cost of absenteeism was analyzed in a scenario analysis. The absenteeism per employee is based on the relative incidence of symptomatic cases in the employed compartment. The total cost is based on the costs of the vaccination program and the costs of employee absenteeism. The cost-benefit is then calculated as the difference between the total cost with intervention and the total costs without any vaccination of the employed population.

Employee vaccination

The estimated season-specific transmission parameters were kept constant when modeling the impact of different levels of employee influenza vaccination funded by the employer. We fixed the age specific coverage in the unemployed

population to the observed coverage in 2013 throughout all simulations [386]. We varied the vaccination coverage in the employed population between 10% and 90% for each season, assuming that all vaccination of the employed population is administered at the workplace and funded by their employer. We assessed the number of averted cases in the employed and unemployed population compared to the reference without vaccination of the employed population. We evaluated the costs and benefits of the vaccination program per employee and for all Belgian employers combined.

Scenario analyses

We ran univariate scenario analyses to elaborate on parameter uncertainty and provide an overview in Table 7.3. First of all, we wanted to investigate the impact of increasing and decreasing the reporting rate by 10% in scenario 1 and 2, since information about this parameter is lacking. In addition, the vaccine effectiveness estimates we used from the I-MOVE study are low compared to other estimates in the literature [302]. Therefore, we applied more optimistic vaccine effectiveness estimates in scenario 3, equal to the highest observed effectiveness by age for each simulated season. Furthermore, we investigated the impact of adding indirect costs of absenteeism to the economic analysis (e.g. the cost of interim replacement, overtime being more expensive and other organizational costs). We assumed this indirect cost to be equal to the direct cost of absenteeism in scenario 4. A recent report estimated this indirect cost to amount between 2.5 and 3 times the direct cost of absenteeism [418]. As such, scenario 4 is still relatively conservative. Finally, in scenario 5, we looked at the impact of removing the sinusoidal function from the force of infection – thereby neglecting the seasonal character of influenza transmission – by setting $z(t) = 1$ during the parameter estimation and health economic evaluation.

Employee incentives

We investigated whether there is scope for incentives in order to persuade employees to get vaccinated, for example by giving vaccinated employees an additional day off or other rewards paid for by the employer. We look into the maximum amount of employee incentives by calculating the benefit-cost ratio per vaccinated employee as a function of the influenza vaccine coverage among all employed individuals.

7.3 Results

We used a dynamic transmission model to inform cost-benefit analyses of employer-funded influenza vaccination. We first present our model dynamics and results for the conservative scenario. Afterwards, we report our scenario analyses that are more/less in favor of influenza vaccination and demonstrate the impact of model assumptions and parameter uncertainty.

We estimated the impact of different vaccination strategies on the burden of seasonal influenza. Figure 7.3 shows the predicted incidence of symptomatic cases (orange line) for 2015-16 using the observed vaccine coverage and the reference data on influenza incidence (orange dots). The grey lines present the predicted incidence if 0% up to 90% of all employees were vaccinated. As coverage among employees increases, the peak and total number of symptomatic flu cases decreased. Moreover, the peak was delayed when coverage increased. The holiday periods slowed down the transmission at the beginning of the epidemic, whereas the Easter break in April caused a steeper decline at the end of the epidemic.

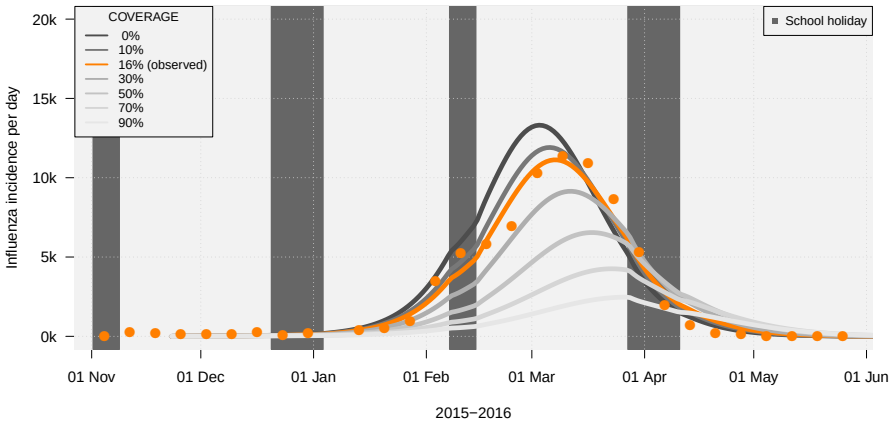
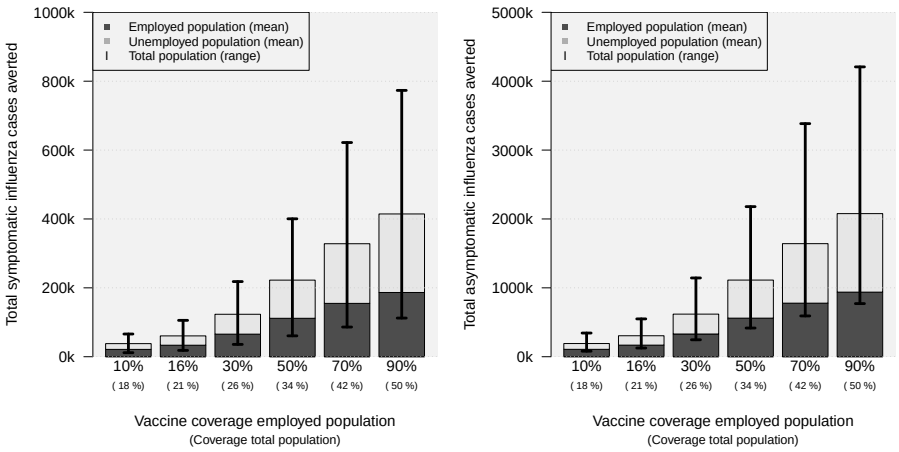


Figure 7.3: Predicted seasonal influenza incidence for 2015-16 by employee vaccine coverage (lines) and reference data (dots). Parameter estimates from the conservative scenario were used for these results.

Workplace vaccination decreased the number of cases both in the employed and the unemployed population. Herd protection plays an important role such that vaccinated employees can serve as a barrier to limit the spread of influenza in the entire population, beyond the employed population. The number of averted cases – each season, average over all seasons – in the employed and unemployed population is given in Figure 7.4. Note that we used no vaccination of the employed population as a reference. The second bar in both

figures represents the impact of the observed vaccine coverage in the total (21%), employed (16%) and unemployed population. As such, we predicted that on average over 60 000 symptomatic cases have been averted each season, of which 55% in the employed population and 45% in the unemployed population. This intervention translated, on average, into a reduction of 15% in the symptomatic cases on the workplace. The relative fraction of cases averted in the unemployed population increased with vaccine coverage among employees. If employers could increase the coverage among employees to 90%, they could avert up to 415 000 symptomatic cases of seasonal influenza in the population, of which about 185 000 in the employed population.



(a) Symptomatic **(b) Asymptomatic**

Figure 7.4: Symptomatic and asymptomatic seasonal influenza cases averted for different workplace vaccine coverages (each season, average over all seasons). The coverage in the employed population and total population is shown on the x-axis. We applied parameter estimates from the conservative scenario and no vaccination of the employed population as a reference.

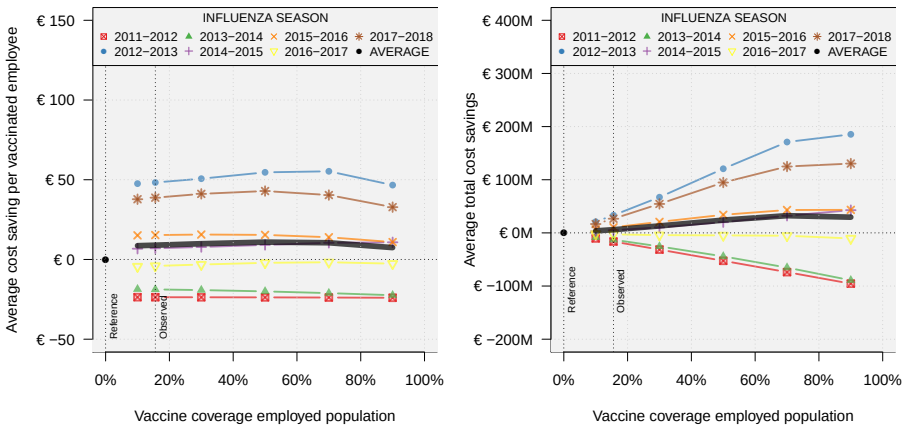
The cost-benefit analysis from the employers' perspective showed a lot of between-season variability. Figure 7.5 presents that in some seasons (e.g. 2012-13 and 2017-18) vaccination is an investment with a high return, whereas for other seasons (e.g. 2011-12 and 2013-14) there is a net loss when vaccinating the workforce. Due to herd immunity kicking in, we observed a small decrease in the return on investment when the coverage in the employed population increased, though the overall results and conclusions are stable within seasons. Considering the seven seasons, we calculated that seasonal influenza vaccination has been cost-saving with an average net savings of around €10

per vaccinated employee. For the Belgian economy as a whole, this translated in an average cost-saving of about €6.2 million when applying the observed coverage. If 90% of the employed population would have been vaccinated against seasonal influenza, on average €30 million would have been saved from the employers' perspective, each season.

As coverage increases in Figure 7.5b, the marginal benefit of employee vaccination decreases, especially so for coverages from 70% and higher. In essence, when a high fraction of employees is successfully vaccinated against influenza, they can no longer transmit the disease to colleagues, and the marginal benefit of vaccination decreases. As such, the optimal investment in employee vaccination between 2011-18 would have been reached at a coverage of 70%. Nevertheless, additional vaccination in employees can still have a pivotal role in protecting their children, parents, partner and other social contacts, as touched upon in previous paragraphs. Hence, herd immunity manifests in the protection of both unemployed individuals and unvaccinated co-workers.

Scenario analyses

We analyzed parameter uncertainty in scenario analyses and present the cost-benefit per employee in Figure 7.6.



(a) Cost-saving per employee **(b) Total savings**

Figure 7.5: Cost-savings per vaccinated employee and total savings for different levels of employee vaccination in different influenza seasons. Conservative scenario.

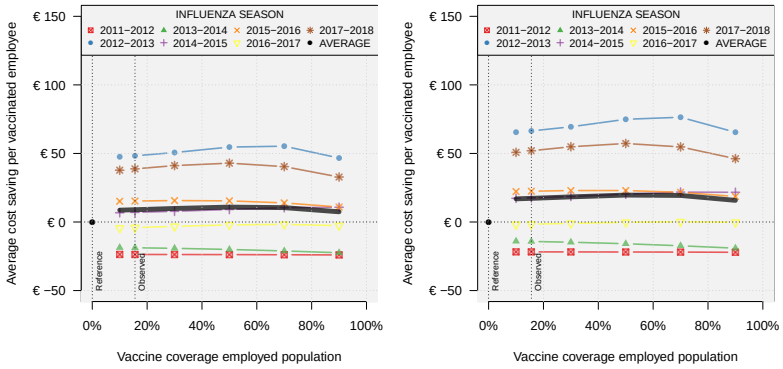
Reporting rate of 60%. If we assumed that the reported incidence accounted for only 60% of the total symptomatic incidence, more cases could potentially be saved and the average cost-savings increased up to €20 per vaccinated employee. For the seasons 2011-12, 2013-14 and 2016-17 a lower reporting rate did not significantly influence cost-savings since these seasons were either low in cases or the vaccine had only a very limited effectiveness.

Reporting rate of 80%. When we assumed that the reported incidence accounted for 80% of the total symptomatic incidence, the average net-benefit decreased. Indeed, employee vaccination in 2016-17 would have caused a net-loss, whereas it was found to be cost-neutral in the conservative scenario. On average, the net-benefit was lower but remained positive at all coverages.

Increased vaccine effectiveness. If we fixed vaccine effectiveness to the reported, age-specific maxima between 2011 and 2018, we observed large increases in the net-savings. As such, employee vaccination would have been cost saving for all seasons up to a coverage of 50%. For two seasons, we predicted a net-cost for an employee coverage of 70% and above. Up to a coverage of 50% employers saved on average more than €40 per vaccinated employee. In total, the net-benefit could have been up to €100 million at a coverage of 70%. Additional vaccination would imply a lower return since the marginal costs exceed the marginal benefits in a population that is already highly immunized. That is, given that vaccines were assumed more effective in this scenario, herd protection effects kicked in sooner. As such, the average net-benefit per employee started decreasing at lower vaccine coverages compared to the reference scenario.

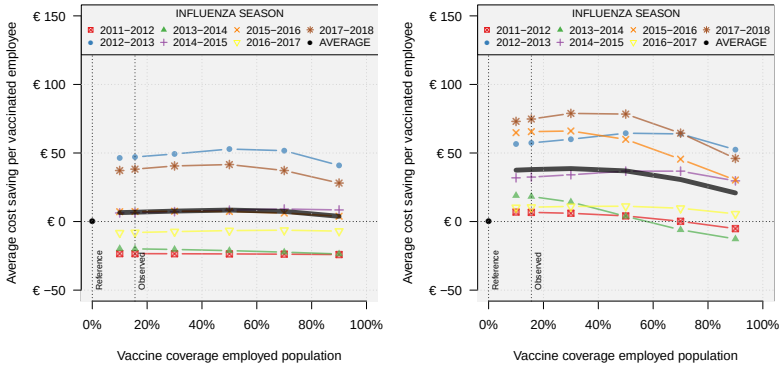
Indirect cost of absenteeism. The scenario in which we included an indirect cost of absenteeism equal to the direct cost of absenteeism resulted in higher cost savings. On average, the cost-benefit would have been up to €50 per vaccinated employee, with a maximum of €150 in the season 2012-13.

Seasonal force of infection. When the seasonal nature of influenza transmission was not taken into account, we estimated an average net loss. While vaccination still delayed the peak of the infection, it had a lower impact on the number of cases. As a result, the model predicted many cases in summer. This is in contrast with the literature on seasonal influenza dynamics in temperate climate countries such as Belgium [387].



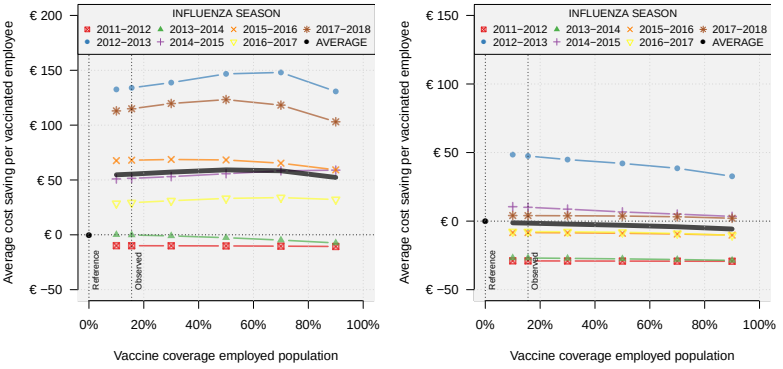
(a) Conservative scenario

(b) Reporting rate 60%



(c) Reporting rate 80%

(d) Maximum VE



(e) Indirect costs of absenteeism

(f) Constant force of infection

Figure 7.6: Scenario analysis of the predicted cost-savings per vaccinated employee per season.

Vaccine incentives

The average daily wage in Belgium was about €300 between 2011 and 2018. Given that the average net-benefit per vaccinated employee in the conservative scenario did not exceed €60 for any season-coverage combination, it was never found beneficial to reward vaccinated employees with an extra day off. At an average net-benefit of €10 per vaccinated employee, there is only a limited financial margin to create incentives for employees to accept vaccination. Furthermore, none of the univariate scenario analyses predicted cost-savings in the range of the estimated cost for a day off. Only a combination of lower reporting rates with increased vaccine efficacy and/or considering indirect costs increases the average cost-saving per employee and, as such, the financial margin to create incentives for employees.

7.4 Discussion

We simulated influenza vaccination as an employer-funded intervention and calculated the averted costs of symptomatic employees interrupting their professional activities. We started from the observed coverage in Belgium and predicted what the impact would have been of increased coverage levels. We found that workplace influenza vaccination was on average cost saving using conservative model assumptions. Substantial differences between seasons were found, implying that the decision for employers to vaccinate their workforce is an annually recurring gamble, which could result in significant losses or gains. This is because some seasons tend to be mild with very few cases (such as in 2011-12) or, in some seasons, the vaccine strains were not well matched to the circulating strains. Note that the season-specific characteristics determined to the largest extent the average cost savings per vaccinated employee, as opposed to the vaccination coverage itself. As such, an employer's decision making process is to a large extent independent of what all other employers decide. When Belgian employers decide to give incentives to their employees they should limit the incentives to an amount between €7 and €11 per vaccinated employee, in order for the intervention to be cost-neutral, based on our conservative approach. Alternatively, they can give larger incentives to only a few vaccinated employees by using a lottery system. The maximum potential savings were estimated to be in the order of €32 million for all employers combined, assuming 70% vaccine coverage in employees. When comparing this to the current vaccine coverage of 16%, there is still a lot of money left on the table, especially in seasons with a high burden and a sufficiently high vaccine effectiveness.

Though currently not considered as a target group for influenza vaccination, employees can play a vital role in reducing the disease and economic burden of influenza. Vaccinating employees substantially reduces the number of cases at the workplace: directly, in vaccinated employees and indirectly in coworkers through herd immunity, thereby reducing absenteeism. Moreover, we observed positive externalities – of which the costs are borne by the employers – to the unemployed population as well. Indeed, vaccinated employees have a lot of contacts with individuals of all ages as observed in Figure 7.2, such as their partner, children, parents and in general with members of their community. As such they can efficiently fulfill their role as barriers to pathogen transmission in society (i.e. herd protection). There are about 4.7 million working individuals in Belgium, which is only 41% of the total population. Even at an employee coverage of 50%, more than 100 000 symptomatic cases could be prevented on average per season in the unemployed population through indirect protec-

tion, which represents 1/3rd of all symptomatic infections in the unemployed population. If all employers would have motivated their employees to get vaccinated and reached 90% coverage, on average 78% of all symptomatic cases would have been prevented, of which almost 230 000 (-74%) cases in the unemployed population and 185 000 (-84%) cases among their employees. Employee vaccination is an interesting intervention from which society, employers and employees all reap the benefits. Previous research from the health care payer perspective found children, health care workers, pregnant women and the elderly to be important target groups for influenza vaccination in Belgium, rather than the general working adult population [30, 38]. However, from the employers' perspective, including the cost of absenteeism, the cost-benefit results change.

Government subsidies can be pivotal to encourage employers to provide and stimulate influenza vaccination at the workplace. Especially so to decrease the losses in seasons with a net-loss, such as the seasons 2011-12 and 2012-13. Given the low cost of vaccination at the workplace (around €36 per vaccinated employee) and the spill-overs to society, employees could serve as an important target group and provide a safety net for vulnerable subgroups of the population and those that cannot receive the vaccine for medical reasons.

We stress the importance of incorporating social contact patterns for healthy and symptomatic individuals. Reduced social contact behavior for symptomatically infected employees has a significant, dampening, influence on the spread of seasonal influenza [349]. The reduction in transmission could be even larger if susceptible employees also limit their social contacts when seasonal influenza peaks. Teleworking, for example, could be interesting for employers to reduce the prevalence of seasonal influenza at the workplace and reduce absenteeism. Teleworking is unfeasible in a number of sectors and industries, but it was estimated to be, at least partially, possible for 50% of the employees in the US [4]. Interestingly, people that do come to work when they are symptomatically infected, are also less productive [365], reinforcing the importance of staying home when showing influenza symptoms.

This paper, documents to our knowledge the first economic evaluation of employee vaccination using a dynamic transmission model and adaptive contact behavior. Lee et al. [221] split their analysis into cost-benefit analyses for the 22 major occupational groups in the US and found influenza vaccination to be cost-saving for the employer for serologic attack rate scenarios of 20% or higher (i.e. pandemics). However, they did not take into account asymptomatic cases and a reduced transmission of influenza when symptomatically infected em-

ployees stay home. The majority of non-placebo-controlled, non-randomized studies that were performed in single companies also found cost-saving results for the employer. A study at a Malaysian petrochemical company concluded that workplace vaccination accrues both financial and health benefits, and that financial benefits increased proportionally to vaccination coverage [345]. Similar studies were performed at a financial services company in Essex, UK [223] and a manufacturing company in Minnesota, US [290]. All of these studies found vaccination to significantly reduce absenteeism. However, employees were vaccinated on a voluntary basis in these studies, requiring caution when interpreting the results, as they are prone to selection bias. Burckel et al. [54] performed an economic modeling study using employment data from a pharmaceutical-chemical company in Brazil. They estimated vaccination to be cost saving at $35.45 in 1997, assuming a rather high vaccine efficacy (between 70% and 89%). In sensitivity analyses, the break-even vaccine-efficacy was found to be 32.5% [54].

The study of Bridges et al. [44] found that if the vaccine strains matched with the circulating strains and the vaccine effectiveness was 86%, workplace vaccination would reduce the lost workdays by 32% per vaccinated employee. However, the economic analysis of such a vaccination program resulted in a net cost of $11.17 per person, compared to no vaccination. When the strains differed, the societal cost increased to $65.59 per person and no decrease in absenteeism was observed. As such, the authors conclude that "vaccination of healthy adults younger than 65 years is unlikely to provide societal benefits in most years" [44]. Another clinical trial with trivalent nasal live attenuated influenza vaccine (LAIV) [284] reported a decrease of 18% in work loss and a break-even cost of $43.07 per person vaccinated. None of these studies took reduced social contact behavior into account.

In the scenario analysis, we noticed the relatively high importance of vaccine effectiveness. The vaccine effectiveness that was used in the conservative scenario, derived from the I-MOVE study [204], is rather low compared to vaccine efficacy reported in the literature [302]. The economic value of innovative vaccines against seasonal influenza, such as a universal flu vaccine, highly depends on their effectiveness. Moreover, there are no guarantees that the industry would be able to supply an additional 4 million vaccines at current production capacities.

This study is limited by the uncertainty on influenza incidence and vaccine effectiveness. We performed scenario analyses to handle parameter uncertainty and present a range of possible outcomes, though a single estimation whether

employer funded vaccination is cost-saving is lacking. Other parameters, such as the relative infectiousness of asymptomatic cases, background immunity and the proportion of symptomatic cases have been estimated based on age-specific incidence. We performed a extensive parameter estimation to prevent local optima, but more data on one of these parameters would improve the estimation of others due to correlations. The age categories in our transmission model were restricted to the data on social distancing due to symptomatic illness from the UK. Additional data on symptomatic contact behavior in different countries would improve the accuracy of transmission models in general. Finally, additional epidemiological data on the influenza incidence and the correlated absence at work with and without vaccination or teleworking, would improve this cost-benefit analysis.

In conclusion, we performed a cost-benefit analysis of employer funded influenza vaccination using a dynamic transmission model. We used Belgian data and observed large between-season differences in terms of incidence, vaccine efficacy and return on investment. We compared the cost of prevention with the cost of employee absenteeism and found that employer funded influenza vaccination was on average cost-saving between 2011 and 2018. The impact on society as a whole is substantial through herd immunity effects and even more promising with next-generation influenza vaccines [279].

7.5 Acknowledgments

We thank Sciensano for providing the ILI+ data in order to fit our model. We are indebted to Esther Kissling and her colleagues at the I-MOVE study for providing the vaccine effectiveness data. Moreover, we acknowledge support from the Antwerp Study Center for Infectious Diseases (ASCID) and the Flemish Research Foundation (FWO, project no. G043815N and a postdoctoral fellowship awarded to LW). We are grateful to the High Performance Computing core facility CalcUA which is embedded in the Flemish Supercomputer Centre (VSC).

Table 7.1: Model parameters and notation. Parameter values are based on literature, assumptions or presented by their initial ranges in the parameter estimation (see text).

Notation	Parameter	Value	Source
Transmission model			
	Age groups (years)	[0-4], [5-19], [20-44], [45-64] and 65+	
	Average population size (2011-2018)	637951, 1888883, 3629810, 2994236, 1977824	[371]
$1/\gamma$	Incubation period (days)	2.0	[349]
$1/\theta$	Latent period (days)	1.5	[349]
$1/\sigma^s$	Clinical infected period (days)	5.6	[349]
$1/\sigma^a$	Subclinical infected period (days)	1	[349]
	Number of infected cases introduced in the population to start the simulation	10	Assumption
ϕ	Proportion symptomatic	Initial range: 0.10 - 0.90	Estimated
q^s	Proportionality factor symptomatic cases	Initial range: 0.05 - 0.095	Estimated
q^r	Relative infectiousness of asymptomatic cases	Initial range: 0 - 1	Estimated
X	Background immunity acquired by previous infection or immunization (population fraction)	Initial range: 0 - 0.50	Estimated
t_i	Introduction of infectious cases into the dynamic model	Initial range: week 30 - 3	Estimated
q^a	Proportionality factor asymptomatic individuals	$q^a = q^s * q^r$	
	Reporting rate	70% (in scenario analysis 60% and 80%)	[368]
μ	Vaccine coverage unemployed population by age group	1.90%, 2.73%, 10.90%, 21.25%, 59.63%	[386]
μ	Vaccine coverage employed population	16% (weighted average by age)	[386]
ϵ	Vaccine effectiveness	see Table 7.2	[204]
Economic analysis			
	Average gross monthly income per season (from 2011-2012 till 2017-2018)	€3192, €3258, €3300, €3414, €3445, €3489, €3558	[372]
	Direct cost absenteeism (per day)	0.086 x average gross income	[418]
	Indirect cost absenteeism (per day)	0 (scenario analysis: 1x direct cost absenteeism)	Assumption
	Vaccine cost per vaccinated employee including administration	€17.30	[261]
	Productivity loss per vaccine administration (hours)	0.5	Assumption
	Indirect cost per vaccinated employee	0.5 x direct cost absenteeism per day / 7.60	Assumption
	Total cost per vaccinated employee	€35.33 – €37.43	Calculation
	Average no. of working days per week	3.9063	Calculated from [373, 401]
	Employment rate by age group	0%, 1.42%, 71.95% , 59.39% , 0%	[374]

Table 7.2: Vaccine effectiveness against any influenza type by age group and season. The mean vaccine effectiveness is shown with the upper and lower limit of the 95% confidence interval. The estimates for 2011-12 are reported in three age groups due to data spareness.

Season	Age group	Effectiveness (%)
2011-12	All ages	5.3 [-21.0 ; 25.8]
	0-19 years	15.2 [-73.1 ; 58.5]
	20-64 years	19.9 [-12.0 ; 42.7]
	65+ years	0.2 [-60.5 ;37.9]
2012-13	All ages	50.0 [37.0 ; 60.3]
	0-19 years	35.6 [-1.8 ; 59.2]
	20-44 years	63.9 [34.2 ; 80.2]
	45-64 years	48.5 [23.8 ; 65.3]
	65+ years	58.5 [29.8 ; 75.4]
2013-14	All ages	23.2 [-4.7 ; 43.7]
	0-19 years	8.0 [-84.8 ; 54.2]
	20-44 years	20.2 [-62.5 ; 60.8]
	45-64 years	23.1 [-31.9 ; 55.1]
	65+ years	42.1 [-10.9 ; 69.8]
2014-15	All ages	26.6 [13.6 ; 37.6]
	0-19 years	28.1 [-2.2 ; 49.5]
	20-44 years	44.7 [12.4 ; 65.2]
	45-64 years	31.3 [8.6 ; 48.4]
	65+ years	3.9 [-30.8 ; 29.4]
2015-16	All ages	19.3 [4.0 ; 32.2]
	0-19 years	-10.6 [-58.5 ; 22.8]
	20-44 years	36.2 [-1.7 ; 60.0]
	45-64 years	37.1 [13.9 ; 54.0]
	65+ years	8.2 [-33.0 ; 36.7]
2016-17	All ages	28.4 [17.5 ; 37.9]
	0-19 years	33.1 [1.0 ; 54.7]
	20-44 years	45.2 [20.6 ; 62.1]
	45-64 years	29.0 [8.7 ; 44.8]
	65+ years	17.7 [-4.5 ; 35.1]
2017-18	All ages	30.0 [19.8 ; 39.0]
	0-19 years	52.1 [33.1 ; 65.7]
	20-44 years	50.8 [27.3 ; 66.7]
	45-64 years	19.4 [-1.7 ; 36.1]
	65+ years	25.4 [4.8 ; 41.5]

Table 7.3: Scenario analyses

Parameter	Conservative scenario	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Reporting rate	70%	**60%**	**80%**	70%	70%	70%
Vaccine effectiveness (ϵ)	Seasonal	Seasonal	Seasonal	**Max**	Seasonal	Seasonal
Indirect cost of absenteeism	None	None	None	None	**Labor cost**	None
Force of infection ($z(t)$)	Seasonality	Seasonality	Seasonality	Seasonality	Seasonality	**Constant**

CHAPTER 8

General discussion

This discussion is written in April 2020, in the midst of the COVID-19 pandemic, with more than 3 million cases globally and the official global death toll at 200,000 on 28 April 2020. It has increasingly become clear that human behavior cannot be neglected in the dynamics of infectious diseases and the ultimate burden of the disease [404]. Indeed, in the absence of antivirals or treatment, or a vaccine, most interventions to prevent COVID-19 infections are centred around social distancing (e.g. staying at home), increased hygiene (e.g. hand washing), wearing face masks etc., all of which rely on the public's willingness to adapt their behaviour [66]. Note that, as opposed to what many BCMs assume, during the COVID-19 pandemic, a lot of prevention measures – and thus the public's behavioral changes – are legally enforced. As such, the focus of behavioral research in the context of infectious diseases should be extended from solely voluntary prevention behavior to hosts' compliance with government interventions [45].

At the same time, this outbreak shows that behavior changes serve a greater purpose than solely preventing outbreaks. Indeed, the current mitigation strategies aspire to: i) 'flatten the curve' not to overload hospitals, ICU wards and respirators [13, 26, 417], ii) buy time for antivirals and vaccines to become available [13, 26, 417], iii) protect vulnerable individuals with underlying health conditions that are prone to severe infection [13, 26], iv) reduce the burden of disease by pushing the effective reproduction number below 1 [13], v) provide a safe working environment – with special attention for essential industries (e.g. hospitals, pharmacies, the food industry etc.) [299], and many more. The feasibility of reaching these targets is contingent on the public's behavior and compliance.

Vaccination against vaccine-preventable diseases has similar objectives: reduce the burden of the disease, providing a safety net for vulnerable individuals that cannot receive vaccination etc. As we noticed in the DCE studies with

respect to vaccination behavior (described in Chapters 3 to 5), people are not purely self-centred individuals that take rational decisions in order to maximize their own well-being. That is, individuals tend to follow social norms and are prone to peer influence [416]. When social distancing, increased hand-washing and wearing face masks will be perceived as the social norm, this will likely incentivize others to adopt such behaviors. At the same time, we know that when vaccines become available, some individuals might still decide against it, e.g. because they perceive the disease as being mild, or they may be afraid of adverse reactions [291].

At this point, it remains uncertain whether infected individuals acquire long-term immunity agains the SARS-Cov-2 virus [300]. In the absence of antiviral treatments and a vaccine, the most important intervention we can rely on today, is individuals' behavior change. Even when vaccines do become available, i) it is unlikely that the production capacity is sufficient to vaccinate enough individuals to acquire herd immunity in the near future [244] – and thus behavioral interventions will still be at place, and ii) individual behavior will remain crucial in terms of vaccine acceptance, hesitancy or refusal.

Behavioral challenges in infectious disease transmission remain. Not only in today's COVID–19 pandemic, but also in future epidemics and for vaccine-preventable diseases that require sustained immunization efforts. In the remainder of this discussion, we will elaborate on the main findings of this thesis, the strengths and limitations, future work and a general conclusion.

8.1 Main findings of this thesis

We opted to discuss the findings of this thesis in a more general sense, linking the findings of the different chapters in a selection of overarching topics we deemed essential to elaborate on. For a discussion of chapter-specific findings, we refer to the discussion sections included at the end of each chapter.

First of all we discuss how behavioral change models have evolved from rational and strictly theoretical game theory models to more realistic models including social norms and peer influence. Next, we elaborate on how data scarcity has been a challenge to the development of superior BCMs and how we generated data to parameterize such models. In the remainder of this discussion, we elaborate on the risks of neglecting behavioral change in transmission models and the health economic analysis of infectious disease interventions and why researchers and policymakers should look beyond vaccine hesitancy in their efforts to increase – or maintain high levels of – vaccination coverage.

Characterizing vaccine behavior: From homo economicus to homo sapiens?

The idea of strategic interaction and free-riding behavior in the context of vaccination – or infectious disease prevention in general – stems from game theory. Game theory is a mathematical approach to decision-making between perfectly rational 'participants' that maximize their 'pay-offs' by incorporating each other's decisions when making their own (see Gibbons [137] for an introduction to game theory). A classic application to game-theory is the 'prisoners' dilemma' [137]. In game-theoretical applications of vaccination behavior, such as the model of Bhattacharyya and Bauch [32], it is assumed that individuals 'will take a free ride' and delay or refuse vaccination while relying on herd immunity, i.e. the indirect immunity provided as an externality of the vaccination decisions of others [114]. Individuals are typically represented as rational decision-makers – also referred to as 'homo economicus' – that aim to maximize an economic objective function.

We systematically reviewed behavioral change models (BCM) for infectious disease transmission in Chapter 2. We introduced a BCM classification based on how information is translated into behavioral change. Models assuming perfectly rational individuals and 'free-riders' have become obsolete. Indeed, an evolution has been observed in the literature towards more realistic models – characterizing decision-makers as 'homo sapiens' that are prone to behavioral flaws – including the impact of social norms, rumours or peer influence

[411]. For example, in the BCM by Shim et al., altruistic motives in vaccine decision-making have been incorporated [362]. They included survey data on influenza vaccination and found that including altruistic motives can shift vaccination coverage towards the 'community optimum', thereby significantly reducing total cost, morbidity and mortality in the community [362]. Observational research confirms the relevance of altruism in the context of vaccination decisions [153, 364, 421]. Other studies have integrated imitation behavior to BCMs maximizing an economic objective function. Often a Fermi function is added to such analyses, which incorporates the idea that individuals tend to do what they did in the past – also referred to as the status quo bias [395]. In the majority of today's BCMs some form of irrational behavior has been introduced [411].

It is striking that behavioral change theories – such as the health belief model or the theory of planned behavior introduced in Chapter 1 – are insufficiently explored in the characterization of prevention behavior in epidemiological BCMs. That is, we are only aware of very few studies that explicitly build on the health belief model in the characterization of individuals' preventive behavior in a BCM (e.g. [108, 190]). Yet, the knowledge and experience from such behavior change theories could be instrumental in resolving at least some of the challenges BCMs are facing, such as predicting the response to interventions and health campaigns, or assessing the extent of explicitly modelling behavior [128]. Whereas social norms are often explicitly taken into account, free-rider incentives were, to our knowledge, never described in any behavior change theory in the context of medical psychology or anthropology. On the other hand, one could argue that such incentives are implicitly integrated in the "perceived susceptibility" or "behavioral beliefs" constructs. That is, prevalence-elastic demand, as attested in the DCE studies, connects vaccination coverage in society to vaccination intentions via perceived susceptibility to disease (as described in Chapter 6). Nevertheless, susceptibility to disease was, in this thesis, always found less influential in vaccination decisions compared to the severity of the disease [416].

The importance of including social norms – or peer influence – in BCMs was confirmed in all DCE study samples described in Chapters 3 to 5. That is, population (or global) and local coverage estimates were consistently found to positively influence vaccines' utility, such that vaccines that already reached a high coverage were found to be preferred to vaccines with a lower coverage in the target population [172, 413, 414, 416]. This is in line with other DCE studies in Australia [154] and in the US [138]. One could argue that free-riding behavior was implicitly observed through VPD frequency specified within the

burden of disease attribute. That is, individuals attached a lower value to a vaccine when the VPD is less prevalent. However, for all PML models in this thesis, we found disease frequency to be relatively unimportant compared to disease severity. Even though a behavioral feedback mechanism was observed between disease prevalence and vaccine utility, it remains unlikely that explicit free-rider incentives are to be held responsible.

This behavioral feedback mechanism was included in the BCM application to measles in Flanders in Chapter 6. In addition to disease frequency, we included endogenous vaccine utility variables for – the perception of – disease severity and for population coverage. Vaccine effectiveness, VRSE and vaccine accessibility were added as exogenous parameters to measles vaccine utility. As such, in our data-driven approach, we characterized human vaccination behavior as a multi-criteria decision including both rational (e.g. time and monetary cost) and irrational (e.g. peer influence) traits. With respect to the categories proposed in Chapter 2, this model would be categorized under 'information threshold' and 'information as a dynamic parameter'.

The findings of our DCE studies and other observational research, together with the dynamics of realistic BCMs, can be helpful in guiding health policies with respect to vaccination. Policymakers and healthcare workers should communicate high vaccine coverage levels to make it clear that vaccination is still the norm. This can be helpful in sustaining high – or reaching increased – vaccine coverage [216]. A vaccination campaign in combination with communication about uptake can trigger a positive dynamic and persuade hesitant individuals to accept vaccination. Beware that social norms or peer influence also work in the opposite direction such that a sudden decrease in vaccine coverage can result in suboptimal coverages in the years to follow [413]. In addition, stressing the need for high coverage and herd immunity as a safety barrier to protect vulnerable individuals from infection can stimulate vaccine uptake. Indeed, Vietri et al. [421] found social responsibility to be an incentive for vaccination in a qualitative study in the US.

Beware that the nature of behavior change included in Chapter 7 is different than the behavioral changes in the other chapters in this thesis. That is, in the economic analysis of workplace influenza vaccination, we incorporated dynamic behavior in response to illness. In contrast, we focussed on prophylactic behavioral changes in the rest of this thesis. Nevertheless, staying at home when showing signs of influenza can be an effective measure to dampen disease spread [208]. At least part of the reduction in contacts can be attributed to the physical inability to go about normal activities. Indeed, the Health-

Related Quality of Life (HRQoL) in terms of mean health utility in influenza outpatients was estimated at 0.6142, whereas mean utility for inpatients was estimated at 0.5851 [463]. However, hospitalization rates were estimated to be relatively low (between 0.184 and 0.644 per 1000) for people of working age [473]. Another factor that could have an impact on limiting social contacts could be the fact that, in Belgium, many workplaces require a sick note from a GP within the first week of absence [400]. Finally, another reason for limiting social contacts might be that individuals have an altruistic motive and want to protect vulnerable individuals from infection. Future social contact studies should query for symptomatic individuals' motivations for limiting their social contacts. This information would be useful for policymakers and to design interventions to convince people of the benefit of staying home when they are symptomatically infected.

Behavioral change data

The need for data to parameterize behavioral change models has been echoed in the literature for the past decade [127, 128]. In Chapter 2, we systematically reviewed behavioral change models for infectious disease transmission and found that many BCMs remain to a large extent theoretical, lacking data-driven parameterization and a validation process [411]. That is, only 15% of the included studies used any data for parameterization or validation [411]. Weston et al. [438] conducted a similar review including 42 papers published between 2002 and 2015. They found about half of the studies they included to have incorporated behavioral data [438]. More recently, some advances have been made in the field with respect to data-driven behavior. For example, Gozzi et al. [143] proposed the use of Influweb data from Italy to characterize behavioral changes as a response to seasonal influenza. They analyzed the responses of the survey distinguishing between three behavioral classes: no, only moderately, and significant change in behavior [143]. Data from the InfluenzaNet network are promising to quantify such behavior changes in relation to seasonal influenza transmission and is collected in a large set of countries: including Spain, France, Italy, The UK, Germany, Sweden, Ireland, Portugal, Denmark and Switzerland [304]. In addition to survey data, other sources of behavioral data can provide promising opportunities to parameterize BCMs. For example, social media data proved to be useful to assess vaccination sentiments as demonstrated by Salathé et al. [342] and Kang et al. [189]. Indeed, the internet and social media were identified as strong platforms to spread false information about vaccine side-effects, conspiracy theories and other vaccine controversies [214].

The DCE studies in Chapters 3 to 5 provide useful data to parameterise BCMs and present additional insights in the relative importance of vaccine characteristics in people's vaccine decision making process. The use of DCE estimates in the development of BCMs is to a certain extent bound to characterizing vaccine behavior as a multi-criteria decision [413]. Preferences have been collected in representative samples in five countries and can be applied in BCMs for a selection of diseases for which a vaccine is available. Yet, in the BCM application for measles in Flanders, described in Chapter 6, we observed quite some assumptions still needed to be made. Even though we have retrieved detailed data on how changing risk perceptions would influence a vaccine's utility, additional information is required on how risk perceptions change in response to disease dynamics and how alterations in vaccine utility translate to increases or decreases in vaccine uptake. We recommend researchers to exploit available behavioral data to a maximum extent in parameterizing their models, while communicating transparently on the assumptions taken for parameters where data is lacking.

The studies by Terris-Prestholt et al. [388] and Quaife et al. [319] on HIV prevention measures in South Africa provide a valuable framework for fully integrated models evaluating infectious disease interventions. They included DCEs to parameterize uptake and substitution of HIV prevention in the health economic evaluation of topical pre-exposure prophylaxis (TPrEP) and candidate multi–purpose prevention technologies (MPTs) [319, 388]. However, some inherent vaccination characteristics warrant a different approach when applying such models to the economic evaluation of vaccination programs. Among others, vaccination requires a binary decision inducing a relatively long protection against the disease, there are only few alternatives available in terms of pharmaceutical prevention measures, and vaccination has been – and remains to date – challenged by vaccine controversies [105].

With respect to the DCE studies described in this thesis, the model estimates cannot be directly applied to parameterize a vaccination intention (cfr. the theory of planned behavior) or a vaccination health belief model. Nevertheless, we believe an updated DCE design, eliciting preferences in accordance with the constructs of the health belief model, could be useful to parameterize an HBM for vaccine uptake. Logworth values could be instrumental in determining weights for the theory's individual constructs, whereas attribute level estimates could be informative to asses vaccination likelihood or probability. In addition, such a model could introduce heterogeneity, by estimating model interactions (e.g. based on demographic variables or past experiences with vaccination or infection). A number of HBM constructs were integrated in the

DCEs described in Chapters 3 to 5. That is, we queried for preferences related to perceived severity (severity specified in the burden of disease attribute), perceived susceptibility (frequency of the disease specified in the burden of disease attribute), perceived benefits (vaccine effectiveness), and perceived barriers (accessibility and VRSE attributes). The data we gathered, are thus lacking preferences about "cues to action" and "self-efficacy" which are included in the HBM. In contrast, the coverage attributes would be useful to parameterize the importance of "normative beliefs", which is an essential construct in the theory of planned behavior [6]. In all but one study (outlined in Chapter 3), we only queried about mild side-effects: this means we cannot parameterize perceptions of severe side-effects, which have had a long history in the field of vaccination [177]. Perceptions on severe VRSE would most likely be more influential in people's choices [338, 416]. Yet, even in an updated DCE design, which matches model constructs to the parameterization of existing behavioral change theories, quite some challenges in terms of data requirements remain. That is, we would still need to gather data on the relation between disease dynamics and changing risk perceptions. The COVID–19 pandemic, has nevertheless created a unique opportunity to collect data about individuals' perceptions. Indeed, a qualitative study about risk perception in Finland has been constructive in tailoring risk communication and influencing behaviour change [242].

Social contact data are intrinsically connected to close-contact infections and are relatively easy to retrieve by means of social contact surveys [169, 276]. Social contact data have increasingly been integrated in the parameterisation of infectious disease transmission models [165, 406, 425]. In addition, prophylactic social distancing behavior can be parameterized by means of such data, as well as decreased social contact behavior resulting from symptomatic infection. The latter was demonstrated in the analysis of influenza workplace vaccination in Chapter 7.

In Chapter 2, we found that the 2009 influenza pandemic has been an opportunity for increased data collection on behavioral changes. When outbreak-driven data collection will take place to a similar extent during the current COVID-19 pandemic, we can expect a lot of behavioral data to become available that bring additional insights on the relation between behavior and disease dynamics. In addition, these COVID-19 behavioral changes will be useful to parameterize outbreaks of other close-contact infections with similar characteristics. Data on such behavioral changes (e.g. improved hand hygiene and social distancing) as a result of fear of COVID-19 have already become available [45, 46, 160, 451]. Note that behavioral data in the context of COVID-19 are

likely prone to government interventions. As such, these data capture both spontaneous voluntary behavioral changes as well as compliance to behavioral interventions imposed by the government. Note that the latter type of models was not included in the analysis in Chapter 2.

In the absence of adequate behavioral data, theoretical assumptions might still be useful. Ignoring behavioral changes in the transmission of infectious diseases and evaluation of prevention measures is probably worse than making assumptions within a theoretical model in the first place. Transparency and communication on assumptions and limitations remains key.

The risk of neglecting behavior

In the economic analysis of workplace influenza vaccination, described in Chapter 7, we implemented data-driven adaptive social contact data for symptomatically infected individuals [109]. Note that this type of behavioral change fundamentally differs from preventive social distancing behavior. In the former case, individuals alter their behavior as a result of experiencing symptoms and thus are not able to go to work, see their friends an family etc., whereas for prevention behavior this is a deliberate choice to reduce the odds of contracting infection. Studies that fail to include altered contact behavior as a result of infection, most likely overestimate the impact of intervention measures. Data on altered contact behavior when experiencing symptoms can – as discussed in earlier paragraphs – be collected through the use of social contact surveys, in a similar fashion as the one performed by Eames et al. [109] or Mossong et al. [276]. For more details about social contact surveys, we refer to a recent systematic review by Hoang et al. [169].

In Chapter 6, we focussed on preventive behavioral changes instead. In this proof-of-concept study, we integrated several behavioral scenarios with significant impact on the future course of measles disease in Flanders. Introducing a vaccine scare was sufficient to drive immunity levels below the required threshold and trigger sustained outbreaks every few years. Similar dynamics have been observed with respect to measles and pertussis in England & Wales following the whole cell pertussis and MMR vaccine scares [23]. In countries or regions with lower vaccine coverage, endogenous BCM dynamics may be sufficient to reintroduce endemic transmission (e.g. due to a low risk perception of measles severity). As of August 29, 2019, four European countries lost their elimination status: Albania, Czechia, Greece and the UK, while endemic measles transmission remains in 12 countries of the region [289]. The surge of measles cases in the European region was found to continue with more than

80,000 cases in the first half of 2019 [289]. This resurgence is at least partially attributable to suboptimal measles coverage in European countries [119]. This is to say that the successes of interventions such as vaccination are in essence dependent on human behavior and the public's willingness to follow recommendations. Neglecting human prevention behavior and assuming a constant vaccination coverage based on expert opinion or past coverage levels can lead to inaccurate predictions. Therefore, we believe it is essential to include behavioral change features in modelling infectious disease – to the very least in sensitivity analysis to explore behavior-induced model uncertainties.

The introduction of BCMs in transmission models has been growing as described in Chapter 2. However, the implementation of BCMs in the economic analysis of infectious disease interventions is still scarce. By neglecting intervention uptake in economic analyses, real-life outcomes may drastically differ with model based estimates due to non-linearities between prevention measures and disease burden. Indeed, due to positive externalities (i.e. herd immunity), the relation between vaccination coverage and ICERs is non-linear. When vaccine coverage remains suboptimal, or susceptible clusters remain in parts of society, outbreaks can still occur and costly responses such as contact tracing or increased vaccination efforts are required to counter endemic transmission [145]. The cost of recent measles outbreaks in The Netherlands (2700 reported cases), The UK (2458 reported cases) and The US (107 confirmed cases) were estimated at $4.7 million, £4.4 million and between $2.7 million to $5.3, respectively [136, 301, 380]. Note that these costs could have been avoided when a sufficient vaccination coverage ($> 95\%$) would have been reached in these populations. Indeed, measles disease satisfies all biological conditions to reach eradication [294]. As such, dynamic vaccinating behavior should be taken into account to ensure realistic predictions of interventions and not to underestimate economic costs. Because in the end, the success of interventions is dependent on human behavior.

DCE-based uptake behavior has been successfully integrated in the impact analysis and cost-effectiveness analysis of HIV prevention measures in South-Africa. Terris-Pretholt et al. performed a DCE-based impact analysis of TPrEP and found that "DCE-based impact predictions varied by up to 50% from conventional estimates and provided far more nuanced projections" [388]. We refer to the work of Quaife et al. for an integrated model using DCE-based uptake of HIV prevention measures in a health-economic analysis [319].

Looking beyond vaccine hesitancy

A lot of research on suboptimal vaccine coverage is focussed on interventions addressing 'vaccine confidence', 'vaccine acceptance' or 'vaccine hesitancy' [104]. "Vaccine hesitancy refers to delay in acceptance or refusal of vaccines despite availability of vaccination services. Vaccine hesitancy is complex and context specific, varying across time, place and vaccines. It is influenced by factors such as complacency, convenience and confidence" , as defined by a WHO SAGE group on vaccine hesitancy [247]. At the same time the SAGE group recognized that strategies beyond those targeted at addressing vaccine hesitancy need to be developed in order to reach high vaccine demand [247].

By means of a DCE in five countries, we aimed to look beyond vaccine hesitancy and quantify the public's preferences with respect to different vaccine characteristics. That is, the studies described in Chapter 3 to 5 are not focussed on specific subsamples that delay or refuse vaccination, but instead quantify preferences with respect to vaccination in the population at large. In addition, we investigated preference heterogeneity by estimating covariate interactions. Looking at normalized logworth estimates from DCEs in different subsamples, we found that vaccination is a multi-criteria decision, i.e. vaccines' utility is determined by a combination of characteristics. More specifically, we found vaccine effectiveness, accessibility and burden of disease to be the most important vaccine attributes, followed by population coverage, mild VRSE and local coverage [416].

Vaccine effectiveness

In Chapter 5, vaccine effectiveness was found to be the most important attribute in vaccine decision-making in 5 out of 10 study populations. Fortunately, most routine vaccines are very effective and protect 85 to 95% of recipients [447]. As such, providing accurate and timely information about vaccine effectiveness can be helpful in stimulating vaccine demand.

In the BCM application to measles in Flanders – described in Chapter 6 – we held perceptions of vaccine effectiveness high and constant as an exogenous parameter. Vaccine utility would however drastically decrease if vaccine effectiveness would be perceived lower, which is to a certain extent the case for influenza vaccines. When the perception of vaccine effectiveness would decrease to 50% for the population at large, compared to 90%, vaccine utility would fall by a number higher than was observed in the vaccine scare scenario. Unsurprisingly, each year only 44% of the target group gets vaccinated against

seasonal influenza, whereas in the Belgian population at large, a coverage of about 20% is reached [386].

We analyzed the cost-benefit of workplace influenza vaccination in Chapter 7 and found vaccine efficacy to be essential in the scenario analysis. If influenza vaccines would have reached an effectiveness of about 50 to 60% in every season, vaccination would have been cost saving in all seasons [415]. We need better influenza vaccines to i) increase influenza vaccine coverage, thereby protecting vulnerable individuals in the population, ii) reduce volatility in employers' return on workplace influenza vaccination, iii) expand the opportunity to incentivize employees, and iv) to improve the general perception of all vaccines' effectiveness (i.e. as a positive externality to overall vaccine effectiveness perception). General vaccine effectiveness perception was found to be on the lower side in France – with 20% disagreeing that vaccines are effective [131]. In Belgium, the same study found 5% to disagree with the same vaccine effectiveness statement.

Accessibility

In Chapter 5, vaccine accessibility was found to be the most important attribute in 4 out of 10 populations: the 'oneself' groups in The Netherlands, France and Belgium and the 'youngest child' group in Belgium [416]. In addition, we found in the DCE study in Flanders, described in Chapter 3, that 40% of the respondents in the child group indicated that they do not question vaccination, it is just something they do when it is offered to them [413]. So just by offering vaccines conveniently, a substantial coverage can already be reached, irrespective of other vaccine characteristics. Therefore, policy-makers can stimulate vaccine uptake by making vaccines easily available at an affordable price.

Note that the relative importance of vaccine accessibility was highest in the adult populations deciding about vaccinations that would be administered to themselves. Ironically, in most healthcare systems, adults' vaccination services are organized in a less accessible way, compared to the vaccination for infants. Also for the Belgian healthcare system, where infant vaccination is usually organized through a system of well-baby clinics and school physicians, while adult vaccination usually requires a prescription, two visits to the GP, a visit to the pharmacy and a co-payments for both the GP visits and the vaccine [413]. Note that Tdap boosters are available at the GP at no cost for adults (except for the co-payment of the GP visit).

In Chapter 7 we looked into the economic evaluation of influenza vaccination on the workplace. Workplace vaccination was found to be, on average, a cost-saving intervention to businesses that – in addition – creates important externalities to society as a whole [415]. We discussed in earlier paragraphs how altruistic motives could be an extra incentive for working individuals to accept this vaccine [153, 364, 421]. In addition, workplace influenza vaccination is relatively cheap, comes with significant economies of scale and is very convenient for employees. The age of the vast majority of employed individuals warrants a better immune response to the vaccine, compared to the elderly [315]. Furthermore, employees are most likely part of a considerable social network – including individuals from different generations – in which the virus can spread. As such, they form efficient barriers to reduce transmission in the population at large [415]. Apart from yearly influenza vaccination, workplace vaccination can be valuable in reaching sufficiently high coverages for Tdap boosters, in catch-up campaigns or in the final steps of eradication efforts. Hence, we believe that workplace vaccination serves as an efficient system – that is yet insufficiently explored – to increase vaccine coverage in adults of which society, employers and employees all reap the benefits.

Vaccination remains attractive if it is offered at first contact with the vaccinator, while being offered to large groups simultaneously. Well-baby clinics and school-based vaccination programs remain crucial in reaching high coverages among infants and children. Yet, for adult vaccinations there is still a lot of room for improvement.

Burden of disease

DCE studies indicated that individuals prefer vaccines that protect against severe [338, 416] and frequent vaccine-preventable disease (VPD) [416]. In the French 'youngest child' group burden of disease was even found to be the most important attribute, as detailed in Chapter 5. While having a prominent role in almost all BCMs that we systematically reviewed in Chapter 2, disease prevalence was found relatively unimportant compared to disease severity among all study populations [416]. Vaccination is to a certain extent victim of its own successes. Individuals may not be able to imagine a world in the absence of vaccination since they are no longer – or only sporadically – confronted with VPD burden. As such, many will lack the ability of creating a realistic perception about VPD frequency and severity. Moreover, the benefits of vaccination are impossible to be evaluated from an individual perspective. At the same time (perceived) risks of side-effects are visible, even though these are mostly short lived and mild (e.g. swelling at injection site, mild fever

or headache) [103]. In addition, vaccination is prone to omission bias. That is, individuals tend to be more risk averse to action – vaccinating at the risk of VRSE – than inaction – not vaccinating at the risk of contracting a VPD [16, 94, 103, 327].

When individuals are confronted with VPD resurgence, apart from increased perception to disease susceptibility, they might perceive the VPD to be more severe as well. The latter was observed after a measles outbreak in France [392]. Both disease frequency as well as severity may feed into the behavioral feedback mechanisms and were introduced as endogenous behavioral features in the BCM for measles in Flanders in Chapter 6. In scenario analysis, we implemented a decay function with a lower limit of only 5% of the Flemish population perceiving measles as a severe disease. Even though the vaccination coverage was lower compared to the default scenario, it was insufficient to cause large outbreaks. Nevertheless, it remains crucial for healthcare workers to provide accurate and timely information about VPDs' burden of disease in order to align vaccine recipients' perceptions with reality.

Vaccine coverage, social norms and peer influence

We integrated data-driven peer influence for measles vaccination uptake in Flanders in Chapter 6 such that current vaccination decisions are influenced by the decisions of peers in the recent past. Population and local coverage were consistently found to be significant in vaccination decisions among all study populations [416]. In addition, we found estimates to be positive, rather than negative, indicating that decisions are driven by social norms rather than free-rider incentives. Linking back to the importance of social norms, peer influence and altruism in the context of vaccination, detailed in the first section of this discussion, it remains crucial to communicate that vaccination is still the norm.

Vaccine related side-effects (VRSE)

In Chapter 6, we simulated the impact of three vaccine scare scenarios: a temporary vaccine scare, a vaccine scare from the start of the simulation and a vaccine scare from the start followed by a suspension of the vaccine from the immunization schedule. The first two scenarios had a strong impact on vaccine utility and vaccine coverage causing recurrent measles outbreaks in the Flemish population. Note that in this model application, we applied the DCE estimates from the Flemish study (Chapter 3), where we did not specify, nor controlled for VRSE severity. Nevertheless, when VRSE were correctly specified – stating

severe VRSE as highly unlikely – they appeared relatively unimportant for all study subsamples, compared to other vaccine characteristics [416].

Even though vaccination has a long and rich history of controversies, and the level of controversy remains high today [177], vaccine choices are not solely determined by (the perception of) VRSE. Nevertheless, it is of great importance for healthcare workers to follow guidelines when confronted with vaccine hesitant individuals. The guidelines by Leask et al. provide a stepwise and tailored approach to communicate with such individuals [220]. The work of Healy et al. also proves useful to communicate with vaccine-hesitant parents in a non-confrontal way [163]. Communication may be focussed on individuals in the so-called "vaccine hesitancy continuum" as proposed by the WHO SAGE on vaccine hesitancy [296]. The role of healthcare workers remains crucial in providing honest information about parents' concerns with respect to vaccination.

8.2 Strengths and limitations

Systematic review on behavioral change models

We systematically reviewed behavioral change models for infectious disease transmission in Chapter 2. We started our analysis in 2010 where a previous review ended [127] and included 178 studies for a full text analysis. As with any systematic review, our search string strikes a balance between completeness and feasibility. It came to our attention that we did not retrieve some studies that would satisfy our eligibility criteria. Nevertheless, we provided important insights in recent advances in the field and identified notable challenges that remain.

Discrete choice experiments to quantify vaccination behavior

This thesis provides valuable insights in the quantification of vaccination behavior. We collected vaccination behavior data in a multitude of countries distinguishing between vaccination decisions in adults and vaccination decisions for individuals' youngest child. We assessed preference heterogeneity by systematically estimating covariate interactions for all DCE subsamples. Nevertheless, multiple testing issues may have played a role in the final selection of covariates included in each model. In addition, survey respondents, when filling out the DCE, had to make a decision between two vaccines. I.e. they had to assign a preference to one of the two described vaccines while not having the option to refuse vaccination.

DCE guidelines specify to perform a qualitative study (e.g. a focus group or interviews) in order to select attributes and attribute levels [74, 213]. We performed such a qualitative study in Flanders (described in Chapter 3) and kept a similar design for other study populations. By not performing a qualitative study for each study population, we might have missed importance attributes. A study by Determann et al. reports on such between-country disparities with respect to altruism considerations [92]. However, we decided to keep the DCE design equal in order to evaluate the impact of the same vaccine characteristics in a selection of countries. Moreover, when essential attributes would have been neglected in the DCEs, this would still provide useful insights in the relative importance between the attributes included.

DCEs query for stated preferences. That is, the participants make choices about vaccination in an artificially constructed situation: study participants sit behind a screen and are provided a narrowly defined information set. Nevertheless, no participant was ever actually inoculated after making a choice. There is a

lack of research assessing the external validity of DCEs. Recent studies by de Becker-Grob et al. found that a DCE could correctly predict influenza vaccine uptake when taking heterogeneity into account [86, 87]. A study by Lambooij et al. tested DCE validity in the context of hepatitis B vaccination and found a correspondence of 80% between stated and revealed preferences [212]. In addition, a systematic review and meta-analysis by Quaife et al. found DCEs to produce reasonable predictions of health-related behaviors. Nevertheless, the authors warn that there is a great need for further empirical research to externally validate DCE findings [318].

We did not include an attribute on the severity of VRSE in any of the DCE studies, which would be required to more accurately simulate a vaccine scare in a BCM application – such as the proof-of-concept described in Chapter 6. When comparing the DCE results from Flanders (Chapter 3) with the DCE results described in the multi-country study (Chapters 4 and 5), we observed the importance of specifying VRSE severity in DCEs. That is, the VRSE attribute importance shifted from being the most important attribute in the Flemish study, to one of the least important attributes in the multi-country study. We altered the specification of the VRSE in the latter study to the frequency of mild VRSE, keeping severe VRSE frequency at 'highly unlikely' in both attribute levels. In addition, VRSE severity was found to be of key importance in vaccine decisions in the UK [338].

Unfortunately, we did not include all model constructs for the health belief model, or the theory of planned behavior to fully parameterize either of these models. Additional data would be required to assess how information influences beliefs and, in turn, these beliefs affect attitudes or intentions, which in the end influence behavior.

Lastly, we did not include the recommendation by healthcare providers in any of our DCE studies. A characteristic that was found to be of great importance in a study by Dorell et al. [100].

A proof-of-concept to parameterize BCMs

Even though we used a data-driven approach to parameterize the behavioral change model introduced in Chapter 6, for a considerable number of parameters we still had to rely on assumptions. The BCM is currently limited to the attributes that were included in the DCE in Flanders in Chapter 3. If circumstances other than the vaccine characteristics included in the DCE would no longer hold, for instance the recommendation of GPs, this would not have an effect on the vaccine's utility level, vaccine coverage in the target group,

and disease dynamics. Moreover, in order to more accurately model measles transmission in a highly vaccinated population, a stochastic model is required.

Flanders is a region with typically a high and stable vaccination coverage [409]. As such, in the integration of our DCE results in a BCM, we had to introduce a number of unprecedented and possibly unrealistic scenarios. That is, just adding a BMC to a default situation seemed insufficient to set up a behavioral feedback mechanism that causes measles outbreaks. This confirms an observation we made in the systematic review (Chapter 2), namely that many BCM assumptions are often chosen to justify a theory. However, we aimed to transparently state the assumptions we made, we set the baseline simulation at the most realistic scenario using observational data as much as possible, and repeatedly indicated the proof-of-concept character of the study.

An economic analysis of workplace influenza vaccination

We simulated the spread of influenza in Belgium using a compartmental age-structured model taking both asymptomatic transmission as well as adaptive behavior of symptomatically infected individuals into account. The role of asymptomatic transmission was found to be essential in assessing the feasibility of control measures in an outbreak by Fraser et al. [121]. Indeed, given that these individuals do not realize that they are infected, they are unlikely to alter their behavior and further spread the pathogen in the population and on the workplace. Moreover, we simulated influenza using a dynamic transmission model, which is advised in the economic analyses of immunization programs [297]. A probabilistic sensitivity analysis (PSA) is currently lacking and would have provided additional insights in the uncertainty of the economic analysis.

Even though we stressed the importance of taking dynamic vaccine uptake into account, we did not do so for the influenza analysis in Chapter 7. Nevertheless, in the baseline simulation we found the average cost-savings per vaccinated employee to be relatively unfazed by the overall vaccination coverage. The importance of taking dynamic vaccine uptake into account becomes larger for scenarios with a higher vaccine effectiveness, in which herd immunity effects kick in at lower coverages compared to the baseline.

8.3 Future work

An updated systematic review on behavioral change models might provide additional insights in how data has been used in the literature between 2015 and 2020. In the light of the recent pandemic, it might be interesting to include BCMs that model compliance with government interventions, such as restrictions in movement and wearing face masks.

In future work, we should optimize the DCE setup and specification. The addition of a no-choice option could be helpful in setting up a binary vaccine outcome as a function of vaccine attributes. The latter was missing when we designed a proof-of-concept of using DCE data to parameterize BCMs in Chapter 6. In addition, an updated DCE study could focus on the parents of newborns, or parents planning to expand their family in order to retrieve a more targeted sample of individuals that were recently – or will soon be – confronted with these decisions for their children. However, it remains challenging to retrieve a sufficiently large sample to accurately estimate people's preferences.

Alternatively, an updated survey design could first probe for attitudinal responses after which – for the remainder of the survey – people get assigned to different DCE questionnaires. As such, separate vaccine utility estimates can be retrieved based on general vaccination attitudes (e.g. refusing, hesitant, accepting). This way, increased heterogeneity can be assessed, which up to now was mostly included by estimation of model covariate interactions and not yet applied in the proof-of-concept in Chapter 6.

In order to project the impact of a vaccine scare on a vaccine's utility, coverage and disease dynamics, one should probe for VRSE severity in an updated DCE design. Even though the true frequency of severe VRSE is highly exceptional, the public's perception might differ significantly from reality. These misperceptions, such as the alleged – but repeatedly refuted – link between MMR vaccine and autism or HPV suspension in Japan based on anecdotal adverse events, have a tremendous effect on vaccination behavior [23, 140, 159]. As such, the VRSE attributes should be updated to four levels, including all prevalence-severity combinations.

A data-driven specification of a vaccine-uptake function is needed to link vaccine utility estimates to uptake in the target population. A no-choice DCE can be instrumental in setting up such a function, as discussed in previous paragraphs. However, beware that the specification of such a relation between vaccine utility and coverage is time-sensitive and requires regular validation.

Combining data from cross-sectional surveys, longitudinal studies on the relation between information dynamics (e.g. burden of disease or VRSE) and risk perception, together with additional insights on how such perceptions shape vaccination decisions, would be required to further develop an integrated and parameterized BCM, for example by building on the structure of the model introduced in Chapter 6. In terms of data collection, additional research should look at a broad spectrum of potential elements that might influence individuals' perceptions with respect to vaccination, and which moves beyond reported infectious disease statistics. Media coverage about infectious disease outbreaks, social media spreading information about vaccine-related side-effects, or past vaccination experiences could, for example, be shaping individuals' perceptions. Qualitative studies have already been used to gather beliefs and attitudes towards childhood vaccination [264]. At the same time, additional research is required to identify and integrate cognitive biases in the context of vaccination BCMs. Confirmation bias was already successfully integrated in a BCM developed by Voinson et al. [423]. Bond & Nolan provide a better understanding on differences in risk perceptions between immunizers and non-immunizers in the context of theories of decision making under uncertainty, while special attention has been given to cognitive biases [39]. They performed a qualitative study in 45 Australian parents and categorized factors that influence vaccine decision-making according to the Health Belief Model, subjective perception risk and risky decision-making theories [39]. Indeed, we believe behavioral change theories, such as the HBM or TPB, are instrumental in designing conceptual models, as they identify a variety of behavioral constructs that are relevant in the context of prevention interventions. Historical data from vaccine-scares could in addition be useful to accommodate a fitting procedure for unknown behavioral parameters, or to validate model findings. The latter was demonstrated in a paper by Bauch & Bhattacharyya [23]. Note that preference heterogeneity, e.g. based on demographic characteristics or past experiences, should ideally be taken into account to better predict observed vaccination uptake and, consequentially, disease dynamics.

When more data becomes available, a probabilistic sensitivity analysis (PSA) should be performed to investigate parameter uncertainty in the model proposed in Chapter 6. Standard errors from the PML models can be useful in providing parameter ranges for vaccine utility. When data on people's perceptions and a vaccine uptake function has become available, uncertainty should be investigated for these parameters as well. We deemed it unnecessary to include a PSA at the current stage of the model. Furthermore, for the cost-benefit analysis of workplace influenza vaccination, a PSA would provide additional insights in the parameter uncertainty.

A more elaborate model should track and monetize the spillover effects of employee vaccination to the unemployed and society as a whole to get a better idea of the total economic picture of workplace influenza vaccination. This way, one can also calculate the magnitude of subsidies the government could provide to stimulate both employers and employees.

In the future, data-driven BCMs should be integrated in the economic analysis of immunization programs.

8.4 Conclusion

Reaching a vaccination coverage of 100% will often be infeasible since some individuals will refuse vaccination while others cannot be vaccinated as a result of medical conditions (e.g. immunodeficiency or pregnancy) or age (e.g. too young). However, for many pathogens it is not required to vaccinate everyone due to (mostly positive) externalities, often referred to as 'herd immunity'. Policymakers and researchers should look at herd immunity as an asset rather than a liability. Indeed, following the results described in Chapters 3 to 5, we found no evidence for free-rider incentives in any study population [416]. In contrast, peer influence, social norms and altruism were consistently found to increase vaccines' value to the public. Communicating that vaccination is still the norm, while refusals are exceptional, is important in maintaining a high – or increasing – vaccination coverage.

When confronted with vaccine hesitant individuals, guidelines can provide a stepwise and tailored approach to communicate with such individuals [163, 220]. However, policymakers need to look beyond vaccine hesitancy in order to reach optimal immunization coverages. More specifically, vaccine effectiveness, vaccine accessibility and VPD burden were found to be key. With respect to vaccines' accessibility, there is a lot of room for improvement for vaccines aimed at the adult population. Workplace influenza vaccination provides an efficient alternative to time consuming visits to both GP and pharmacy, in addition to being a safety barrier to vulnerable individuals in the population at large. Moreover, we need better influenza vaccines to reduce volatility in employers' return on workplace vaccination and to increase coverage.

As for other vaccine characteristics, the majority of the marketed vaccines warrant a high value to the vast majority of the population. Indeed, vaccines provide safe and effective protection against harmful diseases and generally reach high coverage levels [446]. Communication strategies are needed in order to align the public's perceptions with vaccination realities and to counter vaccine controversies increasingly spread through the internet and social media [105, 214, 343].

Health economists and infectious disease modellers cannot risk neglecting behavioral changes due to non-linearities in prevention uptake and disease dynamics. Increased data collection is needed at the interface between risk perception and disease dynamics. Where available, data-driven BCMs are preferred to theoretical models. However, purely game-theoretical models are obsolete. To the very least, modelers should include behavior-induced model uncertainties in a sensitivity analysis.

Summary

Infectious diseases pose a significant threat to global health and prosperity as recently evidenced by the COVID–19 pandemic. As a result, prevention and control of infectious diseases are essential for public health and welfare. Preventing between 2 and 3 million deaths each year, vaccination remains a cornerstone of this endeavor [443]. Vaccination usually results in positive externalities, often referred to as 'herd immunity': successfully vaccinated individuals do not (or hardly) transmit the pathogen they were vaccinated against to others. As such the marginal utility of vaccination decreases (non-linearly) as coverage increases, and endemic transmission can often be halted without vaccinating the whole population, a phenomenon which is crucial for vulnerable individuals who cannot receive vaccination due to age or medical reasons. Mathematical and economic models have proven valuable to simulate and evaluate the impact of prevention measures on the spread, burden and economics of infectious diseases [297]. These models inform and guide policy-makers to prepare for and respond to (re)emerging infectious diseases, particularly when sufficient information from controlled experiments is lacking. However, the impact of prevention measures and other policy interventions are subject to hosts' compliance and demand. That is, decades of progress made in control and prevention of infectious diseases are currently under threat by a worldwide increase in vaccine hesitancy and refusal [217]. The number of people perceiving vaccines as unsafe or unnecessary is growing, fueled by a false sense of security due to a decline in vaccine-preventable diseases, amplification of anti-vaccine messages through social media [105] and continued anti-vaccine exploitation of a fraudulent paper linking the measles-mumps-rubella vaccine to autism [140]. In response, behavioral change models (BCMs) have been developed to incorporate dynamic behavior (i.e. the demand side of prevention measures) into models for infectious disease transmission [127, 411]. Since vaccination yields positive externalities, game theory applies. Hence, BCMs have been developed in which rational-behaving individuals are assumed to free-ride on 'herd immunity', and therefore increasingly refuse vaccination when they perceive more members of the population to be immunized. However, many challenges remain in the development of BCMs that can accurately predict the uptake of preventive measures [128].

In Chapter 2, we present the results of a systematic review on BCMs for infectious disease transmission published in the period 2010–2015. We included

178 papers for full-text analysis out of 5759 unique records resulting from our search string. We observe an increasing trend in published BCMs, frequently coupled to (re)emergence events, and propose a categorization by distinguishing how information translates into preventive actions. Behaviour is usually captured by introducing information as a dynamic parameter or by introducing an economic objective function, either with or without imitation. Approaches using information thresholds and exogenous behaviour formation are also popular. We further classify according to disease, prevention measure, transmission model (we distinguish population, metapopulation and individual-level models) and the way prevention impacts transmission. We found that only 15% of studies used any real-life data for parameterization or validation. Despite recent advancements, we remain concerned that most models are purely theoretical and lack representative data and a validation process.

In response to the findings in Chapter 2, we aimed to study the relative importance of characteristics people consider when making vaccine decisions for themselves, or for their child, with specific attention for underlying motives arising from context, such as required effort (accessibility) and opportunism (free riding on herd immunity). We documented attitudes towards vaccination and performed a discrete choice experiment in Flanders, Belgium, South Africa, France, The Netherlands and The United Kingdom of which we described the results in Chapters 3 to 5. We elicited preferences for six attributes: (1) vaccine effectiveness, (2) vaccine-preventable disease (VPD) burden, (3) vaccine accessibility in terms of co-payment, vaccinator and administrative requirements, (4) frequency of (mild) vaccine-related side-effects, (5) vaccination coverage in the country's population and (6) local vaccination coverage in personal networks. While all six attributes were found to be significant, vaccine effectiveness and accessibility stand out in all (sub)samples, followed by VPD burden. Though statistically significant in all study samples, VRSE frequency appeared relatively unimportant when we specified severe VRSE to be highly unlikely. In addition, respondents attached more value to severity of VPD compared to its frequency. In contrast to what most game theoretical models assume, social norms dominate free-rider incentives.

Measles vaccination is topical to include in BCMs as it was confronted with a vaccine scare and the high transmissibility requires a vaccination coverage of 95% or higher to halt transmission in the population. In Chapter 6, we presented a proof of concept study on how data from DCEs can be integrated to parameterize BCMs. More specifically, we simulated the dynamic uptake of measles vaccine, parallel to a dynamic transmission model for the spread

of measles in Flanders, Belgium using the results of the DCE described in Chapter 3. We fitted vaccine utility data to a vaccine coverage function that determines the uptake of measles vaccine in children at one year of age. Measles transmission dynamics are modelled using a deterministic ordinary differential equation model including births, deaths and vaccination (SIRV). We investigate the impact of 7 different behavioral scenarios on vaccine utility, vaccine coverage and disease dynamics. The addition of a default BCM has no significant impact on disease transmission and increases vaccine coverage slightly. Introducing shocks, such as a vaccine scare or suspending the vaccine from the immunization schedule, causes recurring measles outbreaks in the Flemish population. A temporary vaccine scare of 5 years and a lower risk perception of measles severity did not alter disease transmission compared to the default simulation. A vaccine scare followed by a suspension from the schedule triggers volatility in vaccine coverage ranging between 25% and 85%, with large outbreaks reoccurring every few years.

We included social distancing behavior in an economic analysis of workplace vaccination in Chapter 7. Each year, about 10% of unvaccinated adults contracts seasonal influenza, with half of these individuals developing symptoms. As a result, employers experience significant economic losses in terms of employee absenteeism. Influenza vaccines can be instrumental in reducing this burden. Workplace vaccination is expected to reduce employee absenteeism more than linearly as a result of positive externalities. We simulated the spread of influenza in the seasons 2011-12 up to 2017-18 in Belgium by means of a compartmental transmission model. We accounted for age-specific social contact patterns and included reduced contact behavior when symptomatically infected. We simulated the impact of employer-funded influenza vaccination at the workplace and performed a cost-benefit analysis to assess the employers' return on workplace vaccination. Furthermore, we looked into the cost-benefit of rewarding vaccinated employees by offering an additional day off. Workplace vaccination reduced the burden of influenza both in the workplace and in the population at large. Compared to the current vaccine coverage – 21% in the population at large – an employee vaccine coverage of 90% could avert an additional 355,000 cases each year, of which about 150,000 in the employed population and 205,000 in the unemployed population. While, on average, seasonal influenza vaccination has been cost-saving at about €10 per vaccinated employee, the cost-benefit analysis was prone to significant between-season variability.

In conclusion, policymakers and researchers should look at herd immunity as an asset rather than a liability. Indeed, following the results described in

Chapters 3 to 5, we found no evidence for free-rider incentives in any study population [416]. In contrast, peer influence, social norms and altruism were consistently found to increase vaccines' value to the public. Communicating that vaccination is still the norm, while refusals are exceptional, is important to maintain – or even increase – high vaccination coverage. When confronted with vaccine hesitant individuals, guidelines can provide a stepwise and tailored approach to communicate with such individuals [220]. However, policymakers need to look beyond vaccine hesitancy in order to reach optimal immunization coverages. More specifically, vaccine effectiveness, vaccine accessibility and VPD burden were found to be key in guiding people's vaccination decisions. With respect to vaccines' accessibility, there is a lot of room for improvement for vaccines aimed at the adult population. More specifically, workplace influenza vaccination provides an efficient alternative to time consuming visits to both GP and pharmacy, in addition to being a safety barrier to vulnerable individuals in the population at large. With respect to other characteristics, vaccines warrant a high value to the vast majority of the population. Indeed, vaccines provide safe and effective protection against harmful diseases and generally reach high coverage levels [446]. Communication strategies are needed in order to align the public's perception with scientific evidence and to counter vaccine controversies increasingly spread through the internet and social media [105, 214, 343]. Furthermore, health economists and infectious disease modellers should not neglect behavioral changes due to non-linearities between prevention uptake and disease dynamics. Increased data collection is, however, needed at the interface between risk perception and disease dynamics. If data are available, data-driven BCMs are preferred to theoretical models. Though, purely game-theoretical models have become obsolete. To the very least, modellers should include behavior-induced model uncertainties in a sensitivity analysis.

Samenvatting

Infectieziekten vormen een aanzienlijke bedreiging voor de gezondheid en welvaart wereldwijd, zoals ook blijkt uit de huidige COVID–19 pandemie. Preventie en bestrijding van infectieziekten zijn bijgevolg essentieel voor de volksgezondheid en het algemeen welzijn. Vaccinatie voorkomt jaarlijks 2 tot 3 miljoen doden en blijft tot op heden een fundamenteel instrument voor de preventie van infectieziekten [443]. Vaccinatie wordt meestal gekenmerkt door positieve externaliteiten, vaak ook 'kudde-immuniteit' of 'groepsimmuniteit' genoemd. Dit mechanisme zorgt ervoor dat succesvol gevaccineerde individuen de ziekteverwekker waartegen ze gevaccineerd werden niet (of nauwelijks) kunnen overdragen aan anderen. De endemische verspreiding van een infectieziekte kan op deze manier vaak stopgezet worden zonder de hele bevolking te vaccineren. Dit fenomeen is cruciaal omdat het bescherming biedt voor kwetsbare individuen die vanwege hun leeftijd of door medische redenen niet gevaccineerd kunnen worden.

Het gebruik van wiskundige en economische modellen is waardevol gebleken om de impact van preventiemaatregelen op de verspreiding, ziektelast en economische aspecten van infectieziekten te simuleren en te evalueren [297]. Deze modellen helpen beleidsmakers om zich voor te bereiden – en te reageren – op uitbraken van nieuwe en bestaande infectieziekten, met name wanneer voldoende informatie uit gecontroleerde experimenten ontbreekt. De impact van preventiemaatregelen en andere beleidsinterventies zijn echter afhankelijk van de bereidheid tot naleving, de individuele vraag naar preventiemiddelen (zoals bijvoorbeeld vaccins), en het algemeen gedrag van de doelgroep. Meer bepaald worden decennia aan voortgang die geboekt is bij de bestrijding en preventie van infectieziekten momenteel bedreigd door een wereldwijde toename van terughoudendheid en weigering van vaccins [217]. Het aantal mensen dat vaccins als onveilig of onnodig beschouwt neemt toe, aangewakkerd door een vals gevoel van veiligheid als gevolg van een afname van door vaccinatie te voorkomen ziekten, toename van anti-vaccinatieberichten via sociale media [105] en voortdurende uitbuiting van een frauduleus artikel dat het mazelen-bof-rubella-vaccin koppelt aan autisme [140]. Als reactie hierop zijn gedragsveranderingsmodellen ontwikkeld om dynamisch gedrag (d.w.z. de vraagzijde van preventiemaatregelen) op te nemen in modellen die de overdracht van infectieziekten nabootsen [127, 411]. Derhalve tracht men de impact van bepaalde preventieve maatregelen op de ziektedynamiek accurater te

voorspellen. Aangezien vaccinatie positieve externaliteiten oplevert, staat speltheorie vaak centraal in de karakterisering van gedragsveranderingsmodellen. In zulke modellen wordt er vaak aangenomen dat zich rationeel gedragende individuen vrijbuitersgedrag vertonen door te rekenen op 'kudde-immuniteit' en daarom in toenemende mate vaccinatie weigeren wanneer ze zien dat meer leden van de bevolking worden geïmmuniseerd.

In Hoofdstuk 2 presenteren we de resultaten van een systematische review over gedragsveranderingsmodellen in de context van infectieziekten, die werden gepubliceerd in de periode 2010-2015. Uit de 5759 unieke publicaties die resulteerden uit onze zoekopdracht, hebben we van 178 artikelen de volledige tekst geanalyseerd. We zien een stijgende trend in gepubliceerde gedragsveranderingsmodellen, vaak als reactie op geobserveerde uitbraken van bepaalde infectieziekten. We stellen een categorisering voor door te onderscheiden hoe informatie zich in deze modellen vertaalt in preventieve acties. We zien dat gedrag meestal wordt geïntegreerd door informatie als een dynamische parameter te introduceren, of door een functie met een economisch objectief toe te voegen, die al dan niet rekening houdt met imitatiegedrag. Ook benaderingen met informatie-drempelwaarden en exogene gedragsvorming zijn populair. We classificeren verder volgens ziekte, preventiemaatregel, transmissiemodel (we onderscheiden populatie-, metapopulatie- en individu-gebaseerde modellen) en de manier waarop preventie de transmissie beïnvloedt. Bovendien ontdekten we dat in slechts 15% van de publicaties gebruik gemaakt werd van geobserveerde (i.e. real-life) data voor de parameterisering of validatie van het gebruikte model. Ondanks recente vorderingen blijven we dus bezorgd dat de meeste modellen puur theoretisch zijn en geen representatieve gegevens gebruiken, noch een validatieproces ondergaan.

Als reactie op de bevindingen in Hoofdstuk 2, wilden we het relatieve belang bestuderen van kenmerken die mensen overwegen bij het nemen van beslissingen omtrent vaccinatie voor zichzelf of voor hun kind. We hadden daarbij in het bijzonder aandacht voor onderliggende motieven die voortkomen uit de context, zoals vereiste inspanning (i.e. toegankelijkheid) en opportunisme (i.e. vrijbuitersgedrag door kudde-immuniteit). We bevraagden de houding ten opzichte van vaccinatie en voerden een discrete keuze-experiment uit om het relatieve belang van verschillende kenmerken die beslissingen omtrent vaccinatie kunnen beïnvloeden te onderzoeken. Dit deden we in Vlaanderen, België, Zuid-Afrika, Frankrijk, Nederland en het Verenigd Koninkrijk. De resultaten van deze studies staan beschreven in de Hoofdstukken 3 tot en met 5. We verzamelden voorkeuren met betrekking tot 6 vaccin-specifieke kenmerken: (1) werkzaamheid van het vaccin, (2) de ernst en frequentie van de door vaccinatie

te voorkomen ziekte, (3) toegankelijkheid van het vaccin in termen van eigen bijdrage, vaccinator en administratieve vereisten, (4) frequentie van (milde) vaccin-gerelateerde bijwerkingen, (5) vaccinatiegraad onder de bevolking van het land en (6) lokale vaccinatiegraad in persoonlijke netwerken. Hoewel alle zes attributen significant bleken te zijn, werden voornamelijk de werkzaamheid en de toegankelijkheid van het vaccin als essentieel beschouwd in alle studiepopulaties, gevolgd door de ziektelast van de te voorkomen ziekte. Bovendien hechtten de respondenten meer waarde aan de ernst van de door vaccinatie te voorkomen ziekte dan aan de frequentie ervan. Hoewel statistisch significant in alle studiepopulaties, bleek de frequentie van (milde) vaccin-gerelateerde bijwerkingen relatief onbelangrijk van zodra we specificeerden dat ernstige bijwerkingen steeds zeer zeldzaam zijn. In tegenstelling tot wat de meeste speltheoretische modellen aannemen, domineren sociale normen ten opzichte van vrijbuitersgedrag, als drijfveer voor vaccinatiebeslissingen. Een vaccin met reeds een hoge vaccinatiegraad – zowel in de algemene bevolking als in persoonlijke netwerken – werd namelijk meer gewaardeerd dan een vaccin met een lage vaccinatiegraad.

Vaccinatie tegen mazelen is geschikt om op te nemen in gedragsveranderingsmodellen omdat deze in het verleden geconfronteerd werd met een "vaccine scare" (i.e. een angst voor het vaccin) en omdat de hoge overdraagbaarheid van mazelen een vaccinatiegraad van 95% of hoger vereist om de overdracht in de populatie een halt toe te roepen. In Hoofdstuk 6 presenteren we een proof of concept-studie over hoe gegevens van discrete keuze-experimenten gebruikt kunnen worden om gedragsveranderingsmodellen te parametriseren. Meer bepaald simuleerden we de dynamische couverture van het mazelenvaccin, parallel aan een dynamisch transmissiemodel voor de verspreiding van mazelen in Vlaanderen (België) met behulp van de resultaten van het discrete keuze-experiment dat werd beschreven in Hoofdstuk 3. We hebben de schattingen met betrekking tot het marginaal nut van vaccins afgestemd op een functie die de vaccinatiegraad van het mazelenvaccin bij kinderen van één jaar oud bepaalt. De transmissiedynamiek van mazelen wordt gemodelleerd door middel van een deterministisch differentiaalvergelijkingsmodel dat rekening houdt met geboorten, sterfgevallen en vaccinatie. Meer bepaald werd er gebruik gemaakt van een SIRV model. We onderzoeken de impact van 7 verschillende gedragsscenario's op het maatschappelijk nut van vaccins, de vaccinatiegraad en de ziekteverspreiding. De toevoeging van een standaard gedragsveranderingsmodel – zonder exogene schokken – heeft geen significante invloed op de algehele verspreiding van de ziekte en verhoogt de vaccinatiegraad zelfs enigszins. Het introduceren van exogene schokken, zoals een "vaccine scare" of het schorsen van vaccinatie tegen mazelen uit het standaard vaccinatieprogramma,

veroorzaakt herhaalde uitbraken van mazelen bij de Vlaamse bevolking. Een tijdelijke "vaccine scare" van 5 jaar en een lagere risicoperceptie van de ernst van de mazelen veranderen de transmissiedynamiek niet in vergelijking met de standaardsimulatie. Een "vaccine scare" gevolgd door een schorsing van het vaccinatieprogramma tegen mazelen veroorzaakt schommelingen in de vaccinatiegraad tussen de 25% en de 85%, met grote uitbraken om de paar jaar.

De economische evaluatie van vaccinatieprogramma's is tevens essentieel voor beleidsmakers in het kader van prioritering van schaarse middelen binnen de gezondheidszorg en speelt een belangrijke rol in de beslissing tot (gedeeltelijke) terugbetaling van vaccins. In hoofdstuk 7 hebben we gereduceerd contactgedrag opgenomen in een economische analyse over vaccinatie op de werkplek. Elk jaar geraakt ongeveer 10% van de niet-gevaccineerde volwassenen geïnfecteerd met seizoensgriep, waarbij de helft van deze personen symptomen ontwikkelt. Als gevolg hiervan ervaren werkgevers aanzienlijke economische verliezen door ziekteverzuim. Influenzavaccins kunnen een belangrijke rol spelen bij het verminderen van deze last. Vaccinatie op de werkplek zal naar verwachting het ziekteverzuim van werknemers meer dan lineair doen verminderen als gevolg van – eerder beschreven – positieve externaliteiten. We simuleerden de verspreiding van influenza in de seizoenen 2011-12 tot 2017-18 in België door middel van een compartimenteel transmissiemodel. We hielden rekening met leeftijdsspecifieke sociale contactpatronen en met gereduceerd contactgedrag bij symptomatisch geïnfecteerden. We simuleerden de impact van door de werkgever gefinancierde griepvaccinatie op de werkplek en voerden een kosten-batenanalyse uit om het rendement van vaccinatie op de werkplek te berekenen. Verder hebben we gekeken naar de kosten-batenverhouding van het belonen van gevaccineerde medewerkers door hen een extra vrije dag aan te bieden. Vaccinatie op de werkplek verminderde de ziektelast van griep, zowel op de werkplek als bij de algemene bevolking. Vergeleken met de huidige vaccinatiegraad – 21% in de algemene bevolking – zou een vaccinatiegraad van 90% bij werknemers elk jaar 355.000 bijkomende griepgevallen kunnen voorkomen, waarvan ongeveer 150.000 onder de werkende bevolking en 205.000 onder de rest van de bevolking. Hoewel vaccinatie tegen seizoensinfluenza gemiddeld een kostenbesparing opleverde van ongeveer €10 per gevaccineerde werknemer, was de kosten-batenanalyse onderhevig aan aanzienlijke variabiliteit tussen de verschillende seizoenen.

In het kader van vaccinatiegedrag zouden beleidsmakers en onderzoekers kudde-immuniteit als gevolg van vaccinatie dus eerder als een positief dan negatief fenomeen moeten beschouwen. Inderdaad, op basis van de resultaten beschreven in de hoofdstukken 3 tot 5, vonden we in geen enkele van de

studie-populaties indicaties voor vrijbuitersgedrag [416]. Daarentegen bleken groepsinvloeden, sociale normen en altruïsme consequent de gepercipieerde waarde van vaccins te verhogen in de algemene bevolking. Communicatie die duidelijk maakt dat vaccinatie nog steeds de norm is – en dat weigeringen uitzonderlijk zijn – is belangrijk om een hoge vaccinatiegraad te behouden of deze zelfs te verhogen. Wanneer men geconfronteerd wordt met mensen die aarzelen of weigerachtig zijn om te vaccineren, kunnen richtlijnen een stapsgewijze en op maat gemaakte benadering bieden om met dergelijke personen te communiceren [220]. Om een optimale immunisatiegraad te bereiken, moeten beleidsmakers zich echter niet beperken tot personen die aarzelen of weigerachtig tegenover vaccinatie staan. Meer in het bijzonder bleken de werkzaamheid van het vaccin, de toegankelijkheid van het vaccin en de ziektelast van de te voorkomen ziekte, de sleutel te zijn bij het informeren van individuen in hun vaccinatiebeslissingen. Wat betreft de toegankelijkheid van vaccins is er veel ruimte voor verbetering bij vaccins die gericht zijn op de volwassen bevolking. Meer specifiek biedt vaccinatie tegen influenza op de werkplek een efficiënt alternatief voor tijdrovende bezoeken aan zowel de huisarts als de apotheek, en draagt het bovendien bij aan een belangrijke veiligheidsbarrière voor kwetsbare individuen in de algemene bevolking. Wat betreft de overige kenmerken, zou er een hoge waarde aan vaccins worden gehecht door de overgrote meerderheid van de bevolking. Vaccins bieden immers een veilige en effectieve bescherming tegen schadelijke ziekten en bereiken over het algemeen een hoge vaccinatiegraad [446]. Communicatiestrategieën zijn nodig om de perceptie van het publiek af te stemmen op het aanwezige wetenschappelijk bewijs en om vaccin-controverses tegen te gaan die steeds vaker via het internet en sociale media worden verspreid [105, 214, 343]. Bovendien mogen gezondheidseconomen en modelleerders van infectieziekten, gedragsveranderingen niet negeren gegeven de gevolgen van het niet-lineaire verband tussen de opname van preventiemaatregelen en ziektedynamiek. Er is echter meer wetenschappelijke gegevensverzameling nodig op het raakvlak tussen risicoperceptie en ziektedynamiek. Als zulke gegevens beschikbaar zijn, genieten gedragsveranderingsmodellen die gebaseerd zijn op data de voorkeur tegenover louter theoretische modellen. Puur speltheoretische modellen zijn echter achterhaald. Modelleerders zouden op zijn minst gedragsgeïnduceerde modelonzekerheden moeten opnemen in een sensitiviteitsanalyse.

Scientific output

Publications in Peer-Reviewed Scientific Journals

- Hoogink J, **Verelst F**, Kessels R, Willem L, Beutels P, Timen A, van Hoek AJ, Wallinga J, de Wit GA. Preferential differences in vaccination decision-making for oneself or one's child in The Netherlands: a discrete choice experiment. BMC Public Health. 2020 Jun 1;20:828.
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- **Verelst F**, Kessels R, Delva W, Beutels P, Willem L. Drivers of vaccine decision-making in South Africa: a discrete choice experiment. Vaccine. 2019 Apr 3;37(15):2079-89.
- **Verelst F**, Willem L, Kessels R, Beutels P. Individual decisions to vaccinate one's child or oneself: A discrete choice experiment rejecting free-riding motives. Social science & medicine. 2018 Jun 1;207:106-16.
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- **Verelst F**, Kessels R, Willem L, Beutels P. No such thing as a free-rider? Understanding multicountry drivers of childhood and adult vaccination. *Submitted to BMC Public Health*.
- **Verelst F**, Beutels P, Hens N, Willem L. Workplace influenza vaccination to reduce employee absenteeism: An economic analysis from the employers' perspective. *Submitted to Vaccine*.

Oral Presentations

- **Verelst F**, Willem L, Hens N, Beutels P. Cost-benefit analysis of employer-funded seasonal influenza vaccination: a return on investment? International Health Economics Association (iHEA) world congress 2019, 17 July 2019, Basel, Switzerland.
- **Verelst F**, Willem L, Kessels R, Beutels P. Multi-Country Discrete Choice Experiments to Parameterise Vaccine Demand and Behavioural Change in Models for Infectious Disease Transmission. International Health Economics Association (iHEA) world congress 2019, 16 July 2019, Basel, Switzerland.
- **Verelst F**, Willem L, Hens N, Beutels P. Employer-funded influenza vaccination and employee isolation in Belgium: a cost-benefit analysis. lolaHESG 2019 congress, 23 May 2019, Almen, The Netherlands.
- **Verelst F**, Willem L, Kessels R, Beutels P. Vaccination behavior as a multi-criteria decision: a discrete choice experiment. lolaHESG 2018 congress, 24 May 2018, Hoenderloo, The Netherlands.
- **Verelst F**, Willem L, Kessels R, Beutels P. Extracting the incentives: vaccination behavior as a multi-criteria decision. 10th European Congress on Tropical Medicine and International Health, 19 October 2017, Antwerp, Belgium.
- **Verelst F**, Sannen N, Theeten H. The role of herd immunity in parents' decision making about vaccination. Acting rational or altruistic? 19th European Union for school and university health and medicine congress, 7 September 2017, Leuven, Belgium.

Poster Presentations

- **Verelst F**, Willem L, Beutels P. Behavioural change models for infectious disease transmission: a systematic review (2010–2015). Epidemics 6 congress, 30 November 2017, Sitges, Spain.
- **Verelst F**, Willem L, Kessels R, Beutels P. Extracting the incentives: vaccination behavior as a multi-criteria decision. Epidemics 6 congress, 30 November 2017, Sitges, Spain.
- **Verelst F**, Willem L, Beutels P. Individual behavior and extra-utilitarian ethics in health economic evaluation: an individual-based modeling approach for measles elimination. Behavioral Insights Summer School (BISS), 18 September 2017, Erfurt, Germany.

Presentations by invitation

- **Verelst F**, Beutels P. "This time is different": Economics of a pandemic. SIMID Workshop, 12 May 2020, Blackboard Collaborate Online Environment
- **Verelst F**, Willem L, Kessels R, Beutels P. Measles, behavioral change models in epidemiology and drivers of vaccine uptake: A systematic review & discrete-choice experiment. PhD progress presentation, spearhead vaccinology and infectious diseases, 22 March 2019, Antwerp, Belgium.
- **Verelst F**, Beutels P, Kessels R, Willem L. Vaccine decision making in South Africa: a discrete choice experiment. FWO Scientific Research Group (WOG) meeting, 15 June 2018, Antwerp, Belgium.
- **Verelst F**, Beutels P, Kessels R, Delva W, Willem L. Vaccine decision making in South Africa: a discrete choice experiment. SACEMA Seminar Series, 4 April 2018, Stellenbosch, South Africa.
- **Verelst F**, Willem L, Kessels R, Beutels P. Measles, behavioral change models in epidemiology and drivers of vaccine uptake: A systematic review & discrete-choice experiment. Socioepidemiology Workshop, 9 March 2018, Columbus, Ohio, USA.
- **Verelst F**, Willem L, Beutels P. A systematic review on behavioural change models for infectious disease modelling. SIMID Workshop, 17 May 2017, Antwerp, Belgium.

Conference abstracts

- **Verelst F**, Willem L, Hens N, Beutels P. Cost-benefit analysis of employer-funded quadrivalent influenza vaccination. Epidemics 7 congress, 3 - 6 December 2019, Charleston, SC, USA.
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APPENDIX A

Supplementary information Chapter 3

Summary

This appendix contains methodological details of the Bayesian D-efficient survey design of the DCE in Chapter 3: "Vaccination behavior in Flanders". Moreover, we added the results of a PML model that decomposed the burden of disease attribute into severity of disease and frequency of (or susceptibility to) the vaccine-preventable disease.

A.1 Bayesian D-efficient partial profile design

The design of the DCE, shown in Table A.1, includes five surveys of 10 choice sets with two alternative vaccination programs. The choice sets in each survey were assigned in a random order to the respondents. Each survey was completed by about 218 respondents in the adult group and about 166 respondents in the child group. The choice sets are described by six attributes, three of which have varying levels and the remaining three constant levels. The levels of the varying attributes are indicated in yellow. The constant attributes are shown to present vaccine profiles in full as well as to enable estimating all two-way interactions between the attributes 'vaccine effectiveness', 'VRSE' and 'accessibility'. In each survey each attribute is varying in five choice sets and constant in five choice sets.

Table A.1: Five surveys of the Bayesian D-efficient partial profile design.

Survey	Choice set	Vaccine effectiveness	Burden of disease	VRSE	Accessibility	Local coverage	Population coverage
1	1	50%	Rare & mild	Rare	Co-payment & prescription	60%	30%
1	1	50%	Rare & mild	Frequent	Co-payment & prescription	30%	90%
1	2	90%	Rare & mild	Frequent	Co-payment & prescription	60%	60%
1	2	90%	Rare & mild	Rare	Free & accessible	90%	60%
1	3	90%	Common & severe	Rare	Free & accessible	30%	30%
1	3	90%	Rare & severe	Rare	Free & accessible	60%	90%
1	4	50%	Rare & severe	Frequent	Co-payment & prescription	60%	90%
1	4	50%	Rare & mild	Frequent	Free & accessible	60%	30%
1	5	50%	Rare & severe	Frequent	Free & accessible	60%	90%
1	5	50%	Rare & mild	Rare	Co-payment & prescription	60%	90%
1	6	90%	Rare & mild	Frequent	Co-payment & prescription	30%	30%
1	6	50%	Rare & mild	Frequent	Free & accessible	30%	60%
1	7	90%	Common & mild	Frequent	Co-payment & prescription	90%	60%
1	7	50%	Common & mild	Frequent	Free & accessible	60%	60%
1	8	90%	Rare & severe	Frequent	Free & accessible	90%	90%
1	8	50%	Rare & severe	Rare	Free & accessible	90%	60%
1	9	50%	Common & severe	Rare	Co-payment & prescription	90%	30%
1	9	90%	Common & mild	Rare	Co-payment & prescription	60%	30%
1	10	50%	Common & severe	Rare	Co-payment & prescription	90%	90%
1	10	90%	Rare & mild	Frequent	Co-payment & prescription	90%	90%

Table A.1 Continued: Five surveys of the Bayesian D-efficient partial profile design.

Survey	Choice set	Vaccine effectiveness	Burden of disease	VRSE	Accessibility	Local coverage	Population coverage
2	1	50%	Common & mild	Frequent	Co-payment & prescription	60%	60%
2	1	50%	Common & mild	Frequent	Free & accessible	30%	30%
2	2	90%	Common & severe	Rare	Free & accessible	60%	90%
2	2	90%	Common & severe	Frequent	Co-payment & prescription	30%	90%
2	3	50%	Rare & severe	Frequent	Co-payment & prescription	30%	60%
2	3	50%	Common & mild	Frequent	Co-payment & prescription	60%	90%
2	4	90%	Rare & mild	Rare	Free & accessible	30%	90%
2	4	90%	Rare & severe	Frequent	Free & accessible	30%	60%
2	5	90%	Common & severe	Frequent	Co-payment & prescription	90%	30%
2	5	90%	Rare & mild	Rare	Free & accessible	90%	30%
2	6	50%	Rare & severe	Rare	Free & accessible	60%	90%
2	6	90%	Rare & severe	Rare	Co-payment & prescription	60%	60%
2	7	90%	Common & severe	Frequent	Co-payment & prescription	60%	60%
2	7	50%	Common & severe	Rare	Co-payment & prescription	60%	30%
2	8	90%	Rare & mild	Frequent	Free & accessible	30%	60%
2	8	50%	Rare & mild	Rare	Free & accessible	90%	60%
2	9	50%	Common & severe	Frequent	Co-payment & prescription	90%	60%
2	9	90%	Rare & mild	Frequent	Co-payment & prescription	60%	60%
2	10	90%	Rare & severe	Rare	Co-payment & prescription	30%	60%
2	10	50%	Common & severe	Rare	Free & accessible	30%	60%

Table A.1 Continued: Five surveys of the Bayesian D-efficient partial profile design.

Survey	Choice set	Vaccine effectiveness	Burden of disease	VRSE	Accessibility	Local coverage	Population coverage
3	1	50%	Common & mild	Rare	Free & accessible	60%	90%
3	1	50%	Common & mild	Rare	Co-payment & prescription	30%	30%
3	2	90%	Rare & severe	Frequent	Free & accessible	30%	90%
3	2	90%	Rare & severe	Rare	Free & accessible	60%	30%
3	3	90%	Rare & severe	Rare	Co-payment & prescription	90%	90%
3	3	90%	Common & mild	Rare	Free & accessible	90%	30%
3	4	90%	Rare & severe	Rare	Free & accessible	30%	30%
3	4	90%	Common & severe	Frequent	Free & accessible	90%	30%
3	5	50%	Rare & mild	Rare	Co-payment & prescription	90%	60%
3	5	50%	Common & mild	Frequent	Free & accessible	90%	60%
3	6	90%	Rare & severe	Frequent	Co-payment & prescription	30%	90%
3	6	50%	Rare & severe	Frequent	Free & accessible	90%	90%
3	7	90%	Common & severe	Frequent	Co-payment & prescription	30%	90%
3	7	50%	Common & severe	Rare	Co-payment & prescription	30%	60%
3	8	90%	Common & mild	Frequent	Co-payment & prescription	30%	30%
3	8	50%	Common & mild	Rare	Free & accessible	30%	30%
3	9	90%	Rare & mild	Frequent	Free & accessible	60%	90%
3	9	50%	Rare & severe	Frequent	Free & accessible	60%	30%
3	10	50%	Rare & severe	Rare	Co-payment & prescription	30%	30%
3	10	90%	Rare & mild	Rare	Co-payment & prescription	90%	30%

Table A.1 Continued: Five surveys of the Bayesian D-efficient partial profile design.

Survey	Choice set	Vaccine effectiveness	Burden of disease	VRSE	Accessibility	Local coverage	Population coverage
4	1	50%	Rare & mild	Rare	Co-payment & prescription	30%	90%
4	1	50%	Rare & mild	Frequent	Co-payment & prescription	60%	30%
4	2	90%	Common & severe	Frequent	Free & accessible	30%	30%
4	2	90%	Common & severe	Rare	Co-payment & prescription	30%	60%
4	3	90%	Rare & mild	Rare	Free & accessible	60%	60%
4	3	90%	Common & mild	Rare	Free & accessible	90%	90%
4	4	50%	Rare & mild	Frequent	Free & accessible	90%	60%
4	4	50%	Common & mild	Frequent	Co-payment & prescription	30%	60%
4	5	90%	Rare & severe	Frequent	Free & accessible	90%	30%
4	5	90%	Common & mild	Rare	Co-payment & prescription	90%	30%
4	6	50%	Common & severe	Frequent	Free & accessible	60%	90%
4	6	90%	Common & severe	Frequent	Co-payment & prescription	60%	30%
4	7	90%	Rare & mild	Rare	Co-payment & prescription	90%	90%
4	7	50%	Rare & mild	Rare	Free & accessible	60%	90%
4	8	90%	Common & mild	Frequent	Free & accessible	60%	90%
4	8	50%	Common & mild	Rare	Free & accessible	30%	90%
4	9	50%	Common & severe	Frequent	Co-payment & prescription	30%	90%
4	9	90%	Common & mild	Frequent	Co-payment & prescription	30%	60%
4	10	50%	Common & severe	Rare	Free & accessible	60%	60%
4	10	90%	Common & mild	Frequent	Free & accessible	60%	60%

Table A.1 Continued: Five surveys of the Bayesian D-efficient partial profile design.

Survey	Choice set	Vaccine effectiveness	Burden of disease	VRSE	Accessibility	Local coverage	Population coverage
5	1	90%	Common & severe	Rare	Co-payment & prescription	60%	90%
5	1	90%	Common & severe	Frequent	Free & accessible	60%	60%
5	2	50%	Rare & severe	Frequent	Co-payment & prescription	90%	60%
5	2	50%	Rare & severe	Rare	Free & accessible	30%	60%
5	3	90%	Rare & severe	Rare	Co-payment & prescription	90%	30%
5	3	90%	Common & mild	Rare	Co-payment & prescription	30%	90%
5	4	90%	Common & mild	Rare	Free & accessible	30%	60%
5	4	90%	Common & severe	Rare	Co-payment & prescription	30%	30%
5	5	50%	Common & severe	Frequent	Co-payment & prescription	60%	60%
5	5	50%	Common & mild	Rare	Co-payment & prescription	90%	60%
5	6	90%	Common & severe	Rare	Free & accessible	30%	60%
5	6	50%	Common & severe	Rare	Free & accessible	90%	30%
5	7	90%	Rare & mild	Frequent	Free & accessible	60%	30%
5	7	50%	Rare & mild	Frequent	Co-payment & prescription	30%	30%
5	8	90%	Rare & severe	Frequent	Co-payment & prescription	60%	30%
5	8	50%	Rare & severe	Rare	Co-payment & prescription	60%	60%
5	9	90%	Common & mild	Frequent	Co-payment & prescription	90%	90%
5	9	50%	Common & severe	Frequent	Free & accessible	90%	90%
5	10	50%	Common & severe	Rare	Free & accessible	90%	30%
5	10	90%	Rare & mild	Frequent	Free & accessible	90%	30%

A.2 Multivariate normal prior parameter distribution for the Bayesian D-efficient partial profile design

To construct the Bayesian D-efficient partial profile design for the vaccination DCE shown in Appendix A.1, we used a multivariate normal prior distribution that reflects the prior beliefs about the unknown parameter values associated with the levels of the six attributes. Based on expert interviews and literature review, we ranked the six attributes in descending order of importance and specified mean parameter values and variances for the multivariate normal prior distribution.

Table A.2 shows the six attributes in descending order of expected importance. Based on the listed ranks, we specified prior mean utility values for the main effects of the attributes. The more important an attribute, the greater the a priori mean utility values specified for the main effects of that attribute. We adopted the same ordering of the attribute levels as in Table 5.1, where they are ranked from least to most favored. We had no preconception of people's preferences for both coverage attributes, which corresponds to specifying zero mean utility values. The preference direction for the levels of these attributes could be either increasing (i.e. higher coverage leads to more willingness to vaccinate) or decreasing. The a priori mean utility values associated with the levels of each attribute are symmetric around zero, and thus sum to zero. The latter is imposed by the effects-type coding used for the attribute levels, which means that the levels of the 2-level attributes 'vaccine effectiveness', 'VRSE' and 'accessibility' are coded as 1 and -1, the levels of the 3-level attributes 'local coverage' and 'population coverage' are coded as [1 0], [0 1] and [-1 - 1] and the levels of the 4-level attribute 'burden of disease' are coded as [1 0 0], [0 1 0], [0 0 1] and [-1 -1 -1].

Table A.2: A priori order of importance of the main effects of the six attributes and conversion into mean utility values used in the multivariate normal prior distribution.

Rank	**Attribute**	**Prior mean**			
		Level a	Level b	Level c	Level d
1	Vaccine effectiveness	-0.8	0.8		
2	Burden of disease	-0.6	-0.2	0.2	0.6
3	VRSE	-0.4	0.4		
4	Accessibility	-0.3	0.3		
5	Local coverage	0	0	0	
5	Population coverage	0	0	0	

We also specified prior variances and covariances around the mean utility values for the attributes' main effects. We used values of 0.09 for all attribute levels, because this preserved the preference ordering for the levels of an attribute as much as possible. Following Kessels et al. [197] we specified negative covariances of -0.045 for the 3-level attributes and -0.03 for the 4-level attribute so that we also obtained variances of 0.09 for the derived utility values associated with the last level of each attribute. We computed these covariances using prior correlations of -1/2 for the 3-level attributes and of -1/3 for the 4-level attribute. In the absence of prior information for the interaction effects between 'vaccine effectiveness', 'VRSE' and 'accessibility', we specified zero mean utility values for these. For ease of computation, we also assumed zero prior variances around the utility values for the interaction effects, allowing for no uncertainty around these values. This implies that the prior parameter specification of the interaction effects corresponds to a local instead of a Bayesian approach.

A.3 Panel mixed logit estimates with decomposition of the burden of disease attribute

Table A.3: Panel mixed logit model estimates (means and standard deviations) and significances of the attribute effects obtained from likelihood ratio (LR) tests. Adult Model without and with decomposition of the burden of disease attribute.

Term	Mean estimate (std dev; subject std dev)		LR Chi-square		P-value	
	No decomposition	Decomposition	No decomposition	Decomposition	No decomposition	Decomposition
VRSE						
Common	-0.563 (0.023; 0.058)	-0.542 (0.021; 0.049)	640.612	644.003	< 0.0001	< 0.0001
Rare	0.563	0.542				
Accessibility						
Co-payment & prescription	-0.410 (0.023; 0.058)	-0.398 (0.015; 0.103)	412.568	412.431	< 0.0001	< 0.0001
Free & accessible	0.410	0.398				
Vaccine effectiveness						
50%	-0.487 (0.023; 0.075)	-0.469 (0.019; 0.08)	358.211	353.218	< 0.0001	< 0.0001
90%	0.487	0.469				
Burden of disease						
Rare & mild	-0.423 (0.042; 0.070)		218.655		< 0.0001	
Common & mild	-0.313 (0.042; 0.049)					
Rare & severe	0.204 (0.040; 0.034)					
Common & severe	0.532					
Mild		-0.356		210.109		< 0.0001
Severe		0.356 (0.023; 0.061)				
Rare		-0.076 (0.022; 0.042)		13.714		0.0002
Common		0.076				
VRSE*age group						
Common*[18-34]	0.215 (0.028; 0.044)	0.215 (0.029; 0.044)	57.915	58.679	< 0.0001	< 0.0001
Common*[35-49]	0.022 (0.035; 0.051)	0.018 (0.039; 0.051)				
Common*[50-64]	-0.133 (0.033; 0.051)	-0.138 (0.033; 0.053)				
Common*[65-85]	-0.104	-0.095				
Rare*[18-34]	-0.215	-0.215				
Rare*[35-49]	-0.022	-0.018				
Rare*[50-64]	0.133	0.138				
Rare*[65-85]	0.104	0.095				
Population coverage (x10%)	0.055 (0.007; 0.044)	0.054 (0.007; 0.044)	45.431	44.013	< 0.0001	< 0.0001
Local coverage (x10%)	0.047 (0.008; 0.040)	0.049 (0.007; 0.040)	31.638	35.721	< 0.0001	< 0.0001

Note: Mean estimates corresponding to the last level of an attribute, either as a main effect or involved in an interaction, are calculated as minus the sum of the estimates for the other levels of the attribute.

Table A.3 Cont. Panel mixed logit model estimates (means and standard deviations) and significances of the attribute effects obtained from likelihood ratio (LR) tests. Adult Model without and with decomposition of the burden of disease attribute

Term	Mean estimate (std dev; subject std dev)		LR Chi-square		P-value	
	No decomposition	Decomposition	No decomposition	Decomposition	No decomposition	Decomposition
Burden of disease*age group						
Rare & mild*[18-34]	-0.161 (0.061; 0.089)					
Rare & mild*[35-49]	-0.001 (0.083; 0.094)					
Rare & mild*[50-64]	-0.081 (0.081; 0.074)					
Rare & mild*[65-85]	0.228					
Common & mild*[18-34]	-0.096 (0.060; 0.074)					
Common & mild*[35-49]	0.073 (0.068; 0.070)					
Common & mild*[50-64]	-0.134 (0.050; 0.067)					
Common & mild*[65-85]	0.157		48.614		< 0.0001	
Rare & severe*[18-34]	0.105 (0.055; 0.056)					
Rare & severe*[35-49]	-0.107 (0.076; 0.055)					
Rare & severe*[50-64]	0.053 (0.059; 0.050)					
Rare & severe*[65-85]	-0.051					
Common & severe*[18-34]	0.152					
Common & severe*[35-49]	0.029					
Common & severe*[50-64]	0.162					
Common & severe*[65-85]	-0.343					
Mild*[18-34]		-0.110				
Mild*[35-49]		0.056				
Mild*[50-64]		-0.127				
Mild*[64-85]		0.181		41.816		< 0.0001
Severe*[18-34]		0.110 (0.038; 0.072)				
Severe*[35-49]		-0.056 (0.035; 0.052)				
Severe*[50-64]		0.127 (0.034; 0.061)				
Severe*[65-85]		-0.181				

Note: Mean estimates corresponding to the last level of an attribute, either as a main effect or involved in an interaction, are calculated as minus the sum of the estimates for the other levels of the attribute.

Table A.3 Cont. Panel mixed logit model estimates (means and standard deviations) and significances of the attribute effects obtained from likelihood ratio (LR) tests. Adult Model without and with decomposition of the burden of disease attribute

Term	Mean estimate (std dev; subject std dev)		LR Chi-square		P-value	
	No decomposition	Decomposition	No decomposition	Decomposition	No decomposition	Decomposition
Burden of disease*traditional media						
Rare & mild*not selected	0.126 (0.033; 0.054)					
Rare & mild*selected	-0.126					
Common & mild*not selected	0.044 (0.034; 0.049)					
Common & mild*selected	-0.044		17.930		0.0005	
Rare & severe*not selected	-0.024 (0.044; 0.032)					
Rare & severe*selected	0.024					
Common & severe*not selected	-0.146					
Common & severe*selected	0.146					
Severe*not selected		-0.072 (0.021; 0.100)				
Severe*selected		0.072		12.973		0.0003
Mild*not selected		0.072				
Mild*selected		-0.072				

Note: Mean estimates corresponding to the last level of an attribute, either as a main effect or involved in an interaction, are calculated as minus the sum of the estimates for the other levels of the attribute.

Table A.4: Panel mixed logit model estimates (means and standard deviations) and significances of the attribute effects obtained from likelihood ration (LR) tests. Child Model without and with decomposition of the burden of disease attribute.

Term	Mean estimate (std dev; subject std dev)		LR Chi-square		P-value	
	No decomposition	Decomposition	No decomposition	Decomposition	No decomposition	Decomposition
VRSE						
Common	-0.516 (0.027; 0.118)	-0.526 (0.023; 0.117)	452.542	453.259	< 0.0001	< 0.0001
Rare	0.516	0.526				
Accessibility						
Co-payment & prescription	-0.447 (0.026; 0.155)	-0.460 (0.020; 0.142)	384.639	384.679	< 0.0001	< 0.0001
Free & accessible	0.447	0.460				
Vaccine effectiveness						
50%	-0.519 (0.034; 0.121)	-0.535 (0.024; 0.130)	315.617	317.892	< 0.0001	< 0.0001
90%	0.519	0.535				
Burden of disease						
Rare & mild	-0.614 (0.052; 0.090)		255.510		< 0.0001	
Common & mild	-0.283 (0.036; 0.103)					
Rare & severe	0.271 (0.041; 0.045)					
Common & severe	0.627					
Mild		-0.468		245.297		< 0.0001
Severe		0.468 (0.029; 0.075)				
Rare		-0.182 (0.027; 0.058)		42.844		< 0.0001
Common		0.182				
Population coverage (x10%)	0.077 (0.009; 0.053)	0.078 (0.009; 0.055)	69.391	69.469	< 0.0001	< 0.0001
Local coverage (x10%)	0.058 (0.008; 0.052)	0.062 (0.009; 0.051)	35.822	36.225	< 0.0001	< 0.0001

Note: Mean estimates corresponding to the last level of an attribute, either as a main effect or involved in an interaction, are calculated as minus the sum of the estimates for the other levels of the attribute.

Table A.4 Cont. Panel mixed logit model estimates (means and standard deviations) and significances of the attribute effects obtained from likelihood ration (LR) tests. Child Model without and with decomposition of the burden of disease attribute.

Term	Mean estimate (std dev; subject std dev)		LR Chi-square		P-value	
	No decomposition	Decomposition	No decomposition	Decomposition	No decomposition	Decomposition
Burden of disease*acceptor						
Rare & mild*agree	0.114 (0.041; 0.168)		18.069		0.0004	
Rare & mild*disagree	-0.114					
Common & mild*agree	0.092 (0.037; 0.116)					
Common & mild*disagree	-0.092					
Rare & severe*agree	-0.064 (0.038; 0.046)					
Rare & severe*disagree	0.064					
Common & severe*agree	-0.142					
Common & severe*disagree	0.142					
Severe*agree		-0.112 (0.024; 0.388)		17.210		< 0.0001
Severe*disagree		0.112				
Mild*agree		0.112				
Mild*disagree		-0.112				

Note: Mean estimates corresponding to the last level of an attribute, either as a main effect or involved in an interaction, are calculated as minus the sum of the estimates for the other levels of the attribute.

APPENDIX B

Supplementary information Chapter 5

Summary

This appendix contains details on the PML models including covariate interaction effects of the DCE described in Chapter 5: "No such thing as a free-rider?". Moreover, we added the responses to the vaccine attitude statements in Belgium, France, The United Kingdom and The Netherlands.

B.1 PML model estimates including covariate interaction effects

In this appendix, we provide the results of the PML models including the most important covariate interactions. We estimated six of such models: for each country (Belgium, The UK and France) and for each target group ('oneself' and 'child' groups). For each model, we first displayed the significant covariate effects by means of a bar chart (Figures B.1 to B.6), including a 95% confidence interval. The PML details are provided in Tables B.1 to B.6.

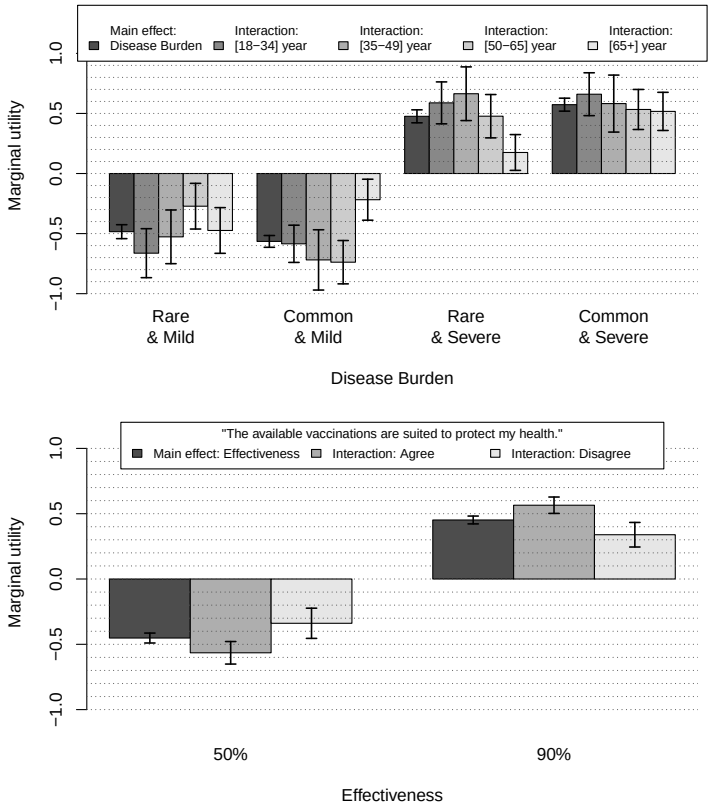

Figure B.1: Marginal utilities for significant covariate interactions with disease burden (above) and vaccine effectiveness (below). 'Oneself' model, Belgium.

Table B.1: Panel mixed logit model estimates (means and standard deviations) and significances of the attribute effects obtained from likelihood ratio (LR) tests. 'Oneself' model Belgium, including covariate interactions

Term	Mean estimate (std dev; subject std dev)	LR Chi-square	DF	P-value
Accessibility				
Co-payment & prescription	-0.433 (0.024; 0.376)	327.736	1	< 0.0001
Free & accessible	0.433 (0.022; 0.370)			
Burden of disease				
Rare & mild	-0.484 (0.058; 0.187)	257.965	3	< 0.0001
Common & mild	-0.565 (0.049; 0.132)			
Rare & severe	0.476 (0.054; 0.099)			
Common & severe	0.573 (0.054; 0.159)			
Vaccine effectiveness				
50%	-0.452 (0.038; 0.153)	192.235	1	< 0.0001
90%	0.452 (0.030; 0.144)			
Population coverage (x10%)	0.086 (0.009; 0.125)	66.439	1	< 0.0001
Mild VRSE				
Common	-0.179 (0.024; 0.112)	58.630	1	< 0.0001
Rare	0.179 (0.022; 0.101)			
Vaccine effectiveness*Protective†				
50%*agree	-0.113 (0.027; 0.162)	18.087	1	< 0.0001
50%*disagree	0.113 (0.028; 0.162)			
90%*agree	0.113 (0.025; 0.127)			
90%*disagree	-0.113 (0.024; 0.140)			
Local coverage (x10%)	0.049 (0.009; 0.084)	18.079	1	< 0.0001
Burden of disease*Age				
Rare & mild*[18-34]	-0.179 (0.087; 0.210)	33.439	9	0.0001
Rare & mild*[35-49]	-0.043 (0.096; 0.251)			
Rare & mild*[50-65]	0.212 (0.087; 0.254)			
Rare & mild*[65+]	0.010 (0.105; 0.269)			
Common & mild*[18-34]	-0.020 (0.081; 0.174)			
Common & mild*[35-49]	-0.154 (0.099; 0.223)			
Common & mild*[50-65]	-0.173 (0.087; 0.200)			
Common & mild*[65+]	0.347 (0.089; 0.246)			
Rare & severe*[18-34]	0.112 (0.085; 0.140)			
Rare & severe*[35-49]	0.188 (0.088; 0.146)			
Rare & severe*[50-65]	0.001 (0.079; 0.170)			
Rare & severe*[65+]	-0.301 (0.068; 0.135)			
Common & severe*[18-34]	0.087 (0.080; 0.146)			
Common & severe*[35-49]	0.009 (0.095; 0.174)			
Common & severe*[50-65]	-0.040 (0.079; 0.185)			
Common & severe*[65+]	-0.056 (0.076; 0.143)			

Note: Mean estimates corresponding to the last level of an attribute are calculated as minus the sum of the estimates for the other levels of the attribute. †Protective: "The available vaccinations are suited to protect my health."

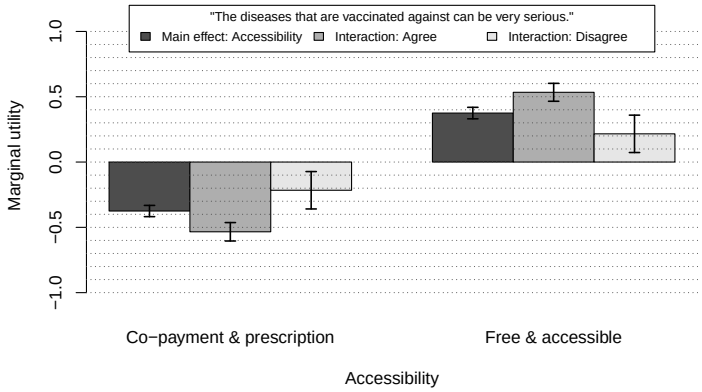

Figure B.2: Marginal utilities for significant covariate interaction with accessibility. 'Youngest child' model, Belgium.

Table B.2: Panel mixed logit model estimates (means and standard deviations) and significances of the attribute effects obtained from likelihood ratio (LR) tests. 'Youngest child' model Belgium, including covariate interactions

Term	Mean estimate (std dev; subject std dev)	LR Chi-square	DF	P-value
Vaccine effectiveness				
50%	-0.584 (0.033; 0.238)	192.237	1	< 0.0001
90%	0.584 (0.041; 0.230)			
Burden of disease				
Rare & mild	-0.380 (0.063; 0.342)	163.220	3	< 0.0001
Common & mild	-0.621 (0.064; 0.458)			
Rare & severe	0.359 (0.054; 0.256)			
Common & severe	0.642 (0.068; 0.351)			
Accessibility				
Co-payment & prescription	-0.375 (0.043; 0.182)	94.231	1	< 0.0001
Free & accessible	0.375 (0.044; 0.177)			
Population coverage (x10%)	0.132 (0012.; 0.138)	93.690	1	< 0.0001
Mild VRSE				
Common	-0.229 (0.030; 0.140)	45.361	1	< 0.0001
Rare	0.229 (0.029; 0.134)			
Local coverage (x10%)	0.074 (0.014; 0.120)	27.390	1	< 0.0001
Accessibility*Severity VPD†				
Co-payment & prescription*agree	-0.159 (0.042; 0.178)	18.556	1	< 0.0001
Co-payment & prescription*disagree	0.159 (0.037; 0.179)			
Free & accessible*agree	0.159 (0.037; 0.185)			
Free & accessible*disagree	-0.159 (0.037; 0.175)			

Note: Mean estimates corresponding to the last level of an attribute are calculated as minus the sum of the estimates for the other levels of the attribute. †Severity VPD: "The diseases that are vaccinated against can be very serious."

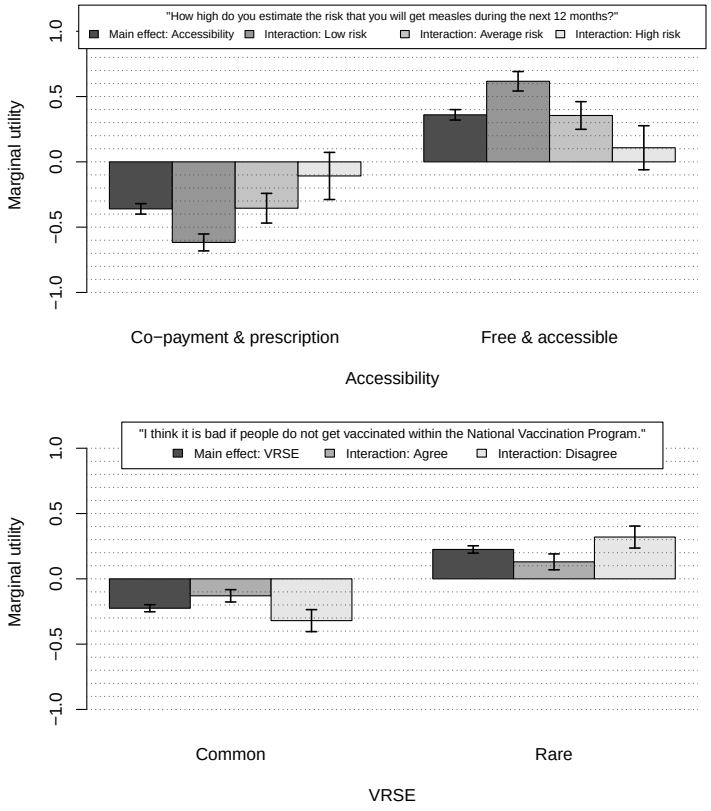

Figure B.3: Marginal utilities for significant covariate interactions with accessibility (above) and VRSE (below). 'Oneself' model, United Kingdom.

Table B.3: Panel mixed logit model estimates (means and standard deviations) and significances of the attribute effects obtained from likelihood ratio (LR) tests. 'Oneself' model United Kingdom, including covariate interactions

Term	Mean estimate (std dev; subject std dev)	LR Chi-square	DF	P-value
Vaccine effectiveness				
50%	-0.720 (0.037; 0.301)	431.561	1	< 0.0001
90%	0.720 (0.034; 0.296)			
Burden of disease				
Rare & mild	-0.545 (0.053; 0.310)	192.478	3	< 0.0001
Common & mild	-0.368 (0.055; 0.438)			
Rare & severe	0.327 (0.046; 0.219)			
Common & severe	0.586 (0.056; 0.259)			
Accessibility				
Co-payment & prescription	-0.360 (0.040; 0.124)	121.213	1	< 0.0001
Free & accessible	0.360 (0.040; 0.120)			
Population coverage (x10%)	0.099 (0.010; 0.128)	94.070	1	< 0.0001
Mild VRSE				
Common	-0.225 (0.027; 0.087)	66.328	1	< 0.0001
Rare	0.225 (0.028; 0.089)			
Local coverage (x10%)	0.084 (0.010; 0.080)	48.389	1	< 0.0001
Accessibility*Measles susceptibility†				
Co-payment & prescription*low risk	-0.257 (0.042; 0.167)	39.611	2	< 0.0001
Co-payment & prescription*average risk	0.005 (0.050; 0.143)			
Co-payment & prescription*high risk	0.252 (0.067; 0.133)			
Free & accessible*low risk	0.257 (0.045; 0.168)			
Free & accessible*average risk	-0.005 (0.046; 0.129)			
Free & accessible*high risk	-0.252 (0.061; 0.134)			
Mild VRSE*Bad if others don't vaccinate‡				
Common*agree	0.095 (0.022; 0.091)	17.408	1	< 0.0001
Common*disagree	-0.095 (0.026; 0.093)			
Rare*agree	-0.095 (0.025; 0.088)			
Rare*disagree	0.095 (0.025; 0.094)			

Note: Mean estimates corresponding to the last level of an attribute are calculated as minus the sum of the estimates for the other levels of the attribute. †Measles susceptibility: "How high do you estimate the risk that you will get measles during the next 12 months?" ‡Bad if others don't vaccinate: "I think it is bad if people do not get vaccinated within the National Vaccination Program."

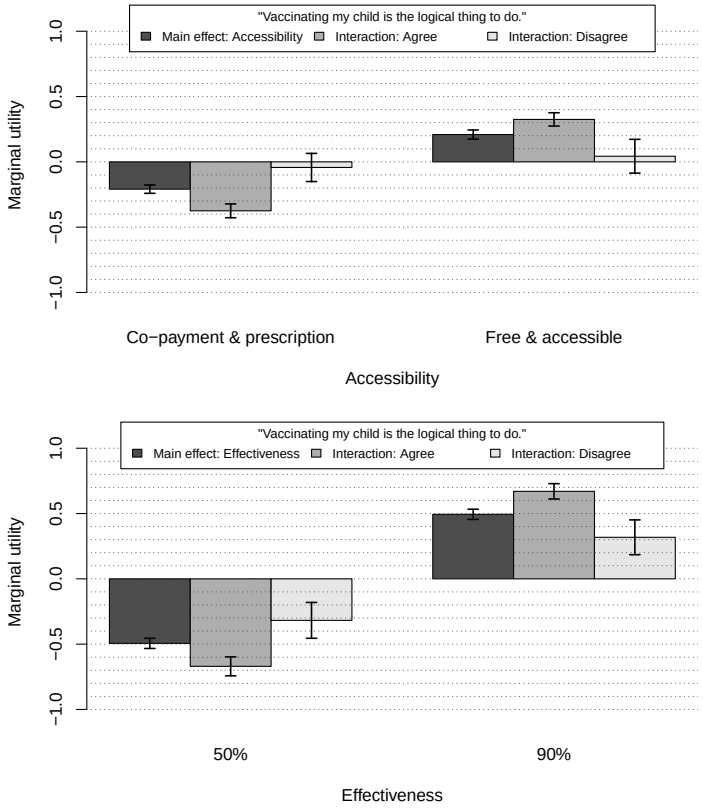

Figure B.4: Marginal utilities for significant covariate interactions with accessibility (above) and vaccine effectiveness (below). 'Youngest child' model, United Kingdom.

Table B.4: Panel mixed logit model estimates (means and standard deviations) and significances of the attribute effects obtained from likelihood ratio (LR) tests. 'Youngest child' model United Kingdom, including covariate interactions

Term	Mean estimate (std dev; subject std dev)	LR Chi-square	DF	P-value
Vaccine effectiveness				
50%	-0.494 (0.039; 0.159)	144.973	1	< 0.0001
90%	0.494 (0.039; 0.152)			
Population coverage (x10%)	0.112 (0.010; 0.107)	95.334	1	< 0.0001
Local coverage (x10%)	0.100 (0.012; 0.100)	68.070	1	< 0.0001
Burden of disease				
Rare & mild	-0.204 (0.048; 0.275)	71.456	3	< 0.0001
Common & mild	-0.359 (0.046; 0.316)			
Rare & severe	0.198 (0.050; 0.174)			
Common & severe	0.365 (0.046; 0.223)			
Accessibility				
Co-payment & prescription	-0.209 (0.032; 0.140)	40.391	1	< 0.0001
Free & accessible	0.209 (0.035; 0.130)			
Mild VRSE				
Common	-0.146 (0.025; 0.094)	31.056	1	< 0.0001
Rare	0.146 (0.023; 0.092)			
Vaccine effectiveness*Logical†				
50%*agree	-0.176 (0.036; 0.137)	26.399	1	< 0.0001
50%*disagree	0.176 (0.038; 0.130)			
90%*agree	0.176 (0.036; 0.142)			
90%*disagree	-0.176 (0.036; 0.136)			
Accessibility*Logical†				
Co-payment & prescription*agree	-0.166 (0.035; 0.132)	25.668	1	< 0.0001
Co-payment & prescription*disagree	0.166 (0.030; 0.134)			
Free & accessible*agree	0.166 (0.036; 0.136)			
Free & accessible*disagree	-0.166 (0.035; 0.127)			

Note: Mean estimates corresponding to the last level of an attribute are calculated as minus the sum of the estimates for the other levels of the attribute. †Logical: "Vaccinating my child is the logical thing to do."

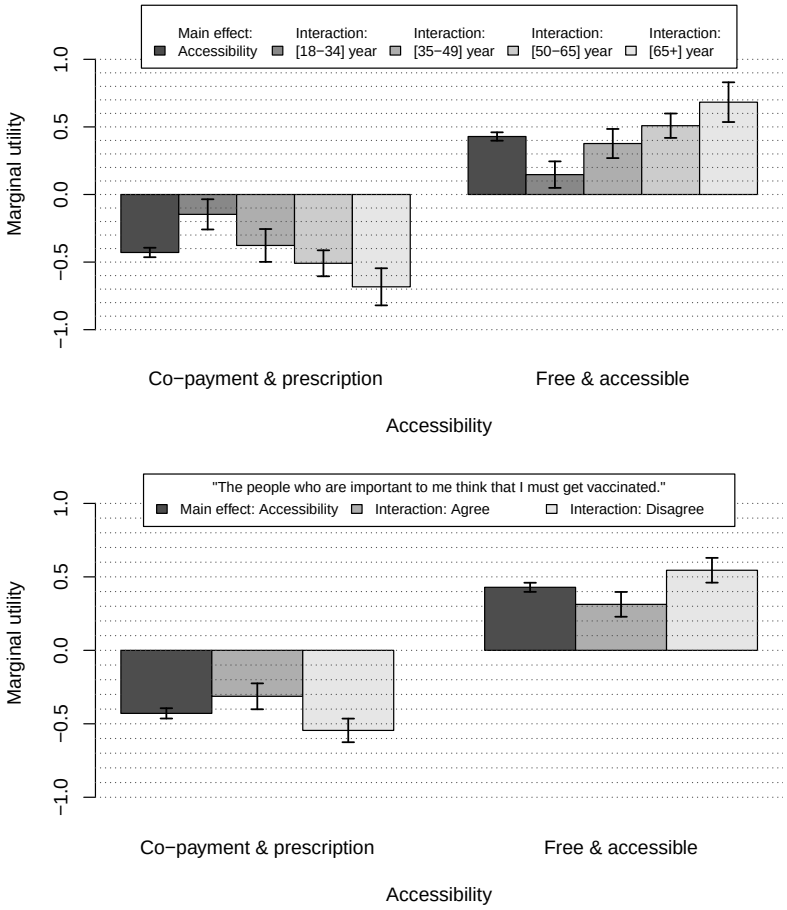

Figure B.5: Marginal utilities for significant covariate interactions with accessibility (both charts). 'Oneself' model, France.

Table B.5: Panel mixed logit model estimates (means and standard deviations) and significances of the attribute effects obtained from likelihood ratio (LR) tests. 'Oneself' model France, including covariate interactions

Term	Mean estimate (std dev; subject std dev)	LR Chi-square	DF	P-value
Accessibility				
Co-payment & prescription	-0.429 (0.035; 0.115)	215.395	1	< 0.0001
Free & accessible	0.429 (0.031; 0.106)			
Vaccine effectiveness				
50%	-0.403 (0.030; 0.237)	137.847	1	< 0.0001
90%	0.403 (0.031; 0.228)			
Burden of disease				
Rare & mild	-0.409 (0.051; 0.399)	125.353	3	< 0.0001
Common & mild	-0.358 (0.048; 0.455)			
Rare & severe	0.295 (0.050; 0.260)			
Common & severe	0.472 (0.052; 0.231)			
Mild VRSE				
Common	-0.184 (0.025; 0.097)	48.017	1	< 0.0001
Rare	0.184 (0.025; 0.102)			
Population coverage (x10%)	0.083 (0.011; 0.143)	47.914	1	< 0.0001
Accessibility*Age				
Co-payment & prescription*[18-34]	0.282 (0.060; 0.092)	42.015	3	< 0.0001
Co-payment & prescription*[35-49]	0.052 (0.052; 0.113)			
Co-payment & prescription*[50-65]	-0.080 (0.045; 0.159)			
Co-payment & prescription*[65+]	-0.254 (0.052; 0.157)			
Free & accessible*[18-34]	-0.282 (0.050; 0.092)			
Free & accessible*[35-49]	-0.052 (0.049; 0.120)			
Free & accessible*[50-65]	0.080 (0.050; 0.174)			
Free & accessible*[65+]	0.254 (0.058; 0.149)			
Local coverage (x10%)	0.069 (0.010; 0.098)	34.527	1	< 0.0001
Accessibility*Peer influence†				
Co-payment & prescription*agree	0.116 (0.026; 0.118)	27.529	1	< 0.0001
Co-payment & prescription*disagree	-0.116 (0.028; 0.109)			
Free & accessible*agree	-0.116 (0.028; 0.110)			
Free & accessible*disagree	0.116 (0.027; 0.107)			

Note: Mean estimates corresponding to the last level of an attribute are calculated as minus the sum of the estimates for the other levels of the attribute. †Peer influence: "The people who are important to me think that I must get vaccinated."

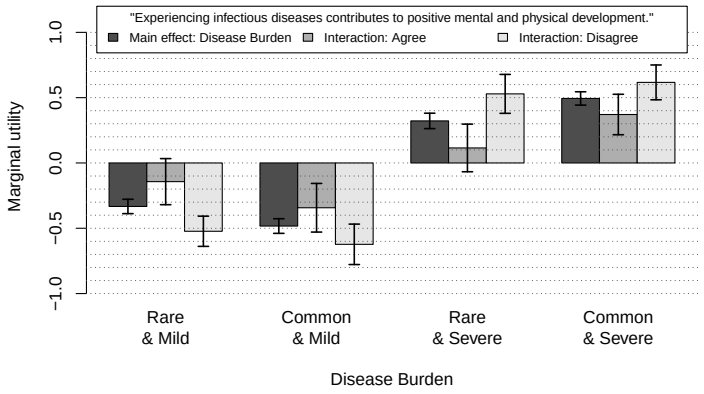

Figure B.6: Marginal utilities for significant covariate interaction with burden of disease. 'Youngest child' model, France.

Table B.6: Panel mixed logit model estimates (means and standard deviations) and significances of the attribute effects obtained from likelihood ratio (LR) tests. 'Youngest child' model France, including covariate interactions

Term	Mean estimate (std dev; subject std dev)	LR Chi-square	DF	P-value
Vaccine effectiveness				
50%	-0.450 (0.028; 0.233)	151.953	1	< 0.0001
90%	0.450 (0.031; 0.273)			
Accessibility				
Co-payment & prescription	-0.330 (0.024; 0.316)	145.020	1	< 0.0001
Free & accessible	0.333 (0.023; 0.296)			
Burden of disease				
Rare & mild	-0.333 (0.055; 0.249)	124.816	3	< 0.0001
Common & mild	-0.483 (0.056; 0.227)			
Rare & severe	0.322 (0.059; 0.178)			
Common & severe	0.494 (0.051; 0.177)			
Population coverage (x10%)	0.092 (0.014; 0.090)	47.444	1	< 0.0001
Mild VRSE				
Common	-0.187 (0.024; 0.112)	47.161	1	< 0.0001
Rare	0.187 (0.024; 0.104)			
Local coverage (x10%)	0.081 (0.011; 0.092)	45.150	1	< 0.0001
Burden of disease*Positive development after infection†				
Rare & mild*agree	0.190 (0.060; 0.216)	27.754	3	< 0.0001
Rare & mild*disagree	-0.190 (0.055; 0.167)			
Common & mild*agree	0.140 (0.058; 0.201)			
Common & mild*disagree	-0.140 (0.057; 0.200)			
Rare & severe*agree	-0.207 (0.055; 0.147)			
Rare & severe*disagree	0.207 (0.055; 0.164)			
Common & severe*agree	-0.123 (0.047; 0.158)			
Common & severe*disagree	0.123 (0.056; 0.376)			
Population coverage (x10%)*Confidence in vaccine info‡				
Population coverage (x10%)*agree	0.062 (0.014; 0.084)	19.992	1	< 0.0001
Population coverage (x10%)*disagree	-0.062 (0.013; 0.087)			

Note: Mean estimates corresponding to the last level of an attribute are calculated as minus the sum of the estimates for the other levels of the attribute. †Positive development after infection: "Experiencing infectious diseases contributes to positive mental and physical development." ‡Confidence in vaccine info: "I have confidence in the information about vaccinations that my care provider (*care provider is your GP or child healthcare professional/paediatrician) gives me."

B.2 Responses to vaccine attitude statements

We display the responses of vaccine attitude statements by country (Belgium, France, The UK and The Netherlands) and by subgroup ('oneself' and 'child' group). These attitudinal statements were not queried in the South African study [414]. Furthermore, we distinguished between statements regarding 'General vaccine sentiments' (Figures B.7 and B.9), and 'Social norms & herd protection' (Figures B.8 and B.10).

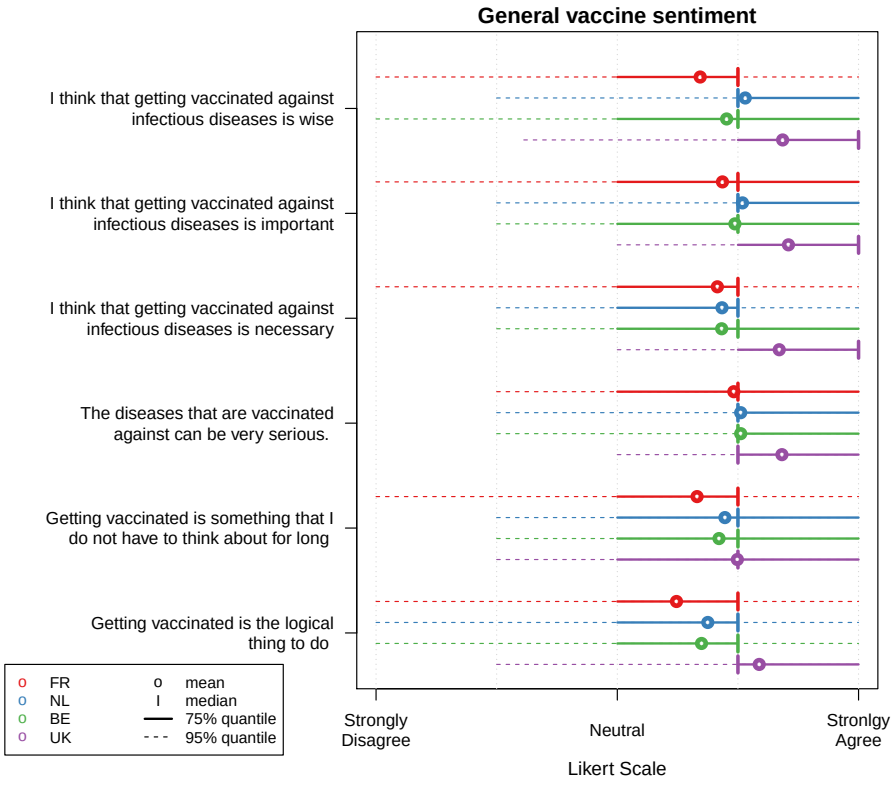

Figure B.7: Likert scale responses to general vaccine statements in the 'oneself' group

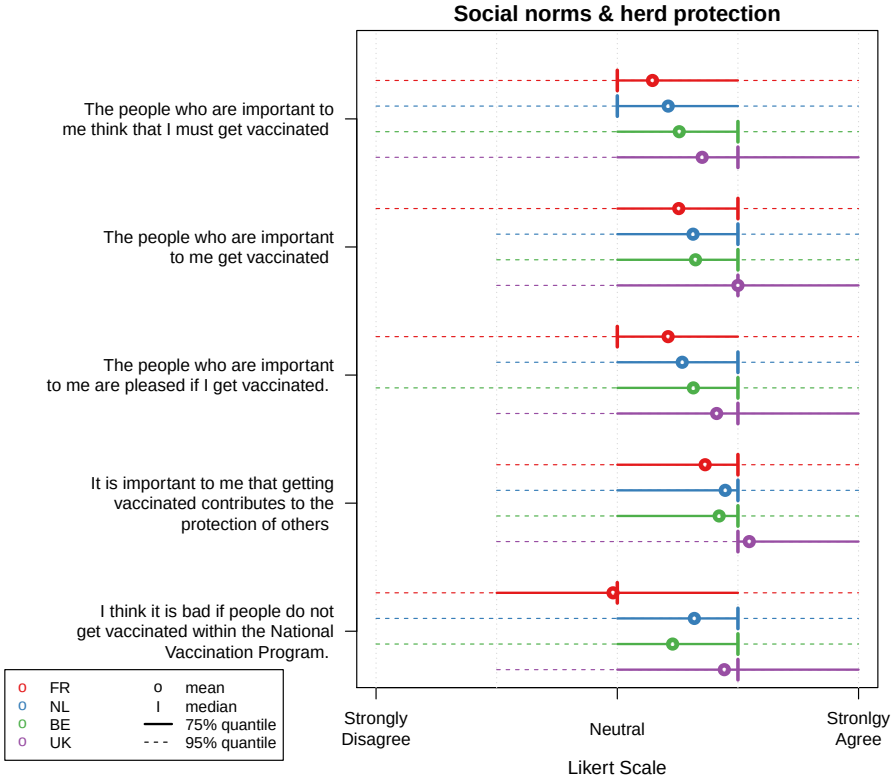

Figure B.8: Likert scale responses to statements with respect to social norms and herd protection in the 'oneself' group

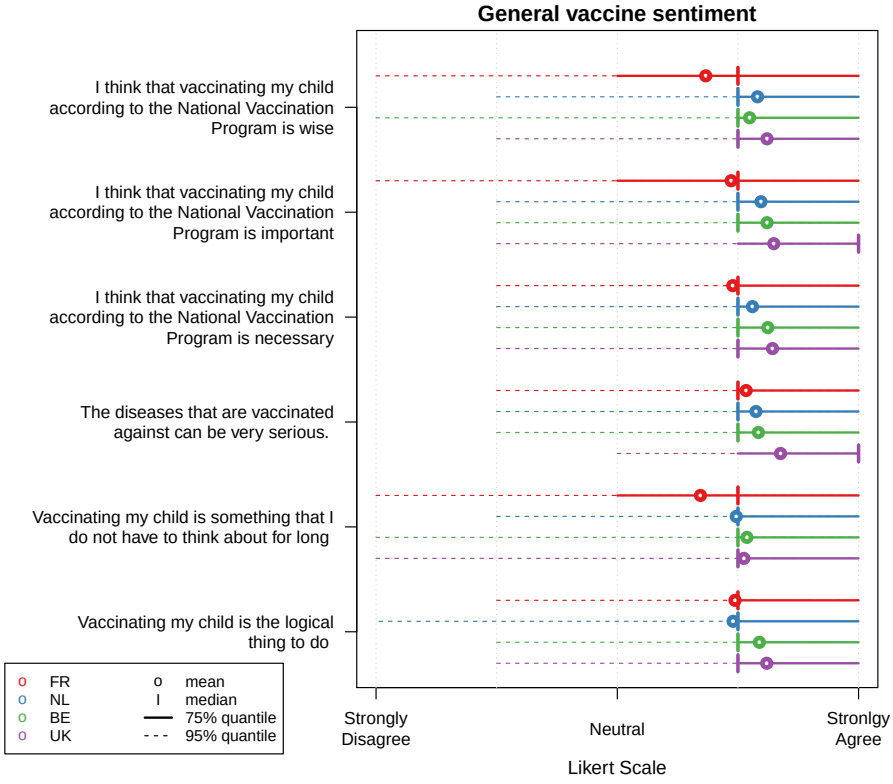

Figure B.9: Likert scale responses to general vaccine statements in the 'youngest child' group

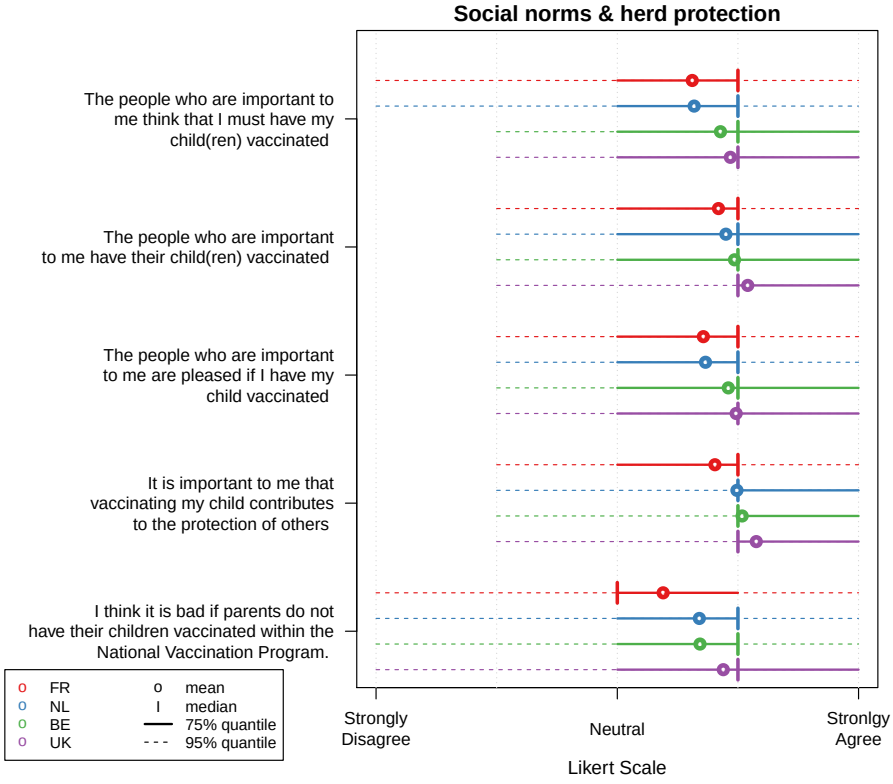

Figure B.10: Likert scale responses to statements with respect to social norms and herd protection in the 'youngest child' group