Faculty of Medicine and Health Sciences

Department of Primary and Interdisciplinary Care - "ELIZA"

Research on health behaviour change determinants in primary care waiting rooms and behaviour changes or artefacts related to this research

Onderzoek naar determinanten voor verandering van gezondheidsgedrag in wachtkamers van de eerstelijnspraktijk en gedragsveranderingen of artefacten in verband met dit onderzoek

Thesis submitted for the degree of
Doctor in de Medische Wetenschappen
at the University of Antwerp to be defended by

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Antwerp, 2023

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Foreword

Forty one years after graduating as a medical doctor, I turned back to my plough to graduate as a doctor in medical sciences. This was not required from a professional point of view, as I had already achieved the position of university professor by the process of validation of acquired experience. However, being a university professor, I just felt a sense of shame not having a PhD like all my other colleagues in the faculty. Further, this appears to be compulsory for awarding of the status of emeritus professorship.

Today, I am very close to retirement, and this is probably my last experience as a student. I was happy to be sufficiently healthy to be able to complete this curriculum, and I have to thank my mentors and friends, Lieve Peremans and Paul Van Royen, who have always been supportive and have motivated me in this project. I also thank Claire Collins who edited this thesis and the four included articles. I finally have to thank my splendid wife, Viviane, for whom this thesis was a greater challenge than for me. This work is a summary of my experience over 41 years of general practice in a deprived environment.

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Chapter 1: General Introduction

The effectiveness of education media in primary care waiting rooms and the related research artefacts

This thesis studies the use and effectiveness of education media, and more specifically posters and pamphlets on the influenza vaccination, in primary care waiting rooms to educate patients and to enhance their health behaviour. The different experimental artefacts that reduce the generalizability of research in primary care, and in particular the so-called Hawthorne effect (HE) also known as observation bias, will also be addressed, in particular in studies considering changes in health behaviour. We will compare the results of a large-scale vaccination campaign using posters and pamphlets in primary care waiting rooms to the natural evolution of vaccination uptake in GPs' customer's base when no intervention is carried out.

GPs waiting rooms are commonly used as areas where patients are exposed to public health advertisements broadcasting messages supposed to improve their health behaviours. Posters and pamphlets are the most common media used in GPs' waiting rooms to circulate public health campaigns. However, there are many simultaneous communications generating an information overload, and often outdated material may be present as the material is not regularly updated. In France, every year in autumn there is a campaign promoting seasonal influenza vaccination. During this campaign, GPs are requested to hang posters and make pamphlets available in their waiting rooms.

Research assessing the usefulness of posters and pamphlets has sometimes demonstrated, with a low level of evidence, an improvement in subjects' knowledge, but never a change in health behaviour. Research assessing changes in health behaviour seems to be biased by many experimental artefacts due to behaviour changes in subjects and investigators. The part of behavioural changes associated with one-off interventions in primary care grafted on the long-term doctor patient relationship remains unclear. One-off interventions are short-term interventions, not sustained over time. This thesis will try to unravel these different research gaps and challenges.

The Jakarta Declaration on Health Promotion and the prerequisites for health

As a practicing general practitioner, I have always been revolted by social inequity in health and against the helplessness of health professionals to influence the lifecycle of most of the more deprived patients

(1). This situation is partly determined by extrinsic factors and can be improved through collaboration between health professionals and social workers by social prescribing. Social prescribing is defined as enabling GPs, nurses and other health care professionals to refer people to a range of local, non-clinical services. This strategy helps sometimes with sustained efforts for guidance, to solve some of these problems (housing, minimum income, access to potable water and healthy food, etc.) (2,3). Nonetheless, most of this inequity is determined by intrinsic factors (schooling and education (4), health lifestyle, social empowerment, sociocultural background, etc.) related to deeply rooted beliefs and attitudes regarding the capabilities of individuals to influence the occurrence of their morbid conditions (5). As described by Fishbein in the reasoned action approach to health promotion inspired by Ajzen's theory of planned behaviour (6,7), this belief has three major components: behavioural beliefs and assessment of the issues, normative beliefs and motivation to comply and control beliefs and perceived power. All three are sustained by background beliefs.

The WHO Fourth International Conference on Health Promotion meeting in Jakarta in 1997 was supposed to lead health promotion into the 21st century. It identified the prerequisites for health as peace, housing, education, social security, social relations, food, income, the empowerment of women, a stable eco-system, sustainable resource use, social justice, respect for human rights, and equity (8,9). The last global conference on health promotion mainly acknowledged a failure of the prerequisites identified in Jakarta in 2019, exacerbated by the COVID-19 outbreak.

Education and health promotion

Education in a multicultural environment brings new challenges. Our education system faces barriers to integrate children and adolescents who do not share the same educational objectives or who are disabled by language barriers or child development disorders. Educative failure, strongly associated with a deprived environment, has an important influence on health behaviour with consequences for life expectancy (10).

Social networks bring people together by sharing and empowering pre-existent beliefs and emotions (11). This can have positive or negative consequences. In most cases, people live their social lives in separate, non-confluent bubbles. Transgenerational communication is difficult but trans-social communication, defined as the communication between different sociocultural groups, is almost non-existent, unless multicultural education based on a comparative approach is promoted in a global environment (12). Spontaneously, educated persons will share beliefs and attitudes with other educated persons and through the exchange of new ideas people are empowered and reach a higher educational and cultural level. A good education and intelligence increases the possibility to listen with an open-minded perspective and to integrate new concepts and skills faster. On the other side, people with a poor educational level have sometimes experienced education failure and developed poor control beliefs and perceived power (10). They will be more likely to hold the belief of a life without the prospect of social progress or of empowerment to acquire new lifestyle skills to improve health. Health professionals in general, and in particular general practitioners (GPs), are the few highly educated persons they know and trust, and they can rather easily meet and interact with (13). However, their expectations in terms of treatment offer are more to relief symptoms at a given time rather than to seek advice to change their lifestyles (14).

Eating habits are embedded in the educational and cultural background of most people, but are also influenced by negative environmental and social context (15). Eating habits have five major

determinants: the intergenerational transmission of food preparation, the availability of ingredients, the price of ingredients, the time available for preparation of meals, the vision and knowledge of the person who is usually responsible for domestic food preparation. In most cases, and in particular in some cultures, women are preparing meals. The school education of girls, female employment with low wages and heavy burden of work, the high price and the low availability of traditional ingredients, the long preparation time of basic ingredients, the empowerment of women in the household and the easy and cheap availability of sweet and fat junk food, has led to profound changes in eating habits. These changes affect feeding rhythms with the disappearance of structured meals and moments of sharing meals. They also affect diets, consisting in an inflation of energy dense ultra-processed foods that contain little or no fibrous material, high in unhealthy types of dietary fat, free sugars, and sodium (16). People with low health literacy levels appear to be more affected by these changes, and obesity in adults is significantly correlated with functional health literacy in multivariate logistic regressions adjusted on other confounders (income, parent obesity, ethnicity, sex) (17,18). Parent obesity is associated with the early onset of obesity in childhood (adjusted OR: 2,53 [1,08-5,94]); adolescent obesity is not associated to parent obesity, but directly to functional health literacy (adjusted OR 5,26 (1,26-22,01]) (18,19).

Well-educated people with good working conditions have a better health status and the longest life expectancy. At the same time people with a lower socio-economic status and hard working conditions experience poorer health status and a shorter life expectancy because of insufficient healthcare services and unhealthy lifestyle (1,20).

Data about the health status of immigrants are mainly based on self-reported health status in cross sectional surveys, but immigrants are less likely than natives to report suffering from a long lasting health problem (21). There were published data of immigrants in three regions of the world namely Europe (22), Northern America (23) and Asia more specific of South Korea (24) and Hong-Kong. In Europe, data is heterogenous as immigrant populations are originally from different regions, with various motivations to migrate and different economic advantages for their host country, some countries like Germany and France falling back on immigrants to operate their industries (22) (i.e. Somalian in Norway (25), Turkish in Germany (26), Maghrebin and sub-Saharan in France (27), and more multicultural in the UK (21)). Although, many studies regarding these populations are lacking data i.e. access to health services, health outcomes, working conditions, migration of married individuals, health status in women and children, and undocumented immigrants. Immigrated women are often a blind spot in public health data as they happen to immigrate after their husband (with or without their children) and are not included in surveys as they don't speak the language of their host country and remain undocumented for a longer time than their husband (28,29). Nonetheless, their role in the education of their children and the perpetuation of traditional attitudes replicating gender inequalities remain central, notably within the family (30). Further, acculturation of immigrant populations in a deprived environment can also lead to a worsening of health behaviour, as noted above regarding feeding, especially in respect of women (31). Public education of these women and their children appears to be warranted in order to reduce social inequities and consequently health disparities (32).

Social determinants in health and related health behaviours

As described above, prerequisites for health and good health behaviour are associated with social determinants. The most influencing social determinants are the education level of the parents (mainly

the mother) and relatives, success in school education, working conditions, income and housing conditions (33). As mapped in figure 1, education to enhance health literacy appears to be a modifiable mediating factor from which the other factors derive.

Paradigms to illustrate the close association between education level and health behaviour are numerous in dental health (34), cervical cancer prevention (35), and smoking (36). In this thesis we chose to use vaccination (37) as the paradigm.

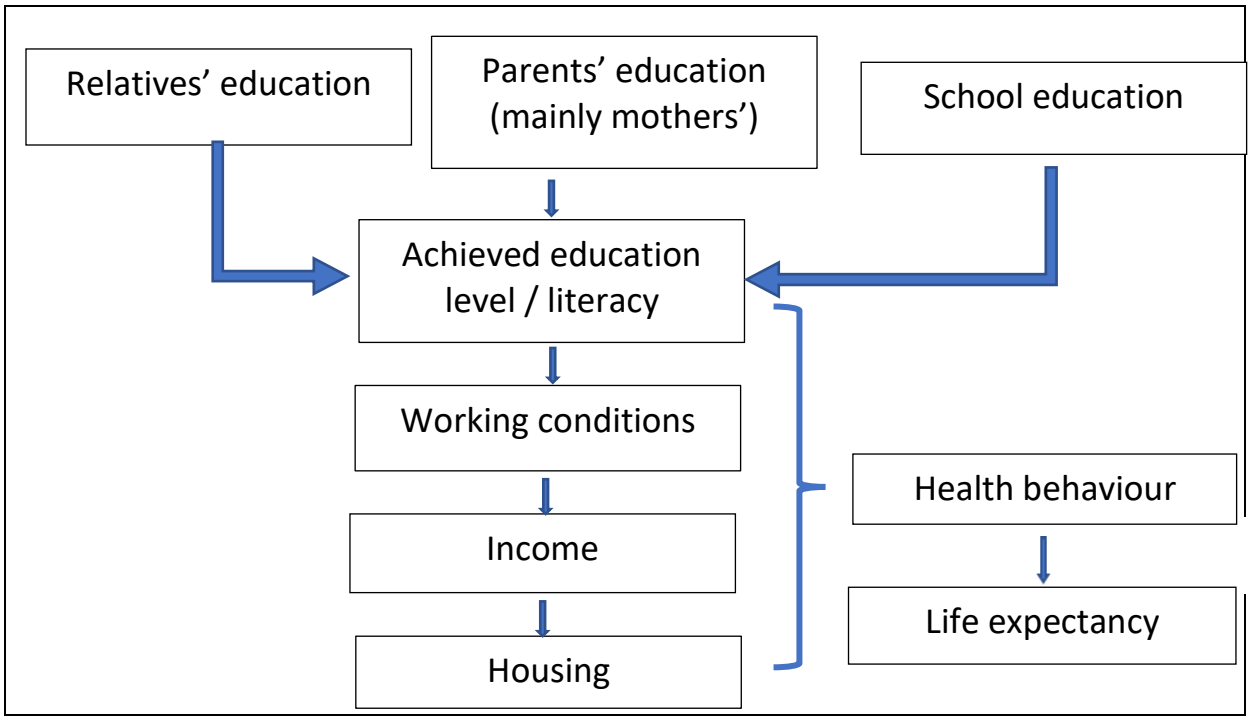

Figure 1: From education to life expectancy (self-creation)

Vaccination as a marker associated with education and health behaviour

Vaccine hesitancy in Europe and in France

Vaccine hesitancy was defined in 2012 by the WHO Strategic Advisory Group of Experts on Immunization (SAGE) working group on vaccine hesitancy as "*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*", suggesting that issues with language or health literacy affected uptake (38,39). As the WHO identified vaccine hesitancy as one of the top ten global health threats in 2019 (40), efforts to define the factors responsible for reduction in vaccine confidence are necessary. Vaccine hesitancy related to losses in confidence in vaccines and immunization programmes is of growing importance, but insufficient to explain the emergence or re-emergence of vaccine preventable diseases such as measles, mumps and pertussis. War, political and socioeconomic collapse, shifting poverty and vulnerability to weather events and climate change are additional factors to consider (41). In the European region, in France inhabitants had a more negative attitude toward vaccine safety during the two last decades (42). In a nationwide telephone survey 41% of respondents reported that they

disagreed that vaccines are safe (43). Vaccine hesitancy determinants like education and socio-economic status do not influence hesitancy in only one direction: higher education may be associated with both lower and higher levels of vaccine acceptance (44). Antivaccination attitudes in 24 countries among 5,323 participants were highest among believers in conspiratorial theories, people with a low tolerance for impingements on their freedom, nonconformists and anti-scientists. This attitude was also seen among people having a strong individualistic/hierarchical worldview. These people have a strong vision on how much control society should have over individuals, and whether hierarchies are desirable. Another reported barrier was a high level of fear and phobia toward blood and needles (45). Foreign disinformation campaigns in social media also tend to increase the number of negative vaccine tweets (46).

Compulsory vaccinations in France

Since January 1st, 2018, eleven immunizations are compulsory in France for children at the age of 24 months (47). They are diphtheria, tetanus, poliomyelitis, pertussis, haemophilus influenzae type B, hepatitis B, invasive pneumococcal infections, Neisseria meningitidis serogroup C, measles, mumps and rubella. Since 2018, vaccination uptake for diphtheria, tetanus, poliomyelitis and pertussis rose to 99.4%, for hepatitis B to 90.5%, and for measles, mumps and rubella to 84%. This assessment was driven through the study of the mandatory certificate of global health examination established by the listed GP, the paediatrician or the mother and child welfare service at 24 months of age, summarizing the vaccinations (compulsory or not) that were dispensed to the child (48). Though these certificates are compulsory since the 15th of July 1970, parents do not always present their children at consultations to complete this global assessment or do not send the certificate to the public health services of the county (*département*). For these reasons, only 30.2% of the certificates reach authorities that extrapolate vaccination uptake deriving from these certificates to the entire French population. This might bias the outcome on social ground (less completion in deprived and less educated populations) (49). To measure the incidence on vaccination behaviour of posters and pamphlets in GPs' waiting rooms, the data collection method to assess an intervention promoting these eleven immunizations based on these certificates seemed difficult to implement, insufficiently precise and barely feasible.

Recommended non-compulsory vaccinations in France

The situation regarding recommended non-compulsory vaccinations differs between countries in Europe and worldwide and vaccination programs adapt quickly in time (50). For instance, the Bexsero® vaccine against Neisseria meningitidis (group B) that has been marketed in Europe since 2013 is recommended in most European national infant immunisation programmes. However there is big variation in implementation from 2015 in the UK (51) and only from October 2022 in France. To illustrate the rationale of the choice for a model of education in primary care on health behaviour through vaccination promotion using posters and pamphlets in primary care waiting rooms, we limited this description to three representative examples that are HPV, COVID-19 and influenza vaccines.

Human papillomavirus vaccination (HPV)

Target population

French recommendations regarding HPV vaccination have changed many times during the last decade. Since 2017, it has been recommended in females between 11 and 14 years of age with two injections of the bivalent vaccine (Gardasil®, Cervarix®), and for females between 15 and 19 years of age with three injections. Since December 2019, HPV vaccination recommendations were extended to males between 11 and 14 years of age. Since February 2020, for persons who did not start their vaccination scheme with Cervarix®, immunization is recommended using the Gardasil 9® 9-valent vaccine. HPV vaccines are reimbursed by insurances like other medications (70% mandatory insurance and 30% complementary insurance (private and payable or provided by the state to low- income households)).

Vaccination uptake and specific hesitancy

HPV vaccination coverage, policies and practical implementation are very heterogenous in Europe. In 31 European countries between 2006 and 2017, 30 of them targeted girls from 9 to 15 years of age and 11 countries also boys. The coverage rate was monitored in 25 countries for girls and varies from: ≥71% in ten countries, 51-70% in seven, 31-50% in four, and ≤30% in four. In Belgium, the uptake was different between Flanders, with a structured vaccination programme since 2010 and a 93% vaccination coverage, and Walloon and Brussels, with a structured vaccination programme since 2011 but a coverage of only 36% (52).

In France, the French Cancer Plan 2014–2019 aimed to have a vaccination coverage of 60% of the whole targeted population to achieve a reduction by 30% of cervical cancers over 10 years (53). However, it is difficult to estimate vaccine series completion between indications of 2 or 3 injections in a rather narrow age range. Estimations are based on the number of vaccination units delivered in community pharmacies collected from the '*Système national d'information inter-régimes de l'assurance maladie'* (National Health Insurances Information System: SNIIRAM) claim database (merging databases from all French mandatory health insurance regimes) and the generalist beneficiaries sample (a nationwide randomized sample of about 500,000 social insured persons). Vaccination coverage does not exceed 30%, and their evolution is diminishing (54,55). Because of its opportunistic vaccination programme, France is situated among the four countries where vaccination uptake is the lowest in Europe. It is also known, though not measured, that many vaccination units delivered by community pharmacies are not injected, mainly related to fear and phobia toward blood and needles in adolescents or religious and cultural beliefs about girls sexuality in the Muslim minority (56). Youngsters have a poor knowledge about HPV and preventive vaccination issues in general. The major challenge for educating adolescents, is to reach them and to communicate in an appropriate way with them. Schools might play a role in health promotion and education (57). The best information channel may be social media, but they can carry positive as well as negative or irrational messages, and literature overall is lacking in systematic and rigorous research examining the effects of social media on HPV related knowledge, attitudes, and behaviours in France (58). In the USA, discussions on Twitter® were frequent about HPV vaccination in the years 2015-2016, they dipped from about 40% of interest to <1% after 2019 with the COVID-19 pandemic; the most forthcoming emotions were fear, sadness, anger and disgust, with few feelings of trust or joy; however, pro-vaccine sentiments were predominant in about 75% (59). In France, with regard to HPV vaccination uptake and deprivation, factors significantly associated both with a lower cervical cancer screening (CCS) uptake and with insufficient HPV vaccination were the lack of a complementary private health insurance ($P = 0.023$ and $P = 0.037$, respectively) and living in a family with a low household income ($P < 0.001$ and $P = 0.005$, respectively). A low education level was associated with a lower CCS uptake ($P < 0.001$). The absence

of CCS uptake in the last three years in mothers was associated with a lower level of HPV vaccination in their daughter (P = 0.014) (60).

Vaccination campaigns

There is no free delivery of HPV vaccines, no vaccination in a scholarly environment with a structured vaccination programme, and no consistent nationwide French vaccination campaign. HPV vaccination is only opportunistic in France, on parents' request or health professional initiative. Although 73% of GPs reported recommending HPV vaccination, up to 50% would not recommend it because of concerns, including changes in patients' health behaviours and doubts about safety or efficacy (61). The French authorities published on the 7th of March 2023 an official release indicating that a widespread vaccination campaign will be launched in colleges for 5th grade students to better fight against the papillomavirus. Vaccination, that will be accessible to all schoolchildren, girls and boys, should increase vaccination coverage and prevent infection. Starting in September 2023, middle school students will be able to be vaccinated free of charge. Parental agreement will be required and vaccination will not be mandatory. A coverage rate of about 30% is expected.

Seasonal influenza vaccination

Target population

In France, the targeted population for seasonal influenza vaccination is all persons aged 65 years and over, vulnerable patients with a chronic condition such as asthma, COPD or diabetes, and pregnant women. Vaccination is also recommended in infants, but neglected because of the 11 mandatory immunizations, while influenza vaccinations are opportunistic and not promoted in children by the influenza vaccination campaigns (62). Since February 2023, French health authorities recommend influenza vaccination in children and adolescents between 2 and 17 years of age using Fluenz Tetra®, a live attenuated nasal spray suspension influenza vaccine.

On the European level, the target populations are also specified by age and chronic conditions. However, ages differ across countries, in infants and young children as in elderly. For instance, regarding the elderly in 2014-2015 (when we implemented our trial), eighteen countries recommended vaccination for individuals ≥65 years of age. In six countries (Germany, Greece, Hungary, Iceland, the Netherlands and Portugal), vaccination was recommended for those aged ≥60 years. Two countries (Malta and Poland) recommended vaccination for individuals aged ≥55 years. Slovakia recommended vaccination for individuals aged ≥59 years. The remaining three countries (Austria, Belgium and Ireland) recommended vaccination for those ≥50 years. However, in Ireland, like in France, only people aged ≥65 years are being offered the seasonal influenza vaccination free of charge, and only for this age group is the vaccination coverage monitored. Note that age recommendations can vary under successive vaccination campaigns (63). It is of note that in Belgium the level of recommendation differs for people between 50 and 65 years of age without chronic disease, where vaccination is recommended based on a shared decision making with the GP, and in people ≥65 years of age where vaccination recommendation is permanent (64).

Vaccination uptake and specific hesitancy

The expected vaccination coverage in the targeted population is 75% as recommended by the WHO in 2003 and still adopted as the objective by French and European health authorities (65,66). Further

recommendations of the WHO do not assume this coverage but update the available vaccines, the target groups, the coadministration of vaccines (67). Vaccination against seasonal influenza consists of a yearly vaccine injection before the start of the epidemic that occurs from early in December to late in February. The standard influenza vaccine is inactivated and fragmented, and encloses four viral strains in accordance with the recommendations of the WHO for the next epidemic in the Northern Hemisphere. As in most European countries, the actual vaccination uptake percentage was 45.7% in 2014-2015, placing France in the upper range in Europe, but far from the expected coverage.

In France, the trend was stable the two next years (2015-2016, and 2016-2017) (63,68). In the following years, the vaccination rate remained stable, with an important rise the first winter after the COVID-19 outbreak (national mean coverage in targeted people: 2016-2017: 45.7%; 2017-2018: 45.6%; 2018-2019: 46.8%; 2019-2020: 47.8%; 2020-2021: 55.8%; 2021-2022: 52.6%) placing France still in the upper range in Europe (69). As for the HPV vaccination, public health estimates are based on the number of vaccination units delivered in community pharmacies collected from the SNIIRAM claim database of the mandatory health insurance and the generalist beneficiaries sample (55).

Beliefs about seasonal influenza (contagiousness, risk, transmission and prevention) are often incorrect in persons with a low educational and socioeconomic level, and associated with a lower vaccination uptake (70). Vaccination is favoured by age (between 65 and 75), by a higher level of education and a higher socioeconomic status (70). For these reasons, influenza vaccination appears to be a good marker for education and socioeconomic level.

Vaccination campaigns

In France, a seasonal vaccination campaign starts every year in October, when the seasonal influenza vaccine is marketed in pharmacies. Persons in the target population receive from their mandatory insurance company an invitation to be vaccinated with a voucher for a free vaccine unit to be delivered by their community pharmacy. The voucher comprises also a free injection of the vaccine that can be given by general practitioners (GPs), nurses, pharmacists or midwives. Referring to the theory of reasoned action, environmental factors and skills and abilities are facilitated as much as possible, and intention to vaccinate is the main factor of effective vaccination (6). At the beginning of the vaccination campaign, advertisements are broadcasted on most of the TV and radio channels. Posters and pamphlets are delivered to GPs to be displayed in their waiting room and to pharmacists to be exposed on their shop windows.

COVID-19 vaccination

Target population

The target population for COVID-19 vaccination has changed with the evolution of the pandemic, the availability of vaccine units, and the logistic problems to be solved for their provision.

The first vaccine to be marketed in Europe was the Comirnaty® vaccine in December 2020, a vaccine containing tozinameran, a messenger RNA (mRNA) molecule with instructions for producing the spike protein from SARS-CoV-2. The vaccine is produced in Germany by BioNTech Manufacturing GmbH® and distributed by Pfizer®. In February 2021, a second mRNA vaccine was marketed, the Spikevax® containing elasomeran, developed by the American company Moderna®, the United States National Institute of Allergy and Infectious Diseases (NIAID), and the Biomedical Advanced Research and Development Authority (BARDA). In February 2021, a first viral vector vaccine was marketed, the Oxford–AstraZeneca COVID-19 vaccine®, renamed Vaxzevria®, using as a vector the modified chimpanzee adenovirus ChAdOx1, developed in the United Kingdom by Oxford University and British-Swedish company AstraZeneca. Due to rare but severe side effects, the administration of this vaccine was suspended in France in March 2021 and withdrawn in July 2021. In March 2021, a second viral vector vaccine was marketed, the Janssen COVID-19 vaccine®, renamed Jcovden®, based on a human adenovirus type 26 that has been modified to contain the gene for making the spike protein, developed by Janssen Vaccines in Leiden, Netherlands, and Janssen Pharmaceuticals, Belgium, a subsidiary of American company Johnson & Johnson. Due to rare but severe side effects, the administration of this vaccine was suspended in France on February 22, 2022, its injection being limited to some exceptional cases. Since May 2021, only mRNA vaccines are injected in France by precautionary principle.

Vaccination strategies and recommendations were elaborated in the different European countries by National Immunization Technical Advisory Groups (NITAGs). These groups of multi-disciplinary experts provided scientific advice to policy makers to enable them to make informed immunization policy and programme decisions. NITAGs faced challenges using their routine approach to develop recommendations for COVID-19 vaccines and the WHO Regional Office for Europe (Regional Office), with the support of the Robert Koch Institute, developed an innovative approach of a series of webinars, provision of materials, and remote technical assistance to address these challenges (71). Advice and recommendations from NITAGs have thus been rather homogeneous across Europe. In contrast, political choices might have differed substantially across different countries, based on public opinion, national points of interest and economic consequences.

In France, the first targeted populations in December 2020 were institutionalized elderly persons and one week later, health professionals, the vaccine being given by authorized vaccination centres in order to guarantee logistic constrains. The choice of a mandatory complete vaccination (2 injections) for health professionals was made on a political level on September 15, 2021 in France like in Greece, Italy, and Hungary following the advice of the European Convention on Human Rights (ECHR) judgement no. 116 (2021) of 8 April 2021 establishing the principle of mandatory vaccination (72). Such a decision was discussed in other countries like the UK (73,74) and Belgium (75) but not implemented.

Gradually, from January 2021, the target population was extended to still younger and healthier populations, following the availability of vaccines, the results of clinical trials and the revisions by the European Medicines Agency (EMA). The “Sanitation Pass” was created in France on June 1st, 2021 (as in Germany, Italy and Latvia), and the European regulation “Vaccination Pass” on January 22, 2022, making *de facto* vaccination compulsory for many activities of daily life.

Vaccination uptake and specific hesitancy

On July 28, 2022, 78.6% of the French population had a complete vaccination protocol (2 injections), and 62.2% had a first booster (76). Vaccine hesitancy has been very heterogenous in Europe ranging from 6.4% of adults in Spain to 61.8% in Bulgaria, based on different attitudes like trust in government or high conspiracy beliefs (77). COVID-19 vaccination will probably be remembered as the summit of social networks misled vaccination hesitancy (VH) with a general anti-vax stance, Twitter® on top, causing fear and anxiety, mainly in the most eager, but also ignorant populations; perceived trustworthiness of foreign vaccine production and testing protocols may have played an important role (78). Being female, younger, of lower income or education level and belonging to an ethnic minority group were associated with being less likely to intend to vaccinate (79). Therefore, COVID-19 VH appears in France as the combination of the influence of social networks as in HPV vaccination in younger populations (59), and of educative and socioeconomic disparities as in seasonal influenza vaccination (80).

The argument to choose seasonal influenza vaccination as paradigm

The work for this thesis started in 2014, far before the start the COVID-19 pandemic, ruling out COVID-19 vaccination for the choice of model to study the influence of education by primary care teams, in particular by posters and pamphlets in waiting rooms, to measure induced changes in health behaviour.

Mandatory vaccinations are poorly associated with education and health literacy as the uptake rate, encompassing 85 to 90% of the population at two years of age mainly reflects imperatives. For this reason, demonstrating a change in knowledge or health behaviour promoting for instance tetanus vaccination in waiting rooms seems a difficult target to meet (81). Data regarding mandatory vaccines are derived from the 24 months of age health certificates, and the final numbers are extrapolated from the 30.2% of certificates collected by health authorities (see above): the poor reliability of these data makes the measure of small differences hazardous to compute.

HPV vaccination was a good candidate. However, opposite mandatory vaccinations, the uptake of 30% is very low and keeps on diminishing, and vaccination hesitancy is major, related to many factors (cost and availability of vaccine units, painful injection, discussed efficacy on clinical endpoints, changes in clinical indications (age, gender, sexual orientation), marketing of new vaccines, etc.) (82). All these confounders make it difficult to identify the best health promotion messages that could possibly enhance knowledge and change health behaviour (83). Assessing the efficacy of health promotion media in general practice waiting rooms (posters, pamphlets, televisions, tablets…) is not relevant when the right triggers to shift patients' attitudes have not been identified. Further, this excess in hesitancy reasons reduces the relative share of responsibility of health literacy in vaccination uptake.

Finally, the best candidate vaccination to assess the effectiveness of vaccination promotion in GPs' waiting rooms appeared to be seasonal influenza vaccination. The population to be vaccinated is constant in France and clearly identified for many years, the vaccination promotion campaigns are repeated every year from the middle of September until the end of November and triggers in promotion messages to shift patients' attitudes are clearly identified. Accordingly, reasons for vaccination hesitancy are clear, and their association to education level and health literacy are well demonstrated (84). People in the target population receive individually an invitation form with a

voucher to collect a free vaccination unit in their community pharmacy, and many health care professionals are assigned to vaccinate them. Environmental factors and individual skills are fully facilitated to achieve vaccination when the intention to vaccinate is existing (6). The same people are infants and young children, elderly or those affected by a chronic condition, and most of them will attend their GP's waiting-room during the time of the vaccination campaign.

Primary health care and health education

All the healthcare professionals, and in particular primary healthcare professionals working in deprived areas, have made the association between education level and health. This association can be well-documented or just empiric, but it is supported by their daily experience.

Motivating persons to change their health behaviour is a day-to-day concern of most of primary health caregivers, willing to prevent the occurrence of diseases or complications of existing chronic conditions in their patients' lives. Preventive education programs in primary care encompass primary, secondary and tertiary prevention.

Primary prevention approach focuses on preventing disease before it develops. In primary care it focusses in children mainly on vaccinations (85), early detection of pervasive developmental disorders (86), prevention of obesity (87) and dental care (88). In adolescents, it focusses on prevention of addictions (89), suicide (90) and intimate violence (91). In adults, primary prevention focusses on intimate partner violence (92), early detection of essential hypertension (93), diabetes mellitus (94) and chronic obstructive pulmonary disease (COPD) (95). In elderly patients, it aims at screening for frailty in order to prevent disability (96). If these are the more common reasons for primary prevention and education, many others of less importance from a public health perspective can be cited, like promoting breastfeeding (97) or detecting pregnancy diabetes (98).

Secondary prevention attempts to detect a disease early and to intervene early at a preclinical phase of the illness, pregnancy or age. Again we find vaccinations for vulnerable populations, mainly for respiratory diseases like COPD (pneumococcal , influenza, covid-19) but also for other diseases like herpes-zoster virus or boosters for tetanus, poliomyelitis, diphtheria and pertussis (99). There are also mass screenings for early detection of cancers in the general population: cervical cancer (100), breast cancer (101) and bowel cancer (102).

Tertiary prevention is often difficult to separate from treatment, as it is directed at managing established disease in someone and avoiding further complications. In order to limit examples, we will only focus on the early detection in diabetic patients of cardiovascular diseases (103), kidney diseases (104) and retinopathy (105).

As seen above, prevention in primary health care encompasses large populations and almost all the fields of medicine. If general practitioners are generally very proactive and promote most prevention procedures in infants and children, they happen to be less incisive for other primary or secondary prevention procedures (106,107). Though the preferentially targeted populations for preventive medicine are the ones with the lowest level of education and health literacy, as they have a shorter life expectancy and an earlier onset of chronic conditions, they are also the most difficult to motivate, even for preventive health checks in an experimental environment (108). Their motivational shortfall is mainly associated to their expectations in terms of health service utilization more directed towards the relief of symptoms (109). For these reasons, instead of reducing health inequities in the less educated populations, preventive medicine might amplify them (110,111).

The waiting room as an educational area

General practitioners use a waiting room where most patients spend time before their encounter with their doctor. This time can be used to educate patients implementing diverse media. The most common are posters and pamphlets. However, practically, these posters are not often replaced, are directed towards outdated campaigns and tackle many different health promotion themes (112). Television screens are also common in waiting rooms. Computers and tablets can also be used (113). By experience, mainly since the COVID-19 pandemic and in the younger populations, the most common occupation in waiting rooms is viewing one's own smartphone and there might be a benefit for GPs to identify heath apps known by their patients (114,115).

Research gaps

The research gaps in the field of education of patients in GPs' waiting rooms are numerous as the topic has seldom been explored:

As noted above, there are many themes for education of primary care patients regarding mainly primary and secondary prevention. The purpose of this education is to change patients' health behaviours aiming at expanding life expectancy in good health. The prime target of this education are patients with a low education level and poor health literacy. These populations are difficult to study as they avoid participating in research and investigators avoid enrolling them in studies as it is difficult to ensure they understand the study recommendations (116).

To develop efficient communication in order to address patients' health behaviours, it is important to identify the barriers that prevent behaviour change. The best models to exemplify health behavioural changes today appear to be the theories of reasoned action and planned behaviour that were used to tackle behavioural barriers to seasonal influenza vaccination uptake (84,117). However, health messages implementing these findings in real life campaigns have not been assessed and a change in behaviour of patients has not been demonstrated.

Using GPs' waiting rooms, where patients spend their time before the encounter with their practitioner, as an area for patient education is common practice. However, the different media that can be used to implement patient education in the waiting room have not been listed and assessed, in particular to demonstrate a change in health behaviour.

Hanging posters and making pamphlets available in GPs' waiting rooms is also of common use. However, the efficacy of this material to change patients' health behaviour has never been clearly established. In particular, in France, the annual campaign promoting seasonal influenza vaccination with posters and pamphlets in GPs' waiting rooms has never been assessed.

In published studies relating to the assessment of health promotion in GPs' waiting rooms, it is always unclear if the observed effect is related to the intervention in the waiting room or to the motivation of the health care professionals who implemented the research. The interference of the doctor-patient relationship and of the behavioural change of patients and doctors in an experimental environment in primary care remains vague.

Finally, in the frame of the long-term relationship between GPs and their patients, the impact of one-off interventions to modify patients' health behaviour has never been assessed compared to the effect of the regular encounters between the GP and his/her patient.

Main research questions and aims of this thesis

The overall aim of this thesis is to test posters and pamphlets as the most common patient education tool in GPs' waiting rooms to change patients' health behaviours using the influenza vaccination campaign as a model, and to clarify the reasons why our findings differ from public health data: experimental artefact or cohort effect?

In this thesis, we will:

- review the different education media used in primary care waiting rooms to educate patients and assess their efficacy to enhance patients' health behaviour (chapter 3);
- make use of the seasonal influenza vaccination campaign to test the usefulness of posters and pamphlets in GPs' waiting room to enhance vaccination uptake (chapter 4);
- sort out the different experimental artefacts that reduce external validity of research in primary care, and in particular the so-called Hawthorne effect, also known as observation bias (chapter 5);
- compare the results of one vaccination campaign to the natural evolution of vaccination uptake in GPs' customer base (chapter 6).

Based on these aims, we formulated the following research question for this thesis:

1) to identify, describe and appraise studies that have investigated the effects of audio-visual aids on health promotion in primary healthcare waiting rooms and to determine which factors influence this impact (chapter 3);
2) to evaluate the effect of an advertising campaign using posters and pamphlets in GPs' waiting rooms on the number of influenza vaccination units delivered in community pharmacies, and to determine predictors of individual vaccination (chapter 4);
3) to refine the definition of the Hawthorne effect (HE) in medical research and outline the progress of research on the HE in terms of its existence and characteristics, to estimate the size of the effect in primary care studies and to estimate the risk of a HE in our research (chapter 5);
4) to assess the possibility of an HE, through comparison of the vaccination rate in the control group of the RCT to a third group of patients enlisted with GPs who were not aware of the RCT at the time the study was conducted and to assess the possibility of a cohort effect in this particular RCT (chapter 6).

Chapter 2: Methodologies used in this thesis

1st Step: A narrative review of the different audio-visual aids used in General Practice waiting rooms (chapter 3)

A systematic narrative review of international literature was used to identify, describe and appraise the different audio-visual aids (AVAs) that GPs use to educate their patients in their waiting rooms. This review was based on the recommendations of the Cochrane handbook (118) and included all observational and intervention studies with abstracts published between 2004 and 2017.

To be eligible, waiting rooms had to be sited outside hospitals, in primary care settings and diverse targeted outpatient clinics (family planning, mother and child, sexually transmitted diseases, etc.).

The included studies could be observational, clinical trials or qualitative approaches. AVAs could be posters, pamphlets, videos on television screens, computers or tablets, education programmes displayed by Bluetooth® association on smartphones, or computer-based education software. The tools had to be visible or available in waiting rooms.

The analysed outcomes were the description of one or more AVAs on health promotion and the assessment of the aid's effect. The secondary outcome was to identify and assess the factors that contributed to this effect.

The review searched Medline, Web of Science, Cochrane Library, Scopus, Google Scholar, and SUDOC (Central French Universities Documentation Service) from 1 January 2004 to 31 December 2017, with language availability restricted to English and French. The tested MeSH keywords algorithm was: (Primary health care OR family practice OR general practice NOT hospitals) AND (patient education as topic OR health promotion) AND (audio-visual aids OR advertising as topic OR pamphlets OR posters).

The quality of the articles was assessed by one researcher through the contemporary CONSORT table for intervention studies (119), and the STROBE for observational studies (120).

2nd step: A RCT to evaluate the seasonal influenza vaccination campaign using posters and pamphlets in General Practice waiting rooms (chapter 4)

To test the efficacy of posters and pamphlets in GPs' waiting rooms in changing patients' health behaviours, we choose to evaluate the advertisement campaign promoting seasonal influenza

vaccination in 2014-2015. From the first step, we knew that the effect of such a campaign was small or controversial, and that we needed a large study cohort if we meant to demonstrate anything (113,121,122).

For this purpose, we conducted a single-blinded 2/1 registry-based cluster randomised controlled trial (RCT). A cluster was defined as the whole group of patients aged 16 years and over, targeted to be vaccinated against seasonal influenza registered in each participating GPs' patients list (patients with a chronic condition requiring vaccination and patients aged 65 years and over). Seventy-five GPs practicing in the area of the Lille-Douai Health Insurance District were enrolled following the order of a randomised list. Their consent to participate was collected by telephone and was confirmed by a written validation. Twenty-five GPs were allocated by a computerised random draw to the intervention group and the remaining 50 GPs to the control group.

The intervention consisted of removing all the material from the walls and tables in the waiting room (except mandatory information) and exposing only the official Health Insurance poster promoting influenza vaccination and leaving on the tables 135 pamphlets of the same campaign. This processing was carried out by the research team. Waiting rooms in the control group were left in their usual state.

The primary outcome was the number of influenza vaccination units delivered by the community pharmacies to the involved patients, retrieved from the SIAM-ERASME claim database of the main mandatory Health Insurance fund. Baseline data were those from the 2013-2014 vaccination campaign.

A univariate analysis was performed to present the baseline characteristics of patients after randomization. To assess the association between the vaccination status and the group, because of the hierarchical structure of the data and the high incidence rate of the main outcome, we used a generalized estimating equation Poisson regression clustering by GP; an exchangeable working correlation matrix was used. Although the trial is randomized and therefore the confounding factors are already balanced between the groups, in order to ensure that the "previous influenza vaccination" factor was fully controlled, the variable "Previous influenza vaccination" was used as an adjustment variable in the model.

The protocol passed the Ethics Committee of the Lille University Hospital (France) and the National Electronic Data and Liberty Commission. It was registered on ClinicalTrials.gov (NCT03239795).

3rd step: A systematic review and meta-analysis evoking the Hawthorne effect (chapter 5)

The trial in step 2 did not support the efficacy of an educational prevention strategy based on posters and pamphlets in GPs' waiting rooms. However, we demonstrated that being vaccinated the previous year maximised the relative risk to be vaccinated the next year (RR=5.63; 95CI: [5.21;6.10]). We noted an increase in the vaccination uptake both in the intervention and in the control group by about 3%, while public health data noted a decrease by 2.4% of the vaccination uptake in the same area. For these reasons, we evoked a Hawthorne effect (HE) that might have masked a difference between groups due to the reduction of the effect size and a rise in the vaccination uptake in both arms of the study population. Resuming the history of the HE, we noted that it's definition was unclear, or even that the existence of the HE was disputed (123). Some authors preferred to use the terms of measurement or participant reactivity (124,125). The HE appeared to be very heterogenous across studies, its size varying between 6.9% and 65.3% in binary variables regarding hand hygiene in hospital

wards (126). The last notable work regarding the definition and the size of the HE was a review and meta-analysis by McCambridge *et al.* published in 2014 with the last included studies published in January 2012 (127).
Thus, we decided to update this review starting in 2012 and finishing in 2022, collecting all the original medical research publications to refine the definition of the HE. Simultaneously, we searched all the studies assessing the size of the effect in primary care research or conducted in outpatients also managed by GPs or in healthy persons (students).
The only searched base was Medline, with the only keyword "Hawthorne effect", as had been done in the McCambridge (128) and the Purssel (126) reviews. Selected articles for the definition were RCTs, reanalysis of RCTs, quasi-experimental or observational studies, historical comparisons or methodology articles. Reviews were considered for discussion and to retrieve unnoticed articles from the reference lists. Definitions given by the authors were extracted and led to an updated definition of the HE and its main causes. The articles contributing to measure the HE in primary care studies were analysed and effect sizes and standard error were computed using generic inverse variance adjusting for the direction of the effect. Odds ratio and 95% confidence interval were computed using random effects. The expected heterogeneity was appraised using the I^2 statistic.

4th step: A new analysis of the RCT in step 2 with a two year follow-up of the research cohort to explain the rise in vaccination uptake (chapter 6)

According to the review in step 3, the risk of a HE was unlikely to explain an increase of 3% in the vaccination uptake in the two arms of our RCT in step 2. A risk of a cohort effect, suggested by the increased probability to be vaccinated the next year after a previous vaccination had to be sought.
A Zelen design 4/2/1 registry-based cluster randomised controlled trial (RCT) was conducted to compute a potential HE, and the trial cohort was followed up for two more years to explore the evolution of the vaccination uptake in the study cohort.
In 2019, we recruited *a posteriori* 100 supplementary GPs not approached previously, following the random order of our list of GPs used for the RCT in step 2. These GPs formed a new control group called by us "Zelen group", who were completely unaware of the RCT in 2014-2015. To search a HE, our intention was to compare the patients from this Zelen group to the controls of the RCT conducted in step 2.
The primary outcome remained the number of seasonal influenza vaccination units delivered in community pharmacies. Data of interest were retrieved at the patient level from the SNIIRAM-Warehouse claim database, a lager database than the previous SIAM ERASME claim database, encompassing all the different mandatory health insurance funds in France. The eligibility criteria of the patients remained the same as in the step 2 RCT: age ≥ 16 years, with a chronic condition indicating an influenza vaccination and/or being aged ≥ 65 years.
The baseline remained the 2013-2014 vaccination campaign, the year of the intervention remained the 2014-2015 vaccination campaign, the two years of follow-up of the cohort were the 2015-2016 and 2016-2017 vaccination campaigns. The baseline cohort was the one followed during the 3 years, without adding new entries (people with a newly diagnosed chronic condition or reaching the age of 65) or censoring exits (deceased patients or patients changing GP), in order to study the behaviour regarding vaccination of the same patients across the years.

The analysis compared baseline characteristics in the 3 groups. To assess the association between the vaccination status and group (intervention/control/Zelen) membership, a generalized estimating equation Poisson regression with an exchangeable working correlation matrix was used, resulting in risk ratios. To analyse the effect of being vaccinated the previous year on being vaccinated the consecutive year, we used a stationary first-order autoregressive transition model with being vaccinated the previous year included as a covariate. To analyse the differences in the evolution of vaccination over time among age groups, point estimates and related confidence intervals, corrected for clustering by GP, were calculated and displayed after stratification per every five years of age.

Chapter 3: Educative efficiency of audio-visual aids in primary care waiting rooms

Short introduction

The overall aim of this thesis is to test posters and pamphlets as the most common patient education tools in GPs' waiting rooms to change patients' health behaviours and to clarify the reasons why our findings differ from public health data: experimental artefact or cohort effect? The first step of this thesis will summarise all existing audio-visual aids found in primary healthcare waiting rooms directed at educating patients during their waiting time described in the literature. It will look at their description and their assessment, in particular regarding posters and pamphlets and their capacity to change patients' behaviour. It also aims to investigate the methodologies and find out the different assessment biases and experimental artefacts that can hinder their findings.

Audio-Visual Aids in Primary Health Care Settings' Waiting Rooms. A Systematic Review

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Published in: the European Journal of General Practice, 2018;24 (1):202-10. DOI: https://doi.org/10.1080/13814788.2018.1491964. (IF 1.38)

Abstract

Background: Health promotion is part of GPs' commitments. Some waiting-rooms have therefore been implemented with audio-visual aids (posters, pamphlets or screens) for health promotion purposes. Few studies have assessed the effect of audio-visual aids in primary care.

Objectives: To identify, describe and appraise studies that have investigated the effects of audio-visual aids on health promotion in primary health care waiting-rooms. To identify which factors influence this impact through literature review.

Methods: Systematic review. Databases were searched by two independent researchers using predefined key-words. Additional publications were extracted from the reference lists of the selected articles. The selection of the articles was performed on the title and abstract, followed by complete reading and assessment. Bias and level of evidence were analysed.

Results: We collected 909 articles. Most of them were not in primary care settings. Fourteen peer-reviewed articles fully meeting inclusion criteria were included and analysed. Good quality studies were scarce. Eight of these articles using videos or slide-shows on TV screens or tablets indicated effects: three of them were significant on patient knowledge with acceptable evidence and three on health behaviour on surrogate endpoints. Audio-visual aids seem to be used or noticed by patients and can induce conversations with physicians. The relevant factors that might influence these effects (duration of exposure, conception quality, theme, target population and time spent in the waiting-room) are insufficiently investigated.

Conclusion: Audio-visual aids broadcasting messages using screens (TVs, computers, tablets, smartphones with Bluetooth® pairing) probably enhance patients' knowledge. A change in health behaviour remains controversial.

Introduction

Promoting good health has long been part of a GPs' commitments (129). A majority of practices have waiting rooms for patients. In developed countries, 70-85% of patients meet their GP at least once per year (130) and most patients spend time in the waiting room. Most GPs promote good health by hanging posters in the waiting room, offering pamphlets or broadcasting health messages on TV screens, but without a clearly defined strategy (113). Methods of communication have been changing over time from the usual pamphlet and poster, to TV screens, tablets, computers and programs associated to smartphones by Bluetooth®, and they offer an immense potential for health (131). All media are potentially efficient if used appropriately (132). At present, there is limited knowledge with regard to how and to what extent these educational aids on health are used in primary healthcare: there are very scarce publications in GPs' offices, most of publications relating to other primary care services, like family planning centres or outpatients integrated primary care consulting rooms. Nonetheless this knowledge is important to create future educational campaigns (133,134).

The aim of this systematic review was to look for available best evidence to inform future primary care practices about the use of audio-visual aids (AVAs) in waiting rooms. Thus, the primary objective was to identify, describe and assess studies exploring the overall impact of AVAs on health promotion within primary health settings and GPs' waiting rooms. AVAs accounted for posters, booklets/pamphlets or screens (TVs, tablets, computers monitors) broadcasting slides, videos or computer programs. The secondary objectives were: (i) to identify and assess the factors that contributed to these effects; (ii) to assess whether the effects induced by posters and pamphlets differed from those induced by screen based aids .

Methods

Study design

For this systematic review of the effects of AVAs (posters, pamphlets and screens) on health promotion in waiting rooms of GPs or other primary healthcare services, we followed the Cochrane's Handbook (118) and included all observational and intervention studies with summaries published from 2004 to 2017.

Search strategy

To be eligible, the studies had to occur outside hospitals and directed to primary health care, defined as general practice and paediatric surgeries (offices), sexual transmitted diseases (STD), family planning and mother & child clinics. Studies could be observational, clinical trials or phenomenological approaches. AVAs could be posters, pamphlets, videos on television screens, computers or tablets, education programs displayed by Bluetooth® association on smartphones, or computer-based education software. The aids had to be visible or available in waiting rooms.

Selection of studies

The main outcome was the description of one or more AVAs on health promotion in GPs' or other primary healthcare services waiting-rooms, and the assessment of the aid's effect. The secondary outcome was to identify and assess the factors that contributed to this effect.

A search equation using MeSH key words was tested before exploring the databases: (Primary health care OR family practice OR general practice NOT hospitals) AND (patient education as topic OR health promotion) AND (audio-visual aids OR advertising as topic OR pamphlets OR posters).

Medline, Web of Science, Cochrane Library, Scopus, Google Scholar and SUDOC (Central French Universities Documentation Service) were searched by two independent investigators from 2004/01/01 to 2014/12/31 and a complementary search from 2015/01/01 to 2017/12/31, with language availability restricted to English and French. Among the collected publications, duplicated were eliminated, then titles and abstracts were read. Articles were excluded if they occurred in hospitals or elsewhere than primary care settings, when dealt with other topics than AVAs or with AVAs elsewhere than in waiting-rooms or not assessing the effect of the AVAs. The references of eligible publications were analysed and relevant publications were retrieved. At this stage, the agreement between the lists was evaluated by Cohen's Kappa. The list of publications included for analysis was finalised by consensus after the articles had been entirely read. (Figure 1)

Quality assessment

The quality of the articles was assessed by one researcher for each selection through the CONSORT table for intervention studies (119), and the STROBE for observational studies (120). Biases and the quality of evidence were evaluated *via* the GRADE criteria (135) and Cochrane's Handbook tool (118). The risk of bias was not a selection criterium. Peer-reviewed articles were separated from not peer-reviewed (academic dissertations), presented as a supplement.

Data analysis

One researcher extracted the relevant data for analysis purposes. All primary or secondary outcome measures were taken into account, and any limitation of the studies was classified as a bias. Because of the heterogeneity of the studies, the lack of a common outcome, and the low level of evidence in most studies, no meta-analysis could be undertaken (Table 1, last column).

Recommendations from the PRISMA statement were used for the presentation of this review (136) and the PRISMA checklist is annexed as supplementary material. Peer-reviewed articles were separated from academic dissertations, and papers reporting on posters and booklets/pamphlets were analysed separately from those reporting on other AVAs. A systematic narrative synthesis was established, information was presented in text form and in tables in order to summarise the analysed articles.

Results

Study selection

The study selection flow-chart is displayed in Figure 1. The search by keywords through databases yielded 909 publications. Eighty duplicates were removed. The great majority of articles were settled in hospitals or in other locations than primary care settings, were assessing education programmes not basing on AVAs, had AVAs displayed elsewhere than in waiting-rooms (mostly pamphlets handed out by the doctor himself, as support of a short intervention), or didn't assess the effects of the aids (for instance carried out a quality assessment of pamphlets or booklets with regard to the level of literacy of targeted patients). The selection by title and abstract, yielded respectively 21 and 26 articles and the second search 5 supplementary. After mutual consensus, 21 publications fully responding to the eligibility criteria were included for analysis, consisting in 14 peer-reviewed articles and 7 academic dissertations. This paper only reports on the peer reviewed articles, academic dissertations being presented as a supplement.

Study characteristics

Table 1 reports the characteristics of fourteen peer reviewed articles(81,137–149), including one in French (138) and the rest in English (81,137,139–149).

The setting (Table 1, column 2: "Practice speciality") was diverse primary health care services, only two studies being explicitly ran in general practice (81,146). In diverse cases, the typology of primary health care wasn't mentioned ("routine PHC") (139,145,148), or seemed orientated towards preventive care (140,144). In six cases, settings were orientated towards mother and child services (137,138,141), family planning (147) and sexual transmitted diseases (142,143). One study was conducted in a community psychiatric clinic (149).

The design (table 1, column 6, "Design, data source") consisted of four open label randomized controlled trials (141,143,146,147), and four quasi-experimental studies (81,139,140,148). The remaining studies were one historical (before vs. after intervention) trial (137), and five cross-section surveys or other observational studies (138,142,144,145,149). Two articles were probably related to the same study, one publishing the result of a single centre (142) in a multi-centre trial (143): for this reason, these two articles are not to be considered as independent studies.

The quality (table 1, column 9, "GRADE assessment") of most articles was mediocre. Not a single study was international and, excepted Warner [20], Gerber [23] and Larsson [25], they were monocentric with a sampling bias. The number of subjects to be included was not calculated in the methodology of most observational or quasi-experimental studies and subsequently, the statistical power was unknown. The results were often reported without confidence intervals. The intervention, with regard to the settings' usual environment was not detailed in the methodology. The absence of external validity prevents all findings to be extrapolated to an international population and the majority could not reasonably be extrapolated beyond the participants.

Used AVAs are summarised in *Table 1, column 3, Audio-visual aid(s) used in the studies*: Three studies were based on posters and/or pamphlets dispatched in waiting rooms (137–139), one describing a complementary use of videos on TV screens in two waiting rooms out of 87, without separate analysis (138). Five were reporting on video interventions on TV screens (81,140–143), one comparing video as

intervention vs. pamphlets as controls (140). One study reported on videos dispatched on smartphones via a Bluetooth® pairing (144). Four studies described computer programs, two using lifestyle tests and printed tailored advices regarding alcohol use and physical activity (145) or diabetes (146), and one a tablet program promoting long acting reversible contraceptive methods (147). The forth computer program used digital signage technology to broadcast a social marketing message (148). Finally, one study used pamphlets, DVD videos and "special events" (like poster competitions) (149).

Risk of bias and limits within studies

There were numerous biases and limits in most of the studies. All the articles that targeted the behavioural change in patients used surrogate endpoints (as reduction of incident STD records rather than a change in sexual behaviour (143)) and some investigated the doctor's behaviour (81,137,149). In one case, the study had been designed for a different purpose than the effect of some AVAs so the validity of the findings concerning the effect of the AVA was diminished (140). Some studies sought to demonstrate the effects in a very specific subgroup of patients, but as the study population included all patients, the effects found could not be attributed to the targeted population (140,146). The lack of description in the methodology with regard to (i) location of the AVAs, (ii) level of exposure and (iii) volume, prevents from reproducing the precise design of the study intervention. One study (143) correlated the waiting time to the level of the effect but the evidence was insufficient. In some studies, the aids were not only present in the waiting-room but also in other locations (137,139,140,142,143,145), and it was impossible to know to what extent the effect was due to the aids in the waiting-room. Mostly the studies were conducted on small sized populations and results did not reach statistical significance, some suggesting a possible trend.

Results of individual studies

Table 1 (2 last columns, "outcome(s) studied" and "main results") summarizes the results. The outcomes described in the articles were organised into sub-groups to facilitate comparison between studies, the first cited outcome being the primary one.

Considering the outcomes searched for in the different studies without accounting if the outcome was the primary one or the level of evidence, health behaviour (HB) was increased in five studies using screens (81,143,144,148,149) out of eight. All of the articles focusing on health behaviour used a surrogate endpoint, the closest to a clinical effect being the delivery of tetanus vaccine units in community pharmacies on medical prescription (thus a change of behaviour in GPs) (81) or the important upgrade of polio vaccination without formal assessment of the causal link (144). Knowledge (K) was increased in four studies using screens (140,141,147,149). In one study using a computer program, knowledge was found negative (146). All the studies using posters and pamphlets solely (137–139) had negative results.

Further data analysis was descriptive, sometimes bivariate but not adjusted on confusing factors. The optimal amount of time for AVAs to be displayed ranging from 1 to 6 months is not supported by evidence (143). Messages aiming at the general population seem to have more effect than those

targeting a specific group of patients. GPs' patients and those consulting STD clinics seem the most receptive to the messages. The presence of other AVAs about different topics does not seem to affect negatively the effect of the assessed AVAs. The use of one or multiple aids about one or several subjects does not impair the efficiency of the aids. However, the presence of other AVAs is generally not mentioned. When considering posters/ pamphlets and videotape recordings/slideshows and computer sessions, videotape recordings/slideshows appear to be more effective on health behaviour change and knowledge. Video clips sharable on smartphones via Bluetooth® were associated with an important increase in polio immunization, but the link of causality is poor and the level of evidence is low. The most efficient AVAs were those created by doctors/primary health teams for their own waiting room, elaborated alone or together with input from reference centres (health authority agencies).

Additional analysis

Computer programs haven't demonstrated any attested efficacy (145,146), when not considering social marketing with digital signage technology (148). Computers were implemented in clinics directed to low literacy populations. The authors acknowledge they overestimated the skills of these populations, not trained to the use of computers. The failure to prove any effect is probably due to a failure of patients to use computers.

Discussion

Main findings

This review noted a great heterogeneity in different AVAs used in primary care waiting-rooms, in their purpose to educate or sensitize patients and in the design used to assess their efficacy. Most of the authors' attitudes were favouring the usefulness of these AVAs, indicating that their implementation in waiting-rooms should follow certain rules to ensure their efficiency. However, the formal assessment of AVA is sustained by a scarce literature. Posters or pamphlets exposed in waiting rooms didn't demonstrate any effect. Videotape recordings/slideshows on TV screens and tablets appear effective on the increase of knowledge with an acceptable level of evidence but evidence remains insufficient to sturdy demonstrate they induce a change in health behaviour. Computer programs haven't demonstrated their efficacy, but they were implemented in low literacy populations, not trained to the use of computers.

Strengths and limitations

Our review has limitations. For the first search (2004-2014), there was no double blinded analysis of the selected articles. However, the selection of the analysed articles was completed by two blinded researchers that led to a high level of agreement and the analysis of the selected articles was conducted according to the Cochrane Handbook (118) and used the GRADE rating scale (135) to evaluate the strength of evidence. As the first search was ending in 2014, an update was necessary for

this article. This update over three years (2015-2017) was carried out by only one researcher. The methods for selection was almost the same: same key-words to search the databases, same review of references, same selection process. As we had noticed in the first search that no articles were found in the Cochrane Library, and that the articles retrieved from Scopus, Google Scholar and in the Web of Science had led to duplicates with Medline, only Medline was searched. The search in the SUDOC had only led to the selection of French academic redactions, not peer-reviewed, and with a very low level of evidence: it was skipped from the second search process, looking only after peer-reviewed articles. As the selection process over 10 years in the first search had led to a high level of agreement, we presume that a search and selection by only one researcher over three years would not have led to an important selection bias.

Another risk of selection bias was the choice of only two languages (English and French) to search publications. The search in other languages or in other sources might not have produced a wider range of studied effects or evidence.

Regarding the limitations related to the articles retrieved for this review, the lack of detail of description about the intervention in the methods section makes it difficult to reproduce and to compare. Most studies were biased and surrogate endpoints were often used. The presence of AVAs in waiting rooms is one way among others to educate and inform patients. It actually was a difficult point of our review, as in some studies other insufficiently described means were implemented and it was not possible to support the part of AVAs in the final outcome. Many articles excluded in this review were reporting on passing pamphlets/booklets out during encounters, to reinforce the message of a short intervention.

Comparison with existing literature

Regarding the setting, the importance of establishing a strategy for health promotion is often present in the literature. Aids should be adapted to a wide population amongst the people likely to be present, in order to address the maximum number of patients. This notion is compatible with that of prevention which targets the general population (150).

Regarding the relevant factors that might influence the effects of AVAS, doctors ought to participate in conceiving and designing audio-visual supports. On one hand, this relies on the fact that doctors best know their patients (151). On the other hand, the GPs' personal involvement affects their motivation to apply the message displayed by the AVA(s): a probable change in their own care behaviour during their encounters with patients creates a bias in the study results (increased Hawthorne effect, not taken into account as confusion factor) (128). The guidance and advice of public health agencies improve AVAs quality and validity (152). Not all the promoted topics were equally efficient, probably because of the heterogeneity of the patients' interest. This is also described in the literature (152). It is for this reason that some institutions suggested that also patients participate to the creation of campaigns (151,153).

The duration the aid is displayed must not be too short or long in order to give enough time to patients to notice it and avoiding its getting banal and ignored. However, the optimal duration is not found in literature. Regarding seasonal interest (seasonal influenza, sexual behaviour…), the topic of the study must be adapted to the period or season (154). Considering the effect of AVAs related to waiting time,

evidence from the studied publications is insufficient and more research is necessary to find out if both are associated and if an optimal waiting time exists.

Evaluation of the inter-influence of other AVAs on the studied effect was impossible in the analysed publications so we were unable to determine if a combination of aids is more efficient than a single one. Nonetheless, only slideshows or videos broadcasted on screens were found associated to an increase in knowledge or some change in health behaviour. The cost of creating AVAs during the implementation of campaigns for health promotion in waiting-rooms is a constraint raised by the authors but not analysed. The location of the supports is also a neglected factor in the publications, despite its relevance to the development of a support.

Excepted three studies where significant results are prone to important biases (141,147,148), the need for more than 10,000 participants in the trials with best evidence in order to reach statistical significance indicates a low effect size requiring large studies. Even though the outcome is statistically significant, the effect is small and might have no clinical relevance. Our study team recently published a multicentre cluster randomized controlled trial on more the 10,000 targeted patients using posters and pamphlets in GPs' waiting rooms that could not demonstrate any increase of seasonal influenza vaccination, acknowledging the lack of efficiency of posters and pamphlets (155).

Conclusion

This systematic review leads to believe that videos or slideshows broadcasted on screens (TVs, tablets or smartphones using a Bluetooth® pairing) in primary care waiting rooms may contribute to improve patient's knowledge, but the effect size might be small, not necessarily relevant, and prone to a Hawthorne effect in the healthcare team. A change in health behaviour on clinical (not surrogate) endpoints still has yet to be sturdy demonstrated. Robust controlled trials on large populations, with a well-defined design and method are required to prove changes in patients' behaviour resulting from media campaigns developed in waiting-rooms.

Short discussion and conclusion

In this article we mainly retrieved three groups of media to enhance *passively* (that means, without any human intervention) patient education in GP waiting rooms: 1) posters and pamphlets, 2) TV screens or tablets broadcasting videos or slideshows and 3) computers with different programs as serious games.

If posters and pamphlets are the most common, they have not demonstrated any effect to change patients' behaviour. In studies that were designed to show such an effect, it was difficult to differentiate the effect of the intervention compared to the motivation of physicians when they spearheaded the poster or the pamphlets.

Videos or slideshows on TV screens or tablets have been the most explored and seem to enhance patients' knowledge. Regarding advertisements for vaccination, only *Eubelen et al.*(81) showed an increase of tetanus vaccination prescription in adults. However, the study was designed by the medical team that implemented it, and the primary outcome to demonstrate a behaviour change was not the release of vaccination units or the injection of vaccines, but the prescription of units by the GP, thus a surrogate endpoint without a direct link to the patient's behaviour.

Computers or tablet programs have not demonstrated any efficacy to change patients' behaviour, but their implementation is not usual in waiting rooms for practical and economic reasons, and studies regarding their effect on knowledge and behaviour of patients are scarce.

Table 1: Principal characteristics of the peer-reviewed articles included in the current review.

Study ID	Practice speciality	Audio-visual aid(s)used in the studies	Topic or general purpose of the study	Aid display	Design, data source	Number of patients	GRADE Assessment	Outcome(s) studied	Main results
2-Ashe, 2006 (13)	Paediatrics	Poster	Antibiotic prescriptions for children with respiratory illnesses	1 month	Historical comparison in doctors' prescriptions	720	Very Low	PP	**PP**: Not SS
1-Assathiany, 2004 (14)	Paediatrics	None, Poster, Pamphlet, (TV videos)	Every educational issue regarding children	Unknown	Survey parents+ physicians	1 830	Very Low	K, U, DPP	**K, U, and D**: Theme dependant, no significance calculation
3-Stephens, 2008 (15)	PHC	Poster	occurrence of patient-physician weight loss conversations	5 days	Quasi experimental	668	Low	D	**D**: Not SS
4-Eubelen, 2011 (16)	GP	Videotape recording	Tetanus booster vaccination prescription by the GP	6 months	Quasi experimental. Local pharmacists	20 109	Moderate/Low	HB	**HB**: Increase vaccination prescriptions (0.79% vs 0.39%, P<0.0001)
5-Frosch, 2008 (17)	PHC	Videotape recording vs. pamphlet	Cancer screening: to enhance autonomous decision making	Once	Quasi experimental, Separate room. Recruited by staff	207	Moderate/Low	D, HB, K	**D and HB**: not SS; **K**: increase with video vs pamphlet (no significance calculation)
6-Goodman, 2015 (18)	PCC	Videotape recording	Influenza vaccination of pregnant women	3 months	RCT, separate rooms, interview by phone	105	Moderate	HB, K	**HB**: not SS (p=0.70); **K** increased protection by vaccination (mother difference=0.49, p=0.003; baby difference= 0.59, p=0.001)
7-Myint-U, 2010 (19)	STD	Videotape recording, poster	Reduce the acquisition of new infections	4 weeks	Survey + Staff observation	1 096	Low	U	**U**: interest of the video: 49-85% watched
8-Warner, 2008 (20)	STD	Videotape recording, poster	Reduce the acquisition of new infections	11x4 weeks	RCT; 3 centres, Clinical records+ local registries	38 635	Moderate	HB, U, K	**HB**: Decrease of encounters for new infection: (HR=0.91 [95CI: 0.84-0.99]) **K, U:** increased perception of STD risk
9-Birukila, 2017 (21)	PHC	Video clip shareable on smartphones via Bluetooth®	Polio vaccination uptake in low literacy communities	unknown	Staff observation	unknown	Very low	HB	**HB**: doubled polio vaccine uptake (no significance calculation)
10-Carlfjord, 2009 (22)	PHC	Computer	Prevention of alcohol use disorders and sedentariness	1 year	Survey, Lifestyle test questionnaire	3 027	Low	U	**U**: interest for 5,7% respondents amongst patients
11-Gerber, 2005 (23)	GP	Computer	diabetes education targeting individuals with low health literacy levels	1 year	RCT, 5 centres, Lifestyle test questionnaire	183	Moderate	HB, K	**HB:** HbA1c: not SS (-0.2 ±2.0); **K**: not SS (0.32 ±2); U: Increase of perceived self-efficacy (1.51 ±1.5)
12-Gilliam, 2014 (24)	FPC	Tablet	Promotion of long-acting reversible contraceptive methods in deprived women	unknown	RCT, tablet vs. usual care, questionnaire, review of chart	52 (per-protocol)	Moderate	D, K, U,	**D**: More discussion with physician (7.1 vs. 32.1%, p=0.02), **K**: increase for LARCM and **U**: interest of the message
13-Larsson, 2015 (25)	PHC	Computer (Digital signage technology)	Social marketing message for increasing radon program participation	3 years	Quasi experimental, 3 centres, crossover: intervention vs. usual	99	Low	HB	**HB:**Increase of radon test kit purchase ($t = 2.69$ [95C: 1.20, 8.47]; $P = 0.01$) and Nutrition program ($\chi^2 = 3.13$; $P = .077$).

14-Pawar, 2016 (26)	*OPC*	*Pamphlets, Videotape recording, "special events"*	*educational information on healthy eating, exercising, and smoking cessation*	*1 year*	*Survey, staff assisted*	*79*	*Very low*	*HB, K*	***HB**: 13% quit smoking (no significance calculation); **K**: not SS*

***Keys*: GP**=*General Practice; FPC=Family Planning Clinic;* ***LARCM**= Long acting reversible contraceptive methods; OPC=Outpatients Psychiatric Clinic;* ***PCC**=Prenatal care centre;* ***PHC**=Other primary health care service;* ***STD**=Sexually Transmitted Disease;* ***SS**=Statistically significant;* ***RCT**= Randomized controlled trial;*

***D**: Discussion with the physician, **HB**: Health behaviour change, **K**: Knowledge improvement, **PP**: Physician prescription change, **U**: Usefulness or interest of the message*

Chapter 4: Educative efficiency of posters and pamphlets in primary care waiting rooms

Short introduction

The most common tool used to inform and educate patients in primary care waiting rooms are posters and pamphlets. As seen in the review above (chapter 3), the efficacy of posters and pamphlets to enhance patients' knowledge and to change their behaviour is discussed. For this reason we conducted this cluster randomised clinical trial, with data retrieved from a large claim database to demonstrate whether an advertisement campaign in GPs' waiting rooms promoting seasonal influenza vaccination had any effect on the vaccination uptake, measured through the number of vaccination units delivered in community pharmacies.

This article was cited as a reference of trials conducted using routinely collected data by:

Kwakkenbos L, Imran M, McCall SJ, McCord KA, Fröbert O, Hemkens LG, et al. CONSORT extension for the reporting of randomised controlled trials conducted using cohorts and routinely collected data (CONSORT-ROUTINE): checklist with explanation and elaboration. BMJ. 2021 Apr 29;373:n857 (156).

Randomized controlled trial on promoting influenza vaccination in general practice waiting rooms

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Published in: The Public Library of Science (PLoS) ONE. 2018;13(2):e0192155. DOI: https://doi.org/10.1371/journal.pone.0192155 (IF: 2.776)

Abstract

Background: Most of general practitioners (GPs) use advertising in their waiting rooms for patient's education purposes. Patients vaccinated against seasonal influenza have been gradually lessening. The objective of this trial was to assess the effect of an advertising campaign for influenza vaccination using posters and pamphlets in GPs' waiting rooms.

Methods: Registry based 2/1 cluster randomized controlled trial, a cluster gathering the enlisted patients of 75 GPs aged over 16 years. The trial, run during the 2014-2015 influenza vaccination campaign, compared patient's awareness from being in 50 GPs' standard waiting rooms (control group) versus that of waiting in 25 rooms from GPs who had received and exposed pamphlets and one poster on influenza vaccine (intervention group), in addition to standard mandatory information. The main outcome was the number of vaccination units delivered in pharmacies. Data were extracted from the SIAM-ERASME claim database of the Health Insurance Fund of Lille-Douai (France). The association between the intervention (yes/no) and the main outcome was assessed through a generalized estimating equation.

Results: Seventy-five GPs enrolled 10,597 patients over 65 years or suffering from long lasting diseases (intervention/control as of 3781/6816 patients) from October 15, 2014 to February 28, 2015. No difference was found regarding the number of influenza vaccination units delivered (Relative Risk (RR)=1.01; 95% Confidence interval: 0.97 to 1.05; *p=0.561*).

Conclusion: Effects of the monothematic campaign promoting vaccination against influenza using a poster and pamphlets exposed in GPs' waiting rooms could not be demonstrated.

Introduction

The French National Health Insurance conducts a seasonal influenza immunization campaign every year but the influenza vaccination rate has been decreasing in people over 65 years of age (from 63.3% in 2009 to 54.0% in 2011), in people under 65 suffering from diverse target diseases (from 40.3% to 33.1%) and in people over 65 with target disease (from 72.3% to 60.7%) in France as well as in many other countries, since 2009 (157). It has never reached the national and European objective of 75% (158,159). For this reason, public advertising has been intensified (TV, newspapers and magazines) and the involvement of health professionals was stimulated, particularly by means of encounters with Health Insurance delegates, and posters and pamphlets to be exposed in GPs' waiting rooms.
GPs' waiting rooms are reconsidered as educational sites in the field of prevention and health education, notably through posters and pamphlets (121,160–162). These media are emphasized by their eased use and their evoking of patients' interest. The increasing number of educational material is correlated to a larger patients' satisfaction (143,163,164). Linking a poster with pamphlets seems to improve patients' knowledge scores and likely influence their health behaviour. The literature indicates no clear strategy in health promotion using audio-visual material in general practitioners' waiting rooms and the effect on patient health behaviour appears to be small (121) or controversial (113,122). If any, more than 10,000 subjects are necessary to demonstrate any effect.
This randomized clinical trial was performed to evaluate the effect of an advertising campaign using posters and pamphlets in GPs' waiting rooms on the number of influenza vaccination units delivered in community pharmacies.

Materials and methods

Study design

The trial was conducted in the area of the Lille-Douai Health Insurance district (Northern France) during the institutional seasonal influenza vaccination campaign of 2014-2015.
It was a single blinded 2/1 registry-based cluster randomized controlled trial design. A computerized random draw was used to allocate GPs in each group. In the intervention group, 25 GPs received and were supposed to expose in their waiting rooms 135 pamphlets and one poster (added to the usual mandatory information) withdrawing all the other posters. In the control group, waiting rooms were kept in their usual state. Fifty GPs in the control group were not aware of the intervention but knew that the seasonal influenza vaccination uptake of their patients would be measured. The outcome was the number of seasonal influenza vaccination units released in community pharmacies. Baseline was defined as the 2013-2014 seasonal influenza vaccination campaign. Data were extracted between October 15, 2014 and February 28, 2015 from the SIAM-ERASME claim database of the Lille-Douai district Health Insurance Fund on patient level. The study was lengthened by one month (February 2015) following the extension of the vaccination campaign duration by health authorities. The protocol had therefore been amended.

The prescription of the seasonal influenza vaccine units was delivered by an individual GP depending on the skills, training and motivation of the latter. This may lead to a potential clustering of the outcome for patients treated by the same GP. To provide valid results, considering the cluster allocation by GP of patients, a correction has to be introduced in computing the number of GPs needed

for the trial, called intra-cluster correlation coefficient (ICC). According to Austin PC, the largest mean difference in power for the analysis of a cluster randomized trial with binary outcomes was used, with an ICC of 0.02, for $\alpha = 5\%$ and $\beta = 20\%$.(165) With a predicted rate of influenza vaccination delivery of 0.65 in the intervention group and 0.60 in the control group, and a target size by GP of 400 patients, 75 GPs had to be enrolled (50 in the control group and 25 in the intervention group).(157)

Target population

The GPs participating in the study had previously been contacted by telephone and had given their written consent. GPs without waiting room, or sharing one single waiting room with several other GPs, or participating in another ongoing study, were not eligible to participate in this study. Language barriers in patients were not considered.
The study population existed of patients over the age of 16, who were registered by the Health Insurance on the participating GPs' patients lists. The target population were patients over the age of 65 or having a chronic disease requiring seasonal influenza immunization (like COPD or diabetes). Patients were informed about the anonymous use of their data and could refuse to participate at any time.

Statistical analysis

A univariate analysis was performed first, to present the baseline characteristics of patients after randomization, respectively in the intervention and control groups. Quantitative variables were expressed as mean with a 95% Confidence Interval (95% CI) of the mean. Categorical variables were expressed as percentages and 95% CI of the percentage. The clustering variable GP was taken into account through the *svydesign* function of the package *survey* (166).

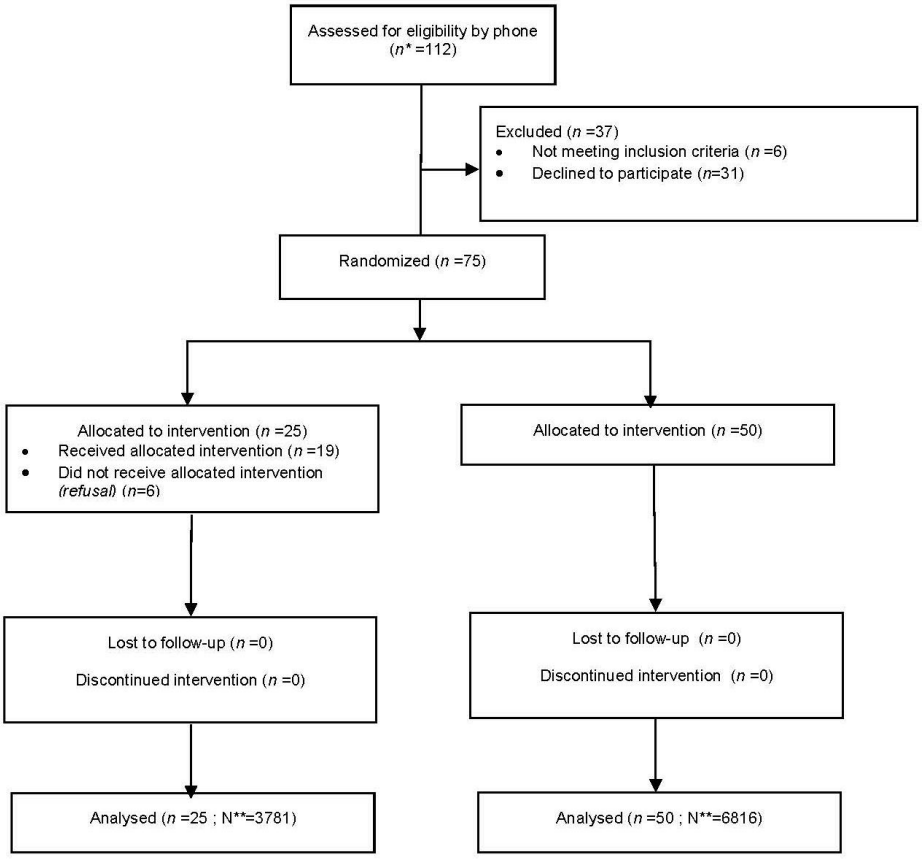
To assess the association between the vaccination status (dependent variable) and the group intervention/control, because of the hierarchical structure of the data and the high incidence rate of the main outcome, we used a generalized estimating equation (GEE) Poisson regression clustering by GP (167); an exchangeable working correlation matrix was used. Although the trial is randomized and therefore the confounding factors are already balanced between the yes/no intervention groups, in order to ensure that the "previous influenza vaccination" factor was fully controlled, the variable "Previous influenza vaccination" was used as an adjustment variable in the model.

The analysis was carried out using R software (version 3.3.1) and the package Geepack (168).

Ethics, regulation and redaction

The study protocol passed the Ethics Committee of the Lille University Hospital (CPP Nord Ouest IV, advice #: HP 14/51) and the National Electronic Data and Liberty Commission (CNIL, advice 1783641 v 0). It is registered on ClinicalTrials.gov (registration #: NCT03239795).
The CONSORT statement has been used to complete this article.

Results



Legend: n* number of general practitioners, N number of patients**

Figure 2 : Trial profile / CONSORT flow chart

Seventy-five GPs were enrolled between July 2014 and September 2015. Twenty-five were allocated to the intervention group and 50 to the control group (Figure 2). Data were collected from 10,597 patients, 7,952 over the age of 65 and 5,308 with a chronic disease (2,632 belonging to both categories). All patients were included for analysis, 3,781 in the intervention group and 6,816 in the control group (Figure 2 . Trial profile / CONSORT flow chart)

Patients were comparable in both groups at baseline, thus during the 2013-2014 vaccination campaign (Table 2). Most patients were female (57.8), 89.1% of the patients had seen their GP and 46.2% had been vaccinated against influenza.

Table 2. Baseline characteristics (October 2013-February 2014) by study condition

Characteristics	Category	Control group (n=6,816) % [95% CI]	Intervention group (n=3,781) % [95% CI]
Gender	Male	41.8 [40.2-43.5]	42.5 [39.9- 45.1]
Age		69.0 [68.0-70.0]	69.4 [67.8-81.2]
Age≥ 65 years		74.8 [71.8-77.5]	74.9 [70.2-79.1]
Chronic disease		50.0 [47.2-52.8]	49.6 [45.3-54.0]
Influenza vaccination	2013-2014	46.4 [44.0-48.9]	45.6 [41.1-50.2]

Legend: n=numbers, 95% IC=95% confidence interval, y=years

During the study period, groups remained comparable (Table 3), the median consultation rate per patient with his GP was 3.1. At least one medical consultation was performed for 84.6% of the patients (exposed to the intervention).

Table 3. Study characteristics (October 2014-February 2015) by study condition

Characteristics	Category	Control group n=6,816 % [95% CI]	Intervention group n=3,781 % [95% CI]
Influenza vaccine delivery	2014-2015	49.0 [46.6-51.4]	48.9 [44.3-53.5]
	October 2014	34.1 [32.2-35.9]	33.6 [30.3-37.1]
	November 2014	12.1 [11.0-13.3]	12.6 [10.8-14.8]
	December 2014	2.2 [1.9-2.5]	2.0 [1.5-2.7]
	January 2015	0.4 [0.3-0.7]	0.3 [0.2-0.6]
	February 2015	0.0 [0.0-0.1]	0.1 [0.0-0.2]
Consultation rate (n)	During study	3.05 [2.78-3.33]	3.37 [2.97-3.77]
At least one consultation	During study	83.8 [76.6-89.0]	86.0 [75.1-92.6]
	All 2014	88.9 [83.8-92.6]	89.4 [76.8-95.5]

Legend: n=numbers, 95% IC=95% confidence interval, y=years

No difference was found regarding the number of influenza vaccination units delivered (Relative Risk =1.01; 95%CI = [0.97 to 1.05]; p=0.561). A vaccination performed on the previous year increased revaccination probability (RR=5.63; 95%CI: [5.21 to 6.10] p<0.001) (Table 4).

Table 4. Factors associated with increased vaccinations. October 2014 - February 2015.

Characteristic	Relative Risk	95% CI	p
Randomization	1.01	0.97-1.05	0.561
Previous flu vaccination	5.63	5.21- 6.10	< 0,001

Legend: 95% IC= 95% confidence interval

Discussion

Main results

An effect of the monothematic campaign promoting vaccination against influenza using a poster and pamphlets exposed in GPs' waiting rooms could not be demonstrated basing on the number of influenza vaccination units delivered in pharmacies.
Other studies evaluating audio-visual material in waiting rooms could not demonstrate any effect of posters and pamphlets (137,169–171). A study conducted in Quebec did not demonstrate the effect of posters in waiting rooms on the number of vaccinated patients (170). Lagorce found no effect of a poster and a pamphlet on the incitement to consult a doctor for women with bladder disorder (169). A study performed in 1998 showed an increase of the knowledge score regarding vaccination against poliomyelitis in patients who had been exposed to a video. Reading a pamphlet did not increase the knowledge of those who had been exposed to the video (171). No effect of posters in waiting rooms was proven on the decrease of antibiotic use in general practice (137).
Most of the previous studies that demonstrated an effect of audio-visual material (all type) in waiting rooms of GPs were of limited quality with a major risk of bias.(172) Only one Grade B randomized clinical trial published by Warner demonstrated a significant effect of video on incident sexually transmitted infection (STI) among patients visiting a STI-screening private hospital (143).
All themes used in audio-visual material do not have the same efficiency. It seems that patients remember the messages they feel concerned with.(138) The theme of vaccination is predominant in GPs' waiting rooms.(173) Studies assessing this theme are controversial.(170,171,174)
Literature confirms that the intervention of the GP remains the main factor to improve immunization rates.(175) Patients are more receptive to messages submitted in waiting rooms if their doctor is motivated and proactive during the encounter.(113,176) His action increases the message of institutional public health organizations.(177) He can influence beliefs about vaccines, increase patient self-efficacy and facilitate the transition from intention to behaviour. The effect of posters and pamphlets on the vaccination intention, as written institutional media, is more normative.(7)

Limits

The perspective of the influenza vaccination campaign was considered from a primary care point of view as opposed to the public health perspective previously accomplished by the French Health Insurance. The robust design of this study included a sufficient number of patients therefore the lack of demonstrated effect is unlikely correlated to an insufficient power of the trial: if an effect exists, it is insufficient to be considered as clinically relevant, i.e. able to enhance substantially the seasonal influenza vaccination uptake. Through randomization groups were comparable from baseline to the end of the study. The generalized mixed linear statistical model with maximized likelihood adjustment gave a precise evaluation of the effect on the main outcomes.
A possible bias could involve the share of patients vaccinated directly by a nurse without being exposed to the GP intervention as some patients may have received the invitation to be vaccinated directly from the Health Insurance. Nonetheless, the present study has been randomized and the groups are being comparable leading to conclude that this lack of exposure to the intervention was comparable in both groups, without other influence on the result than limiting the impact of the intervention. Some

GPs of the intervention group refused partially or totally to redesign their waiting rooms when the intervention was positioned. This barrier signs that the trial was performed in real live conditions. The intention to treat analysis of the outcomes considers this limit and no per-protocol analysis has been conducted. Another limitation is that vaccines provided by pharmacies have been considered as full vaccinations. The research group stated in the study protocol that the number of vaccines provided by pharmacies that were not injected to patients was negligible: this hypothesis is the usual one used by health authorities to investigate the vaccination coverage rate but has not been investigated.(157) However, the number of delivered and not injected vaccines is probably comparable in both arms of the trial. As patients under the age of 16 were not enlisted with a GP by the health insurance before 2017, no data were collected in patients under the age of 16 with a chronic disease (like asthma). Encounters with a different GP than the one by whom patients were enlisted was not taken into account.

The influenza immunization rate increased in both arms of the study compared to the prior year. Contemporarily, at regional and national level, the number of vaccinated people decreased. The Hawthorne effect, i.e. the trend of people to change their behaviour when they know that they are under observation, might have masked the effect of posters and pamphlets. (178) The study group carries out a new study to compare the control group in this study with a new control group enrolled *a posteriori* and measure the Hawthorne effect (Zelen Design (179)).

Conclusion

The findings of the present trial do not support the efficacy of an educational prevention strategy based on posters and pamphlets in GP waiting rooms with regard to health behaviour change. Nonetheless, an important Hawthorne effect in this trial is suspected, and the next step of the study group will try to measure it.

Short discussion and conclusion

Considering the important power of this study, the chance for an even small effect of an advertisement using posters and pamphlets in GPs waiting rooms seems scarce. The study was designed to avoid as much as possible any kind of experimental artefact: enrolment of participating GPs was conducted following the order of a randomised list of GPs currently practicing in the district of the Lille-Douai Health Insurance, enrolled GPs were allocated by randomisation into the two arms of the study without their knowledge regarding the controls, the waiting rooms of the GPs in the intervention arm were reshuffled by the research team and no implication of the participating GPs was requested to collect data (excepted the count of the influenza vaccination units prescribed by themselves that was neglectable). However, the vaccination uptake in the study cohort increased by 3% between 2013-2014 and 2014-2015. At the same time, public health estimates based on the number of vaccination units delivered in community pharmacies collected from the SNIIRAM claim database of the mandatory health insurances and the generalist beneficiaries sample (55) showed a decrease of vaccination uptake in the same district of 2.4%. Though neither databases nor the patient sampling method are comparable, this difference remains questionable and a Hawthorne effect (HE) might have masked a difference between groups with a small effect size. But what is precisely the definition of the HE, how does it occur, and what is its expected size?

Chapter 5 : Experimental artefacts affecting behavioural change research in primary care

Short introduction

The first impression when someone looks at the definition of the Hawthorne effect (HE) is that it is unclear and disputed. A majority of authors define the HE as an observer effect, that is a behavioural change in patients under observation in an experimental environment. Some other authors, referring to the original Hawthorne experiments conducted by Roethlisberger and Dickson at the Hawthorne plant in Cicero, near Chicago (Illinois, USA) between 1924 and 1933, dispute the effect, assigning the noticed experimental artefact to a messy experimental design. However, *McCambridge et al*. refined the definition of the HE in health care studies conducting a systematic review in 2014. They underlined its complexity and the involvement into the effect not only of subjects, but also of investigators and of the study design itself. Their definition of the HE was: "awareness of being observed or having behaviour assessed engenders beliefs about researcher expectations. Conformity and social desirability considerations then lead behaviour to change in line with these expectations" (127).
Considering McCambridge's review as a real effort to describe and define the HE, our intention was to update their definition conducting an update of their systematic review. We oriented our work more specifically towards primary care, for a better applicability to the research in this field and to give an approach of its size in primary care research.

Defining and evaluating the Hawthorne effect in primary care, a systematic review and meta-analysis

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Published in: Frontiers in Medicine, Family Medicine and Primary Care. 2022;9:1033486. DOI: https://doi.org/10.3389/fmed.2022.1033486. (IF: 4.592)

Abstract

Background: In 2015, we conducted a clinical trial (RCT) in primary care to evaluate if posters and pamphlets dispensed in general practice waiting rooms enhanced vaccination uptake for seasonal influenza. Unexpectedly, vaccination uptake rose in both arms of the RCT whereas public health data indicated a decrease. We wondered if the design of the trial had led to a Hawthorne effect (HE). Searching the literature, we noticed that the definition of the HE was unclear if stated. Our objectives were to refine a definition of the HE for primary care, to evaluate its size, and to draw consequences for primary care research.
Methods: We designed a PRISMA review and meta-analysis between January 2012 and March 2022. We included original reports defining the HE and reports measuring it without setting limitations. Definitions of the HE were collected and summarized. Main published outcomes were extracted and measures were analyzed to evaluate odds ratios (OR) in primary care.
Results: The search led to 180 records, reduced on review to 74 for definition and 15 for quantification. Our definition of HE is "an aware or unconscious complex behavior change in a study environment, related to the complex interaction of four biases affecting the study subjects and investigators: selection bias, commitment and congruence bias, conformity and social desirability bias and observation and measurement bias". Its size varies in time and depends on the education and professional position of the investigators and subjects, the study environment, and the outcome. There are overlap areas between the HE, placebo effect and regression to the mean. In binary outcomes, the overall OR of the HE computed in primary care was 1.41 (95% CI: [1.13;1.75]; I^2=97%), but the significance of the HE disappears in well-designed studies.
Conclusion: The HE results from a complex system of interacting phenomena and appears to some degree in all experimental research, but its size can considerably be reduced by refining study designs.

Keywords: Effect modifier/epidemiologic, Scientific experimental error, systematic review, primary health care, Hawthorne effect.

Introduction

By autumn of every year, the main French mandatory health insurance scheme conducts a promotional campaign for seasonal influenza vaccination in mass media and in health facilities. General practice surgeries can participate in this campaign by hanging posters and making pamphlets available in their waiting rooms. Advertising using posters and pamphlets in waiting rooms shows no evidence of effectiveness in terms of increasing knowledge or changing the health behavior of patients (180). We conducted a cluster randomized controlled trial (RCT) with 10,597 patients assessing the 2014-2015 campaign in France confirming these findings (155). No difference was demonstrated on vaccination uptake between waiting rooms advertising for influenza vaccination (intervention) or not (controls) (P=0.561). However, the immunization rate increased by about 3% in both arms of the trial compared to the baseline (previous year). At the same time, a decrease in coverage of 2.4% was observed district-wide by public health authorities. As our trial targeted a change in behavior in primary health care, we considered the possibility of a Hawthorne effect (HE) to explain this difference and felt the need to have greater insight regarding this effect (155).

The Hawthorne effect (HE) was first observed in relation to six, partly overlapping, experiments carried out from 1924 to 1933 at the Hawthorne plant, a large factory complex of the Western Electric Company in Cicero (Illinois, USA), also reputed to have generated Al Capone's original fortune (181). The most thorough publication was issued by Roethlisberger and Dickson which presented data from the six experiments (182). Elton Mayo, a Harward business professor, was not the director of the studies, but as he became the main interpreter of the Hawthorne experiments, his name remains associated with the research (183). The study group examined the effects of various incentives on the productivity of two groups of volunteer workers, and the good story was that whatever experiment was applied, the trend of productivity was upwards in both groups (184). However, this does not fit with the two last experiments (183). The term 'Hawthorne effect' or 'observer effects' to describe the performance or behavior improvement of people involved in research, arising exclusively when under observation, was first used in 1953 (185). In 1974, Parsons described the HE as a failure of the experimenters to realize how the consequences of subjects' performance affects what subjects do (123). Indeed, the internal validity of the Hawthorn experiments was biased by the selection of a small number of volunteer participants, attrition due to the removal of operators because of gross insubordination, and potential antagonism between management and employees (Dickson was an officer of the Western Electric Company) (183). In 2011 Levitt and List recovered the original results of the Hawthorne illumination experiments and reanalyzed the outcomes, finding "some weak evidence that workers respond more to experimental manipulations than to naturally occurring changes in light (186)."

In 2010, French and Sutton published a narrative review calling the changes in the people being measured in an experimental environment 'measurement reactivity'. They merged this designation with other terms including 'assessment reactivity', 'mere measurement' 'question-behavior effect' or 'self-generated validity' (124). Further, in 2017 Paradis and Sutkin recommended the use of the phrase 'participant reactivity' when considering the triad participant, observer and research question (125). One common point of all effects appearing in an experimental environment, whatever their designation, is the considerable heterogeneity of their size across studies (187,188).

In 2014, McCambridge et al. published an often cited systematic review to elucidate the existence of the HE, the conditions of its appearance and its estimated size (127). They noted that it was relevant to clear the term HE in health sciences, as it was evoked in relation to a range of methodological

phenomena. To define the HE, they stated that "*awareness of being observed or having behavior assessed engenders beliefs about researcher expectations. Conformity and social desirability considerations then lead behavior to change in line with these expectations*". They came to the conclusion that "*Further research on this subject should be a priority for the health sciences, in which we might expect change induced by research participation to be in the direction of better health and thus likely to be confounded with the outcomes being studied* (127)."

In 2020, Purssell et al. conducted a systematic review and meta-analysis regarding the HE in hand hygiene (HH), based on the many publications in the field related to the guidance for HH promoted by the World Health Organization (WHO) ("My Five Moments for Hand Hygiene" initiative) in 2009 (189). It confirmed the considerable heterogeneity in outcomes, the HE ranging from −6.9% to 65.3%. Probably in line with this heterogeneity, they didn't complete the meta-analysis (126). Hand-hygiene behaviors have markedly changed since the COVID-19 outbreak (190). For this reason, the outcomes regarding hand hygiene in hospital wards as in the community are probably outdated.

Noting the considerable inconsistency regarding the phenomenon, the primary objectives of this review were, 1) to refine the definition of the HE and outline the progress of research since 2012 (last inclusions in Mc Cambridge's review) on the HE in terms of its existence and characteristics and 2) to estimate its size in primary care studies, expecting the already described heterogeneity.

Material and methods

Eligibility criteria, information sources and Search strategy

Considering the definition, publications related to research in the medical field, in particular those regarding health professionals and patients, were included. Reports needed to contain a clear definition or outcome measuring the HE. Included methodologies were clinical trials and their reanalysis, quasi-experimental or observational studies, or historical comparisons. Reports published in French or English, with an available abstract, were included. Only reports published after the review by McCambridge were considered (publication range: Jan 2012- March 2022). We ensured that no reports were overlapping with McCambridge's review (127).

Reports outside the field of medicine or human behavior related to health and those citing the HE without definition or outcome measurement were excluded. Narrative or systematic reviews with meta-analysis were considered for discussion and to retrieve unnoticed reports from the reference lists, but excluded from this review. Didactic records and letters to the author or editor were also excluded.

Considering the appraisal of the size of the HE, included reports had to be conducted in primary care, in outpatient clinics or in healthy persons. Only published outcomes were considered and only primary outcomes were computed, without limitation. Included designs were RCTs, post-hoc analysis of RCTs, historical comparisons (pre-post comparisons) or observational studies. Studies conducted in hospital wards, in particular HH studies, were excluded.

The use of the term "Hawthorne effect" in health sciences is gradually increasing though its definition remains unclear. It is still more often used without any connection to the original studies in the Hawthorne plant, with a meaning of alteration of behavior related to an experimental background. In other disciplines its meaning has mutated over time to become still more controversial (127). As our purpose was to investigate the HE in primary care research, we limited our investigations to medical

research and our information sources to Medline and to the reference lists of the reviews. We hypothesized that the research in the reference lists of the reviews would provide any material that we would have missed by not exploring other sources. Beside this, PsycINFO and the Web of Science were searched to discuss the results.
The search used PubMed as the mean search engine. As McCambridge (127) and Purssell (126) did, we used 'Hawthorne effect' as the only keyword, though it is not a MeSH term (which is 'effect modifier'). Filters were set for the availability of an abstract, for language (English, French), and for date range (2012-01-01 to 2022-03-31), as McCambridge's last included report was published in January 2012. We deliberately chose not to use the keywords 'observer effect*','participant reactivity' or merely 'reactivity' with another complementary term, in order to be consistent with McCambridge's approach. The main difference with our search is that beside reports quantifying the HE, we also searched for reports giving a definition of the term. The terms 'reactivity', 'placebo effect' and 'regression to the mean' were explored to discuss their interaction with the HE.

Selection process

Initial selections of records were independently undertaken by two reviewers based on the availability of the record, the type of report, the title and the abstract. All full text reports meeting the inclusion criteria at this point were read. Reports retrieved from the reference lists of the papers and meeting the inclusion criteria were treated similarly. A consensus meeting of the two reviewers led to the final list of reports included in this review. All reports included were independently fully analyzed by the same two researchers.

Synthesis methods and bias assessment

The same two researchers independently appraised the risk of bias and the level of evidence during review of the selected full text reports using the Cochrane tool (118).
Publication bias was assessed by a funnel plot using Review Manager 5.3®.
The narrative results regarding the definition of the HE have been summarized in Table 5 with the description of the study, definition the authors used and a quality appraisal.
All published binary outcome measures of the mean outcome in studies conducted in primary health care, outpatient clinics or healthy persons (for example, students) have been included in a Microsoft Excel® table. Studies included in the meta-analysis are summarized in Table 6. Unpublished measures were not sought. Retrieved studies and measures were imported into Cochrane Review Manager 5.3® to compute effect sizes and standard error. Generic inverse variance was used, adjusting for the direction of the HE (i.e. increase or decrease). Odds ratio (OR) and 95% confidence interval (95% CI) were computed using random effects in the context of an important difference in weight of the studies. Heterogeneity was computed using the I^2 statistic. The result is presented as forest plot. A supplementary sensitivity analysis was computed to differentiate odds-ratios and heterogeneity by study design (Table 7) and by level of evidence of the studies (Table 8) as the size of the HE appears to be associated to the quality of the research.

Ethics statement and reporting

No ethical statement is required in France for systematic reviews reusing already published data (research method classification MR-004).
The redaction of this review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement update 2020 (191).

Results

Study selection

Of the 180 records found on Medline, two were excluded because of unavailable abstracts. Forty-four reviews provided two supplementary records from citation searching. Twenty-nine records were excluded based on title and abstract. Twenty reports were excluded after full reading because they cited the HE without definition or outcome measures. Twice two records reporting on the same study were included as they were complementary reports regarding the outcomes: Buckley (192) and Ikpeze (193), and Dal-Ré (194) and Pate (195). After the final selection, 74 new English-language reports were included and analyzed for definition and 15 for evaluation of the size of the HE in primary healthcare or outpatient clinics or healthy persons. No report in the French language was found (Figure 3).

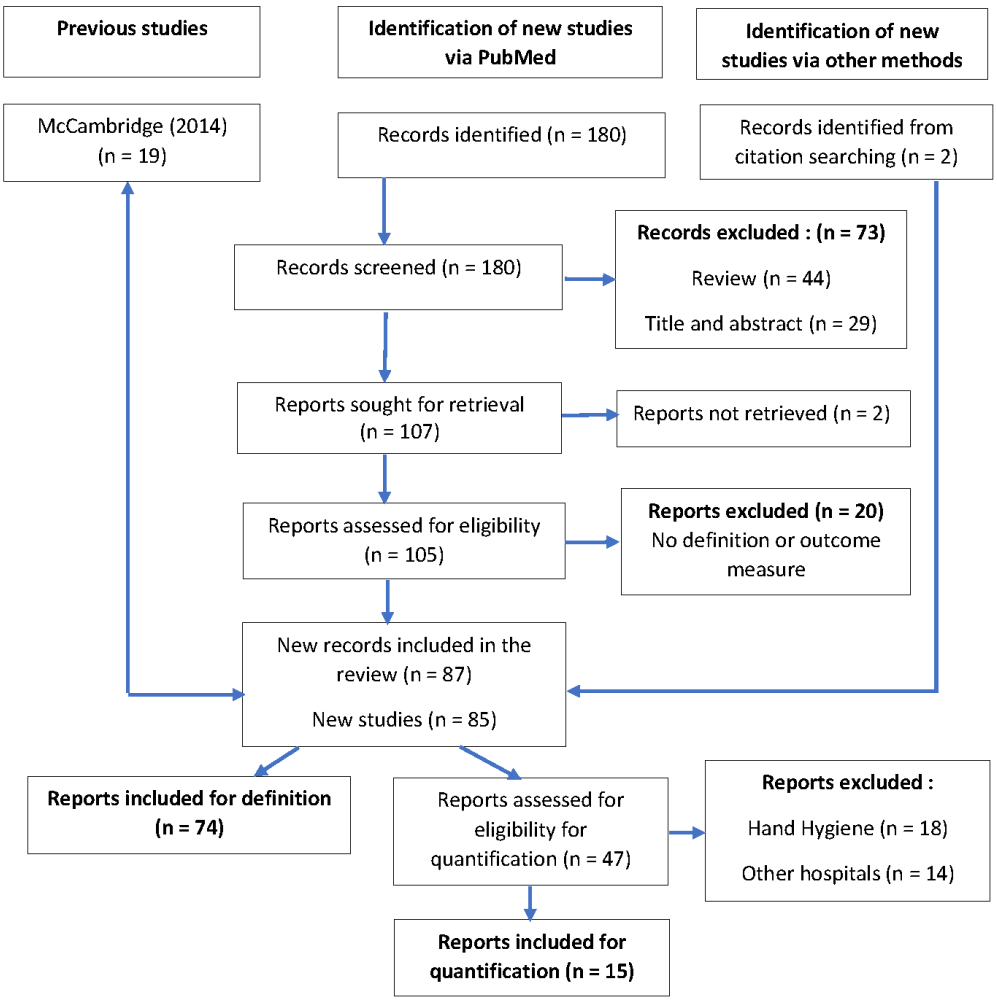

Figure 3: PRISMA 2020 Study flow diagram

Study characteristics

Of the 74 selected reports in the definition branch, 15 were randomized controlled trials (RCTs) (196–210), two were not randomized controlled trials (211,212), three were studies nested in RCTs (213–215), seven were retrospective reanalysis or discussions of RCTs (116,194,195,216–219), three were pilot studies prior to a RCT (220–222), and one was a RCT protocol (223). Further, there were 18 observational studies (224–241), 18 pre-post intervention studies or audits (192,193,242–257), one diagnostic accuracy study (258), four qualitative or mixed method studies (259–262), one mixed method study protocol (263), and finally one methodology protocol to build up research quality guidelines (187). (Table 5)

Of the 15 purposely selected reports in primary care, outpatient clinics or healthy subjects in the meta-analysis branch, the appraisal of the HE was based on a retrospective cohort pre-post intervention analysis in one study (242), in three studies on a post-hoc comparison of the RCT population to a non RCT population (195,201,264), in three studies on the comparison of study parameters between enrolment and randomization in a RCT (199,214,221), in two studies on the comparison of persons consenting vs. not consenting to participate in a study (216,237), in two studies on the follow-up of study populations exposed to repeated measurements (247,265), and in four studies comparing a

population being aware of exposure to observation or assessment to a population who were not aware (204,234,253,266). Main binary outcomes that were inputted in the tables of the review manager to compute effect size and standard error were sleeping time (199), anti-malarial drug prescriptions (204), time up and go measure (221), self-reported alcohol consumption (266), pain intensity (214), and subjective shared decision making (265) in the RCTs or RCT feasibility studies. It was antibiotic selection in a quasi-experimental RCT (201). In post-hoc analysis of RCTs, it was influenza vaccination rate of students (264), acceptance of a video-recording (216), and the rate of COPD acute exacerbations (195). In observational studies, we computed fall rates (242), protocol adherence (247), quality of care (234), school enrolment (237) and spontaneous eye blinks (253) (Table 6).

Risk of bias within studies

According to the Cochrane tool (118), in the definition branch, six studies had a low risk of bias (198–200,202,203,210), 18 studies had a moderate risk of bias (195,197,201,204–207,209,214–218,220,222,228,239,249), 38 had an important risk of bias (192,193,208,211–213,219,221,224,226,227,229–238,240–242,244–248,250–258), and two studies had a very important risk of bias (194,243). Nine studies were not assessable with the tool (protocols or qualitative/mixed methods studies) (116,187,196,223,259–263).
In the meta-analysis branch, one study had a low risk of bias (199), seven a moderate risk (195,201,204,214,216,264,266), and seven a high risk (221,234,237,242,247,253,265).

Results of individual studies

The included studies covered all five continents. The populations consisted of patients and various health professionals (students, nurses, physicians…) in different hospital wards or in primary care and the community. The most commonly studied outcome was the World Health Organization (WHO) guidance for hand hygiene (HH) ("My Five Moments for Hand Hygiene" initiative (189)) in 13 studies (224,226,228,230,231,235,236,241,248,249,252,259). It is noticeable that no study targeting this topic was conducted since the COVID-19 outbreak, except two qualitative ones (259,262). Other outcomes were very heterogenous and linked to behavioral factors in health professionals and in patients (for example completion of medical records, management protocol adherence, quality audits, antibiotic prescription, sleep duration, alcohol consumption) or other aspects (for example falls, skin infection, glomerular filtration rate, glycaemia).

Results of syntheses

Definition of the Hawthorne effect in medical studies

Based on this review, our definition of the HE in medical studies is "an aware or unconscious complex behavioral change in a study environment, related to the interaction of four biases affecting the study subjects and investigators: selection bias, commitment and congruence bias, conformity and social desirability bias, and observation and measurement bias".
A selection bias: The subject agreeing to participate in a study is interested in its outcome, expects a benefit and trusts the investigator (237,262). Characteristics of people who consent to participate in

clinical trials often differ from patients who decline participation (195,215). The investigator has a special interest in the field of the study, has more knowledge and is more skilled in this field than the average health professional (216). As participants' health literacy is essential to the ability to adhere to the study intervention as well as the ability to remember the details of the recommendations made to participants during visits, investigators will tend to include patients with a higher level of literacy (116).

A commitment and congruence bias: Signing the informed consent, the subject agrees to comply with the artificial experimental life rules and is willing to respect these rules as much as possible, far more than in real life (197). This is especially true for ambulatory active patients (like primary care patients) compared to passive inpatients (236). Signing his (or her) contract with the sponsor, the investigator agrees to follow good clinical practices, feels like part of a project, and has often to agree to undergo complementary training (247). In order to minimize the number of patients lost to follow-up, s/he will be particularly careful to strengthen the follow up rules with the subject (116,219,229,247).

A conformity and social desirability bias: As described by McCambridge, the "awareness of (…) having behavior assessed engenders [in the subject] beliefs about researcher expectations. Conformity and social desirability considerations then lead behavior to change in line with these expectations(127)." This is also true for the investigator: in case of uncertainty in the answers to an assessment scale, the investigator will tend to quote systematically in order to be in line with the expectations of the study that s/he shares (195,220,234).

An observation and measurement bias: The HE is often mitigated to the observation bias, without going more in depth into the concerns of this effect. The awareness of being possibly observed, assessed and singled out engenders in the subject and in the investigator a special emphasis regarding the three previous biases (116,228,257). A direct observation (for example HH studies) engenders the largest HE (226), but depends on the authority status of the observer (235). If the observation remains distant, but the subject or the investigator has to complete repeated measurements or questionnaires, his/her interest in the field of the questionnaire will tend to change his/her behavior or beliefs (187,195,206,265). This measurement bias is also described as 'measurement reactivity' or 'reactivity' (124,187,206,267).

Heterogeneity of the Hawthorne effect

We found important differences across studies or within individual studies regarding the HE. Four main groups of factors seem to determine this heterogeneity: education and literacy or professional position, mental health conditions, environmental factors of the study setting and the type of outcome measures.

The education or professional position of health professionals: There were important differences between nurses (more prone to HE) and physicians, and in physicians between medics (more prone to HE) and surgeons (188,249). In subjects, the level of literacy and deprivation had an important influence with less marked HE in subjects with a lower level of education (236), though the embarrassment caused by the attendance of an observer might be higher in this population (227). Further, as already described, investigators tend to enroll in trials patients with a better health literacy as a means to ensure they understand and remember the recommendations made to participants during visits (116).

Mental health conditions modify the HE: The presence of symptoms such as anxiety and depression contribute to enhanced behavioral changes when people are aware of observation (216,218,240).

Environmental factors of the study setting: Regarding HH, the effect was clearly more marked in medicine wards than in surgery or anesthesia wards in hospitals (188,249,259). Primary care patients, playing an active role in the patient-doctor relationship, were more prone to the HE then more passive patients in a hospital setting. The HE was less pronounced in deprived dwellings, possibly increasing health inequalities (236).
The main outcome measure: The more the main outcome is linked to psychological or behavioral factors (for example sleep agendas (199), alcohol consumption (209)), even when measured with blinded assessors, the more the effect is notable. The baseline level of the variable interferes also: the larger the deviation from the targeted value is at baseline, the more a HE has to be expected (241). However, as we will discuss below, this point has to be mitigated by a regression towards the mean (197,214,217). The direction of the targeted variation of the HE is also important: when the variable is expected to diminish (for example antibiotic prescription (222)), the relative reduction is more important than when it is expected to increase (for example carpal tunnel release (192,193)).

Duration of the Hawthorne effect

The onset of the Hawthorne effect in a study environment is very fast (231). In HH studies, it was estimated to take 14 minutes after the appearance of the observer before health professionals altered their hand washing behavior, increasing further after 50 minutes (241). In sleep agendas for sleeping trouble, there was a significant improvement in sleeping duration between the baseline measure and the measure at randomization; insulin resistance and fasting glucose improved simultaneously (199). In chronic kidney disease, there was an improvement in the glomerular filtration rate during the 3-month run-in phase of a RCT, in a disease where this usually worsens over time (220). In neck pain, intensity of the pain diminished between screening and randomization (214).
The HE disappears totally or partially after the end of the observation or when the subject is released (207,240,255). In the case of long lasting studies, the HE decreases gradually as the study environment becomes commonplace for the participants (204,242,257).

Size of the Hawthorne effect

As explained above, we only considered the appraisals of the effect on binary outcomes made in primary care research, in outpatient clinics and in persons in good health (students) for the calculation of the size of the HE. Hand hygiene studies were ruled out of our research since Purssell et al published their meta-analysis (126). Our findings could only confirm theirs, and we consider these results as outdated as the COVID-19 outbreak considerably changed HH habits (190).
To compute the size of the HE, we purposely selected fifteen studies with different designs where the HE was appraised by different approaches (see study characteristics and Table 2- supplementary material).

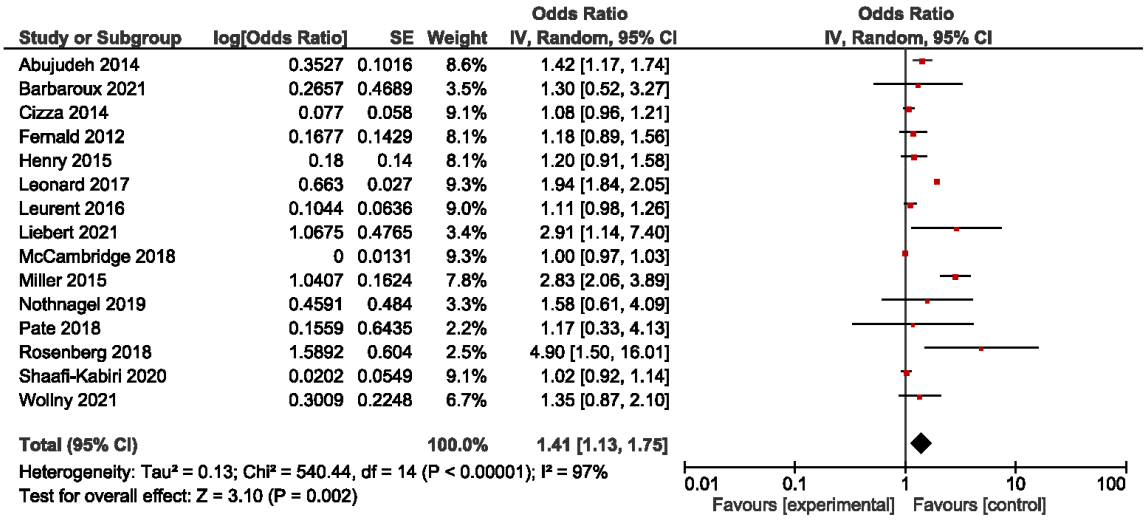

Figure 4: Size of the Hawthorne effect: forest-plot of the meta-analysis

We computed in all studies an OR of 1.41, 95% confidence interval [1.13;1.75] (Figure 4: forest-plot). In sensitivity analysis, we analyzed separately the studies by design (Table 7) and by level of evidence (Table 8). It is notable that in RCTs, and in quasi-experimental or post-hoc analysis of RCTs, the HE appeared to be not significant (95% CI respectively [0.98 ; 1.19] and [0.99 ; 1.44] with a weak heterogeneity (I^2 respectively 57% and 0%). The same observation is valid for studies with a high to moderate level of evidence (95% CI: [0.99 ; 1.09], I^2: 13%). A significant HE with a high level of heterogeneity appears in observational studies and studies with a low level of evidence (95% CI respectively [1.22 ; 2.66] and [1.27 ; 2.50], and I^2 respectively 97% and 95%).

Table 7: odds ratio and heterogeneity by study design

Design	*N*	*OR*	*95% CI*	*Chi²*	*df*	*P*	*I² (%)*
RCTs and pilot RCTs	6	1.08	[0.98 ; 1.19]	11.58	5	0.04	57
Quasi-experimental and post-hoc	4	1.19	[0.99 ; 1.44]	0.04	3	1 00	0
Observational	5	1.80	[1.22 ; 2.66]	126.32	4	<0.0001	97

Keys: N: number, OR: odds-ratio, 95% CI: 95% confidence interval; df: degrees of freedom

Table 8: odds ratio and heterogeneity by level of evidence

Level of evidence	*N*	*OR*	*95% CI*	*Chi²*	*df*	*P*	*I²(%)*
High/moderate	8	1.04	[0.99 ; 1.09]	8.02	7	0.33	13
Low	7	1.79	[1.27 ; 2.50]	128.67	6	<0.0001	95

Keys: N: number, OR: odds-ratio, 95% CI: 95% confidence interval; df: degrees of freedom

Reporting biases

Regarding heterogeneity in the meta-analysis of all the studies, it is notable that the I^2 computing at 97% illustrates that the whole of the variance can be explained by heterogeneity. However, this heterogeneity is to be imputed to observational studies and studies with a poor methodology.

Sensitivity analysis found that heterogeneity and the significance of the HE for binary outcomes disappears in well-designed controlled studies.
Regarding the overall publication bias, the chimney plot did not illustrate an exaggerated risk with a well-balanced distribution of the results around the total OR. (Figure 4: funnel plot)

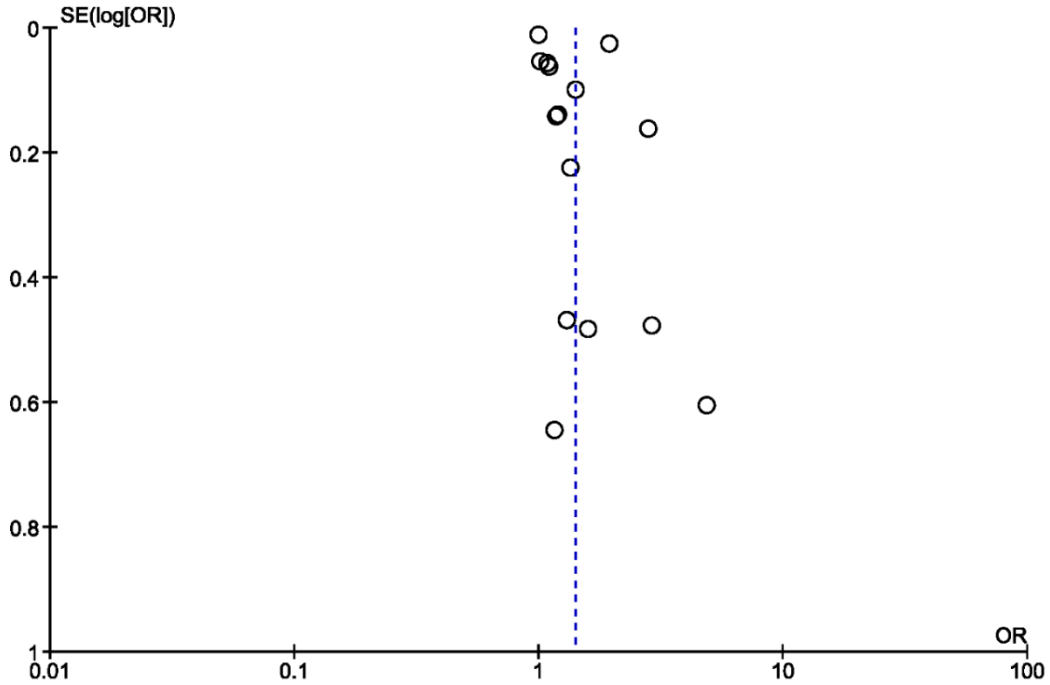

Figure 4 : Funnel plot of reports included in the meta-analysis

Discussion

Summary of evidence

Researchers are still not unanimous regarding the existence of the HE and there is considerable inconsistency concerning the description and definition of the phenomenon (262). The point is not a denial of an experimental artefact which is unanimously agreed. The dissension relates to the description of what happened at the Hawthorne plant (125,186). Rather than calling this artefact 'participant reactivity' we chose to keep the folkloric name of Hawthorne effect as it is contemporarily used in health sciences, refining its definition. It is an experimental artefact that reduces the external validity and size effect of studies, with a combined OR for binary outcomes that can be carefully (due to heterogeneity) estimated at 1.41 (95%CI: [1.13;1.75]) when considering studies conducted in outpatient clinics and with healthy persons. However, the significance and the heterogeneity of the HE is to be imputed to observational studies and studies with a poor level of evidence, as it disappears in well-designed RCTs or quasi-experimental studies. As a complex system of biases and psychological interferences, all related to a change of behavior in subjects and in investigators, it is more dynamic than the summation of each individual bias.
The size and influence of the HE depends on the population being studied, the educational level and the social position of the investigators and subjects, the mental health status of the investigators and subjects, the studied variable, its initial value and its expected variation, and the duration of the

experiment. It is possible to reduce this complex system analyzing the behavioral beliefs and assessment of the issues of the intervention, the normative beliefs and motivation to comply and the control beliefs and perceived power as described in the theory of planned behavior or reasoned action (117).

Up until recently, the HE has mainly been linked with observation bias, though the interaction between observation and selection bias has already been described (188,237). To this point, the use of the term 'Hawthorne effect' was of little interest as it was considered to be limited to the fact of observing a subject or an investigator in an experimental environment. The various publications of McCambridge have created a new association with social desirability bias and conformity bias (127,268,269). After having completed this review, we acknowledge the reality of what we chose to continue calling the Hawthorne effect, not only as an observation bias or as a summation of biases, but as a complex system that more or less creates an artefact in all research. Describing the HE as selection bias, commitment and congruence bias, conformity and social desirability bias and observation and measurement bias is enlightening but somewhat simplistic as there are feedback loops existing between the research targets, methods and population explaining the important heterogeneity and temporal instability of the effect (270).

The HE must not be confused with other biases that are not related to bio-psychological, social or behavioral factors, as for example attrition bias (271) or contamination bias (116). Furthermore, there are important overlap areas between the HE, the regression towards the mean (RTM) and the placebo effect. The RTM is a statistical phenomenon that occurs when repeated measurements are made on the same subject or unit of observation. It happens because values are observed with random error, that is a non-systematic variation in the observed values around a true mean (272). When patients are enrolled into a trial based on a deviating value of the main outcome and randomized a couple of weeks or months later, it can happen at randomization that the deviation of the main outcome is considerably reduced (197,199,214,221). It is than difficult to differentiate the part of the HE and the one of the RTM. Regarding the placebo effect, similar to the HE, its definition is controversial which makes the distinction between the two effects difficult to exemplify. This effect is assumed to be caused by the special type of patient-provider interaction associated with giving and receiving a treatment, or in other words the treatment ritual (273). This patient-provider interaction can also be described without the prescription of any treatment, for instance a patient who experiences pain reduction because of an interview with a warm and empathic physician (273). However, in this case the term of placebo effect, related exclusively to the medication, should not be used.

As a consequence, we can assume that all medical research, qualitative or quantitative, is inevitably prone to the HE which limits its external validity, starting with the conscious or unconscious selection of the study population and of the investigators, leading to blind spots in medical knowledge.

Strengths and limitations of this study

As an update of McCambridge's review (127) and a continuation of Purssell et al's review (126), we chose to use but one keyword term: 'Hawthorne effect'. Hence, and we may have missed reports using as keywords the names of biases that are part of the HE (e.g. 'observation bias', or 'social desirability bias') or alternative terms of the HE (e.g. 'measurement reactivity' or 'participant reactivity'). It is probable that our search strategy has been too specific, thus insufficiently sensitive. However, our choice was confirmed during the selection phase by the finding of reports using other terms appointing the same object or pointing to studies using these other terms.

The use of the term 'Hawthorne effect' is widely used in medical sciences as we could note through the incrementally growing number of records citing it during the last ten years in our search. It appeared to be relevant to refine the definition of the term as it is used contemporaneously in medical research in general and in primary care in particular. This is evident in ten years after McCambridge's review even though they had already noted a dissociation appearing in the meaning of the term in medical sciences in regard to other disciplines (127). For this reason, we only searched reports related to the medical field and we limited our search to Medline and the reference lists of the review articles that we retrieved. This choice might have been too specific and for this reason we deepened our search using PsycINFO and the Web of Science in order to enlarge the consideration of the results in the discussion. The search in reference lists and in other sources found, with two exceptions of reports that were considered in this review, records deriving from other disciplines, mainly from psychology and education sciences. It was notable that psychologists tended to use the term more in line with what happened at the Hawthorne plant and were more critical regarding its use, while medicals were more prone to use the term meaning an experimental artefact connected to behavioral changes in an experimental context, disregarding its origins. Considering the important number of reports that we analyzed and the definitions that were verified, the risk of having missed a definition due to a too specific search seems minimal.

The limitation of our search to reports written in English and French might also have been detrimental. We missed two reports in Chinese about acupuncture, one in Japanese regarding HH, one in Dutch about drug effects, one in Spanish about behavior of diabetic patients and one in German about clinical coding. None of these reports gave a clear definition of the HE or could have been included in our meta-analysis. Further, the Dutch report might be confused between HE and placebo effect.

Some caution in the interpretation of the meta-analysis is necessary related to the fact that binary results (before-after or overt-covert comparisons) cannot exemplify a complex system. We note that adding 'apples and oranges' may cause suspicion, but brought up less heterogeneity than HH studies using the same comparator in different hospital wards. This is related to the fact that the computed data for comparison in the meta-analysis are effect sizes and standard errors.

Considering the literature, this heterogeneity in the analysis of all studies, was expected and we could have decided not to publish the computation of the meta-analysis as per Purssell et al (126). In line with some authors, the sensitivity analysis confirmed the association between poor methods and the arise of a HE (124,125). When analyzing separately RCTs and quasi-experimental studies, or studies with a good level of evidence, we noted that the presence of a HE in binary outcomes was no more significant with an acceptable heterogeneity. Rather, in observational studies or studies with a low level of evidence, the HE appeared to be significant, though with all of the variance possibly explained by heterogeneity.

Implications of the results for future research

Randomized controlled trials

Randomized controlled trials (RCTs) in parallel groups are prone to the HE, but as groups are equally exposed to the effect, its impact on the main outcome might be reduced (268). This might be an explanation of the minor impact of the HE on binary outcomes. This is particularly true when the RCT is blinded, and if possible double blinded. However, blinded studies are often difficult or impossible to implement for ethical, practical or financial reasons. Blinding won't prevent the selection of subjects

to improve the homogeneity of the included population in order to enhance the chance of demonstrating statistically significant differences and reduce attrition bias or the occurrence of serious adverse events in a linear form of reasoning. Concomitantly, it won't prevent the selection of investigators with deeply rooted beliefs (like the role of cholesterol in leading to cardiovascular diseases) and a conformism that might be strengthened by complementary education, here again to improve homogeneity in completing the clinical record forms (CRF) (274).

RCTs are often cluster randomized in primary care for feasibility reasons. The randomization level is mainly the GP-investigator, and the cluster is defined as the group of patients of this GP. As a matter of fact, this emphasizes the influence of the selection of investigators on the results. The introduction of the intra-class correlation coefficient in the calculation (ICC) of the sample size is supposed to erase the effect of this bias on the results of the main outcome, but in most cases this ICC is estimated without certainty, based on the literature. Knowing the heterogeneity of the HE, the feasibility of computing exactly this ICC seems inaccessible.

The main risk, when the HE is not correctly mastered in a RCT, occurs when the effect size of the main outcome is small. If the size of the HE turns out to be important, it might overwhelm the results of the main outcome and lead to a negative trial (116). This is an important fact to consider when designing future RCTs in primary care or analyzing the events that led to a negative trial.

As noted, patients change their behavior by the start of the trial, and baseline values are prone to the RTM (195,199,214,221). For these reasons, it can be recommended to separate enrolment in trials and randomization by about one month, and to repeat outcome measures at the randomization visit. The analyzed baseline measures will be those at randomization, already modified by experimental artefacts, before the implementation of the intervention.

Implementing a RCT in primary care also means a profound disruption in the patient-doctor relationship. The latter changed during the past decades from a paternalistic model to a more balanced model of mutual participation (275). This relation can also be described by the family physician's ongoing commitment to the patient and his/her family as persons (276). The physician will carefully choose among his/her patients, based on this mutual understanding, which patients s/he feels comfortable proposing participation in a trial to. This means that the physician who signed the study contract and the patient who signed the informed consent will both lose their freedom to share decision making regarding a particular condition of the patient even in trials that try to avoid this barrier (277). In the PaCUDAHL-Gé trial (278), general practitioners had to propose to their insufficiently or unscreened for cervical cancer female patients home vaginal self-sampling or usual physician sampled cervical smears. Patients included in the study could accept or refuse screening. The interest to include in the study all their eligible patients, whatever their decision, was repeated several times to the investigators by the study team. However, of the 300 included patients, 299 were screened (96 smears and 203 self-sampling) with only one who refused screening. It is also of note that no never-screened female patient was included. As cervical cancer screening is strongly associated with the level of health literacy, the preference of investigators to include patients with a higher level of literacy contributed to the exclusion of never screened women (116).

Based on the findings of this review, we assessed whether the RCT we implemented regarding the impact of posters and pamphlets in GPs' waiting rooms had been biased by a HE (279). The design of our study was a cluster randomized trial were GP-investigators had no CRFs to complete as data were collected from a health insurance claim database. The GP-investigators were not affected by the main outcome as it was the delivery of seasonal influenza vaccines in community pharmacies to patients targeted by this vaccination. The intervention was a reshuffle of the wall decoration of their waiting

room, pre-existing posters and advertisements being taken away and replaced by one single poster promoting seasonal influenza vaccination, and the available reading material was removed and replaced by pamphlets of the same campaign. GP-investigators gave their consent for this transformation without participating in it. GPs from the control group had their waiting room unchanged and had only to give their consent to access their data in the claim database. In this design, the only involvement of the GP-investigators that might have biased the study was to give their consent to a study were the vaccination coverage of their patients was assessed. This means 1) that they believed that seasonal influenza vaccination was important in their patients targeted for this vaccination and 2) that they were confident in doing their best to reach this objective. This means a selection bias of the GP-investigators, but no observation bias (the observation of their outcomes being totally remote), no special commitment or congruence bias (their only commitment was signing the consent and accepting the reshuffle by others of their waiting rooms), and no special conformity or social desirability bias unless the one intertwined with the selection bias. It is thus that we believe that the HE in our study was minimal.

Observational studies

The HE probably has more consequences for the outcome of observational studies than RCTs, as it directly influences the results, without the balance of a control group. This statement matches with the findings regarding observational studies in our meta-analysis.

The selection of the investigators in primary care will be influenced by the interest of the investigator in the topic and the prevalence of the studied condition among his/her patients. If patients are in general comparable, the way they are managed and educated by their physician might deeply differ due to a different level of commitment (i.e. for patients with addiction mainly managed by a small proportion of highly invested primary care physicians) (280). For similar reasons, the specialty of the physician can also lead to the selection of more complicated patients (e.g. diabetic patients or hypertensive patients managed by diabetologists or cardiologists are probably more difficult to balance and need heavier interventions than those managed by GPs though there is a lack of literature describing the difference in the burden of disease).

Observational studies will also ignore all the persons who are affected by a condition but are not aware of it or are not willing to address the condition. Similarly, it will ignore people who are not participating in diverse screenings. This highlights the problem of blind spots in primary care research.

Compared to usual care, conformity and social desirability will probably change the managing behavior of the investigator, the level of adherence and compliance of the patient, and the data collected in the CRF. Retrospective data will be altered also by conformity as well as by memory failure, with a trend to embellish vague recollections.

Qualitative research

Qualitative research collecting data rooted in semi-structured individual or group interviews will probably be biased by the HE when the interviewee is a patient or a doctor and the interviewer is a doctor him/herself. The relationship between a patient and a doctor or between two doctors will tend to increase social desirability bias and conformity bias, because the interviewee is willing to meet the interviewer's supposed expectations. This deviance might be even more underlined by the signing of a consent form and the recording of the interview that accentuates the need to provide an interest

(281). As a criterion of reflexivity, a qualitative researcher is recommended to describe researcher characteristics that may have influenced the research, so including this HE (282).
Along the same lines, people who have a poor level of literacy or education will be more prone to refuse the interview as they are frightened they will not to be able to reach the expected level of interest in the interviewer's supposed expectations. Persons who feel guilty about breaking the rules in light of the norms of their social group (for example screening secretly for cervical cancer) will refuse the interview due to shame or fear of being discovered, or may not be willing to go further into transgression. In both cases, essential information will be lost to evidence.

Conclusions

The Hawthorne effect results from a complex system of interacting psychological and social phenomena and appears in all experimental research thereby diminishing external validity. It combines the mobilization of feedback loops at different levels and time, encompassing social selection, individual motivation, commitment and congruence, social conformity and desirability and the awareness of being observed, several times assessed and singled out. There are overlap areas with the regression towards the mean and the placebo effect. Observational studies or studies with a poor level of evidence are more prone to a HE.

Table 5 : synthesis of reports defining the Hawthorne effect

#	Article	Study-characterisitic	Population	Setting	Field	Duration	Number of inclusions	Main Outcome	Results	Definition	Level of evidence
1	Abujudeh, 2014 [72]	Pre-post-intervention observational study	Department of radiology	Boston (MA) USA	Patients falls	78 weeks	327 falls in 5,080,512 radiology examinations	Fall rate, fall reports	An Increase, a plateau, and a decrease in incident reports	Awareness of being observed increasing reports, behaviour change in line with expectations and banalization with the time	Low
2	Afsarlar, 2016 [73]	Historic comparison	Male children in ER	Huston (TX) USA	Testicular torsion	10 months	28 controls, 29 intervention	Perioperative parameters	Improvement	Behaviour change in health professionals under observation	Very low
3	Ardestani, 2020 [42]	Study nested in a RCT	Post-stroke patients	Indianapolis (IN) USA	Gait analysis	ND	15	Spatiotemporal kinematics	Decrease of loading on the paretic limb unobserved	Observational awareness, differences between observed and unobserved conditions	Low
4	Arnold, 2020 [25]	Open label cluster RCT (protocol)	Nursing homes	Capital region of Denmark	Acute UTI	10 months	11 nursing homes and 637 residents	Antibiotic prescription for acute UTI	ND	a behavioral change with knowledge of trial participation	ND
5	Barron, 2022 [88]	Diagnostic accuracy study	Patients with compensated cirrhosis	Christchurch, NZL	Diabetes screening	ND	20	Screened diabetes	OGTT is the standard screening test for diabetes	participants were asked not to modify lifestyle behaviour during the study, some may have done so	Low
6	Blondeau, 2019 [26]	RCT	Patients with glaucoma non responding to latanoprost	Sherbrooke, Quebec, Canada	Ophthalmology	ND	83	Intraocular pressure	Reduction of intraocular pressure between enrolment and randomization	This selection bias can be affected by regression towards the mean and therefore may create a false clinical impression. When a patient enters a study, his compliance to the treatment can increase.	Moderate
7	Bhimani, 2016 [40]	Not randomized controlled trial	Rehabilitation ward nurses	St-Paul (MN) USA	Occupational health	10 months	62 nurses	Work-related musculoskeletal nursing injuries	50% reduction in work-related musculoskeletal nursing injuries (not significant)	Nursing injury rates dropped before quality improvement interventions were put in place by self-engagement	Low

8	Briët, 2017 [27]	RCT (cross-over)	Household	Ghana	Malaria prevention	10 months	83 households	Use of insecticidal nets	Fan use does not increase net use. Selection of households making a higher use of nets	Behaviour change in health professionals under observation	High
9	Buckley, 2013 [21]	Pre-post-intervention observational study	Arm, shoulder and hand surgery	Rochester (NY) USA	Carpal tunnel release	8 months	Retrospective cohort: 39-patients. Prospective: 35 patients	DASH questionnaire	No difference between patients signing an informed consent or not	Alteration of the responses to a questionnaire resulting from the awareness of participation in a study	Low
10	Chandok, 2012 [74]	Pre-post-intervention observational study	Primary care	London (Ontario) Canada	hemochromatosis	12 months + 60 months	ND	Genetic screening practices in non-study populations	Increase in HFE gene mutation testing, but constant proportion of patients with mutation	Improvement or modification of behaviour by a population as a consequence of it being affected by knowledge of studies	Low
11	Cizza, 2014 [28]	RCT	Obese outpatients	Bethesda (MD) USA	Sleep	81 + 121 days	125 subjects	Sleep parameters	Improvement between baseline and randomization	Behaviour and biochemical change in subjects under observation by the investigator; time dependent	High
12	Dal-Ré, 2018 [23]	Appraisal of a RCT: Salford Lung Study	COPD patients in primary care	Salford, UK	COPD	ND	ND	ND	ND	Behaviour change in investigator and patient under observation	Very low
13	Di Bona, 2020 [55]	Retrospective cohort study	Patients with severe asthma	Bari and Foggia, Italy	Asthma	10 months	15 consecutive patients	Patient-reported outcomes	improvements of all outcomes from baseline	a change in the behavior of an individual that results from their awareness of being observed	Very low
14	Edwards, 2013 [29]	RCT	Anaesthetists	Auckland NZL	Anaesthetics	12 months	400 medical records	Quality assessment grid	EMR better completed than handwritten records	Behaviour change in health professionals under observation and social desirability bias	High
15	El Saed, 2018 [56]	Observational cohort study	Healthcare workers	Riyadh, Saudi Arabia	Hand Hygiene	10 months	15,883 Hand hygiene opportunities	WHO guidance	Considerable overestimation of hand-hygiene compliance	Behaviour change due to awareness of being observed	Low

									during overtly observation		
16	Fassett, 2014 [50]	Pilot study (before RCT)	Patients with chronic kidney disease	Brisbane, (Queensland) Australia	Chronic kidney disease	27 months	80 subjects out of the 132 included in the LORD RCT	estimated glomerular filtration rate	glomerular filtration rate improved during the 3 month run-in phase by 0.48 ± 2.90 ml/min/1.73 m^2/month	Improvement or modification of study outcomes during the run-in phase of studies, modifying baseline outcomes.	Moderate
17	Fernald, 2012 [30]	Quasi-experimental RCT	Primary care physicians	Texas, North-Carolina USA	Skin and soft tissue infections	7 months	91 family physicians (14 intervention, 77 control)	Antibiotic selection and prescription for abscesses	No difference between clinicians who participated in follow-up case reviews and 77 clinicians who did not	Study subjects' behaviour or study results are altered by the subjects' awareness that they are being studied or that they received additional attention	Moderate
18	Garrouste-Orgeas, 2012 [31]	RCT	Patients >18 admitted to intensive care	France	Intensive care	12.5 months	2117 patients	Prevention of medical errors	Efficacy to avoid errors for insulin administration and tube/catheter removal	Better performance of health professionals during study implementation disappearing after the end of the study	High
19	Goodwin, 2017 [57]	Observational study	Primary care patients and family physicians	Cleveland (OH) USA	Primary care encounters	4 months	138 family physicians in 84 practices	Effect of the observer on diverse criteria	Longer visit time, better history taking, structuring of the interaction and treatment planning	Behaviour change due to awareness of being observed and effect of the observer on the interaction in vulnerable patients	Low
20	Guerrero, 2013 [41]	Not randomized trial	Housekeepers	Cleveland (OH) USA	Infection control	6 weeks	117 sites	Disinfection of artificially infected surfaces	Improvement of disinfection of infected surfaces	Direct observation and real-time feedback	Low
21	Hagel, 2015 [58]	Observational study	Healthcare workers	Jena, Germany	Hand hygiene	5 months	8,158 Hand hygiene opportunities	WHO guidance	Strong positive correlation between directly observed compliance and	Tendency of people to behave differently when they know that they are being observed, including the psychological effect of being singled out,	Moderate

									electronically recorded	noticed, or made to feel important	
22	Hameed, 2017 [59]	Observational study	Family planning clients	Pakistan (70 districts)	Health service quality satisfaction	2 months	1,404 interviews at health facilities, 1403 at home	Service quality and satisfaction questions	Experiences reported in exit surveys at facilities were strongly biased positively for both experiential and perception-based questions	Health care providers pay more attention to their treatment and care of clients ("courtesy bias")under surveyors' observations	Low
23	Henry, 2015 [45]	Post-hoc analysis of a RCT	Depressive patients in primary care	San Francisco (CA) USA	Physician patient relation	ND	135 investigators 867 subjects	Acceptance of video-recording	Selection in investigators and subjects. No change induced by video recording	Selection and behaviour change in health professionals under observation	Moderate
24	Humalda, 2020 [32]	RCT	Patients with chronic kidney disease	The Netherlands	Nephrology	9 months (3 + 6)	99 patients: 52 intervention vs. 47 control	Sodium excretion	Decrease during the intervention and increase during maintenance phase	Participants' awareness of being in a sodium intervention study might have affected the outcome even without exposure to the intervention.	High
25	Ikpeze, 2018 [22]	Pre-post-intervention observational study	Arm, shoulder and hand surgery	Rochester (NY) USA	Carpal tunnel release	8 months	Retrospective cohort: 39-patients. Prospective: 35 patients	QuickDASH questionnaire	Informed consent did not significantly alter patient responses to the QuickDASH questionnaire	Patients may alter responses to a questionnaire based upon the awareness of participation in a study	Low
26	Janssen, 2020 [53]	Cluster RCT (protocol)	Mindfulness-based stress reduction	The Netherlands	Mental health in teachers	12 months	66 participants	Five Facet Mindfulness Questionnaire	ND	Participants' awareness of being in a sodium intervention study might have affected the outcome even without exposure to the intervention.	ND
27	Kennedy, 2013 [75]	Pre-post-intervention observational study	Healthcare workers, Trauma and Orthopaedics	Cork, Ireland	quality control practice	24 months (12 group	Group A: 105 Group B: 93	Measurement of the tip apex distance in	The quality of operative fixation improved objectively	Psychological influence on individuals of being aware that their work is being examined, directly or	Low

						A, 12 group B)		dynamic hip screws	following the institution of new form of outcome assessment	indirectly, and the quality of their efforts consequently improving	
28	Kovacs-Litman, 2016 [60]	Observational study	Physicians vs. nurses, Hospital	Toronto, (Ontario), Canada	Hand hygiene	2 months + 3 days	4,906 Hand hygiene opportunities	WHO guidance	Covert observation produced much lower compliance than recorded by auditors. Difference in nurses >> physicians	Audits not only overstate performance overall, but can lead to inaccurate inferences about performance by professional groupings due to relative differences in the Hawthorne effect	Low
29	Kurtz, 2017 [61]	Observational study	Nurses in 5 intensive care units in 4 hospitals	Texas, USA	Hand Hygiene	18 days	65 nurses 3,620 Hand hygiene opportunities	WHO guidance	The presence of an observer did not significantly alter the behaviour of the nurses regarding their hand hygiene behaviour	A 20% difference in the hand hygiene adherence rate of the first 2 hours of observation and the last 6 hours of observation	Low
30	Laborie, 2022 [76]	Before and after observational study	Breastfeeding	Lyon, France	Breastfeeding	24 months	655 infants (301 before and 354 after)	Breastfeeding at discharge	significant improvement in both any breastfeeding and exclusive breastfeeding at discharge	Participation in medical research has been increasingly recognized to modify caregivers and patients' behavior, regardless of the study design or intervention. Awareness of being observed which is related to a "social desirability consideration". Improvement of caregiver behavior, technical knowledge, and their awareness of the importance given to breastfeeding. After an initial peak, the Hawthorne effect is known to diminish owing to habituation	Low

31	Lakomek, 2020 [62]	Prospective cohort study	Patients with out-of-hospital cardiac arrests	Osnabrück Germany	Cardiopulmonary resuscitation	6 + 10 + 12 months	292 patients: 95 + 94 - 103	chest compression quality	The compression depth did not show increase after activation of sensor-feedback CPR	behavioural change due to an awareness of being observed	Low
32	Leonard, 2017 [77]	Pre-post-intervention observational study	Primary health care clinicians	Tanzania	Protocol adherence	Intervent.10 weeks Assess. 18 month	96 clinicians 4512 patients interviews	4 measures of protocol adherence and 3 feedback visits	Being part of a project that encouraged quality, clinicians increased the quality of care in the short, medium and long-(18 months) term	When faced with the immediate attention and scrutiny inherent in any intervention, clinicians improve adherence but adherence falls as the attention diminishes	Low
33	Leurent, 2016 [33]	RCT	Healthcare workers	Tanzania	Management of anti-malarial drug prescriptions	24 months	19,579 patients in 18 facilities	Performance of a rapid diagnostic test and prescription of an anti-malarial drug	Improvement of the performance of tests and lower prescription of anti-malarial drugs in negative tests	Behaviour change in health professionals when their activity was overtly assessed (patients' interviews). U-shaped association in time	Moderate
34	Liebert, 2021 [51]	Pilot study for a RCT	Patients with Parkinson's disease	South Australia	Effectiveness of photobiomodulation to mitigate clinical signs of PD	12 months	12 participants: 6 immediately treated and 6 waitlisted	Time up and go measure of mobility	Improvement of time up and go measure between enrolment and treatment, and after 4 weeks of treatment	Occur in response to participation in research or being observed during a study. Appears to be transient, being short-lived during the treatment period and much diminished by 3 months. The waitlisted participants showed an improvement in outcome measures before treatment began	Low
35	Malchow, 2016 [63]	Deception observational study	Patients with a trans-femoral prosthesis for ≥ 6 months	Pittsburgh (PA), USA	Prosthetics and orthotics	30 minutes	3 patients	Gait cycle durations and several kinematic parameters	Users of lower limb prostheses appear affected by the presence of observers	Psychological phenomenon under the umbrella concept of reactivity, stating that people will act differently when they are aware of being observed	Low

									analysing their walking pattern		
36	McDonald, 2018 [78]	Pre-post-intervention observational study	Healthcare workers in 2 medical wards	Montreal (Quebec) Canada	Hand Hygiene	4 months (2 overt + 2 covert)	418 Hand hygiene opportunities	WHO guidance	Dramatic increase of the compliance rate in overt compared to covert observation	Behaviour changes when the observed person is aware of being watched leading to a limitation or an obstacle to the accuracy of direct observation	Low
37	McDermott, 2016 [34]	RCT and cohort	health checks to identify risk of cardiovascular disease	Primary care, London, England	cardiovascular disease	18 months	12,459 participants	completion of the health check within 6 months of invitation	Uptake of a health check following an invitation letter is low and is not increased through an enhanced invitation method using the QBE. The offer of a £5 incentive did not increase the rate.	Larger effect sizes were observed for behaviours that the reviewers rated as easier to perform and more socially desirable.	Moderate
38	McKay, 2022 [89]	Qualitative study	Healthcare workers (nurses, registrars)	NSW, Australia	HH	1 month	3 nurses + 1 registrar?	acceptability of using video monitoring for hand hygiene auditing	Fears, concerns for patients, changes to feedback,	non-representative samples subject to the Hawthorne effect	ND
39	McLaws, 2018 [79]	Pre-post-intervention observational study	Healthcare workers in 2 wards	Sidney (NSW) Australia	Hand Hygiene	24 months (2 x 3 audits)	Medical wards: 1,087,196 Surgical: 683,561 Hand hygiene opp.	WHO guidance	Increase of the compliance rate in overt *vs.* covert observation. Medical wards > surgical. No significant improvement by repeated audits	Epidemiologic errors associated with direct human auditing	Moderate
40	Miles, 2018 [13]	Methodology	develop guidance on	Manchester, UK	Measurement reactivity	ND	ND	To produce guidelines	overall effects of asking questions	**Measurement reactivity** has been defined as being present	ND

		(protocol to produce guidelines)	how to minimize bias in trials due to measurement reactivity					through an expert workshop	on objective and subjective measures…there is considerable heterogeneity in effects…lack of pre-registration of protocols…publication bias	where measurement in a research project results in changes in the people being measured. The changes can be behavioural, emotional or cognitive (e.g. beliefs)… There is also evidence that people taking part in research do so partly because they see personal benefit in doing so, including access to monitoring of their own health	
41	Miller, 2015 [64]	Observational study	Community health workers in primary care	Oromia region, Ethiopia	Childhood illness	2 months	137 health workers, 790 children	WHO Health Facility Survey tool (quality of care)	Differences between the two estimates relatively small for most of the indicators and borderline significant for only one indicator	Health workers perform better than under normal circumstances because they are being observed	Low
42	Morberg, 2018 [46]	Appraisal RCT	Patients with Parkinson's disease	Odense (Denmark)	Efficiency of Transcranial Pulsed Electromagnetic Fields	ND	95 participants	Unified Parkinson's Disease Rating Scale (UPDRS)	Concerning the UPDRS, no treatment effect was found between the active group and the placebo group, albeit both groups improved	the Hawthorne effect should not be viewed upon as a single entity but rather as entities affecting outcome measures throughout the full study period. The Hawthorne effect should be seen as a potential cause of symptom alleviation in addition to the other causes likely to affect study outcomes, being the placebo effect, spontaneous remission, regression to the mean, selection bias, investigators measuring bias, participant reporting bias and fluctuation	Moderate

										over very short time spans (hours) of PD symptoms. Information meeting…already creating positive expectations of symptom alleviation... may also have changed behavior in us as investigators prior to study initiation	
43	Nair 2018 [35]	Open label RCT	Mothers with at least one child <5 years	Pune district in Maharashtra, India	Assessment of the TrackCare app	6 months	749 mothers (200 phone group, 100 control group, 449 cross-section control group (6 x 75))	Childre seeking care	No difference in proportion of children seeking care	the participants are aware of their movements being monitored and repeated surveys (for validating recall) has the potential to alter health care seeking behaviour. The possible effect of altering a health-related behaviour as a result of exposure to a measurement device is called reactivity.	Moderate
44	Nothnagel, 2019 [43]	Feasibility study for RCT	Chronic neck pain patients	Jena, Germany	Assessment of pain intensity between enrolment and baseline	ND	42	Average pain intensity (VAS)	Reduction of pain intensity between enrolment and baseline	participants are more likely to enter a study when their pain is particularly intense… Regression to the mean is a purely statistical phenomenon, describing the general tendency for extreme values to converge towards a middle level… a person may change her or his behavior, experiences, emotions, etc., when becoming a study participant…interpreted as a type of reactivity to the situation, where a person is being systematically investigated and "observed". A possible reason for this effect may be increased attention to factors that are	Moderate

										related to the study outcomes… Thus, independent of the natural course of the disease, the inclusion procedure and the enrolment into a study may, in itself, have a major impact on the main study outcomes.	
45	Pan, 2013 [65]	Observational study	Healthcare workers by category	Taipei, Taiwan	Hand Hygiene	12 months	23,333 Hand hygiene opportunities	WHO guidance, 3 categories of observers	Compliance observed by medical students was significantly lower as than by infection control nurses and unit ambassadors	Performance usually improving when health care workers know that they are under observation, depending on professional category and category of observer	Low
46	Pate, 2018 [24]	Appraisal of a RCT: Salford Lung Study (SLS)	COPD patients in primary care	Stalford, UK	Management in Primary care of COPD	12 months	Comparison of 1403 patients in the usual care arm to 16758 non trial matched patients in the Clinical Practice Research Datalink (CPRD) primary care database	rate of acute exacerbations of COPD	more exacerbations recorded in trial patients and behavioural changes in patients and general practitioner coding practices	the trial population may not be representative of the wider COPD population… participants or practitioners modify their behaviour due to an awareness of being observed... behavioural changes—for example, coding practices or number of COPD medications prescribed by GPs	Moderate
47	Persell, 2016 [52]	Test-Randomized controlled trial	Primary care physicians	Chicago (IL) USA	Management of antibiotic prescription	24 months	3,276 encounters before and, 3,099 during intervention	Appropriate and inappropriate antibiotic prescription	Large reduction in antibiotic prescription compared to the prior year regardless of the intervention or in controls	Behaviour change in primary care physicians in case of assessment. Possible floor effects in case of low baseline inappropriate prescription	Moderate
48	Petersen, 2021 [47]	Appraisal of two	Primary care patients with	Ulm, Germany	Management of type II diabetes	ND	ND	HbA1c	A limited effect size due to considerable	This effect is attributable to subjects' knowledge of being part of a study, i.e., being	ND

		multicenter RCTs	type II diabetes						improvements also in the control group	observed and having data collected… Asking questions, for instance, induces rethinking about the current behavior… increased attention paid to the subjects by their HCPs… monitoring effort of clinical research associates… those control group patients that received a higher quality of standard care also showed larger improvements… it is expected that the majority of improvements induced by study effects occur between the first and the second data collection	
49	Petrini, 2021 [90]	Mixed methods (cross sectional survey + pair groups)	Health providers in an a Department of Anesthesiology and Critical Care Medicine	Philadelphia (PA) USA	Prevent burnout (human resources management)	ND	58 physicians, 10 fellow physicians, 16 Certified Registered Nurse Anesthetist	Stanford Professional Fulfillment Index	identify important areas for improvement, build community, and target interventions to improve the well-being	deciding to call attention to a phenomenon may influence its manifestation… the act of observing influences an outcome	ND
50	Płaszewski, 2022 [93]	Mixed methods (web-based survey + focus groups) (study protocol)	registered physiotherapists located in Poland	Nationwide, Poland	Knowledge, skills, beliefs, and attitudes towards evidence based medicine	ND	About 1000 physiotherapists	In the cross-sectional survey: Evidence-Based Practice Profile Questionnaire	ND	people could change their behaviour or answer differently when being observed	ND
51	Quick, 2017 [66]	Observational study	Women in second pregnancy	Bradford, UK	Pregnancy health practices	3 years	316 (158 matched pairs)	5 health behaviours and birth weight	Improvement in the number of women reporting any alcohol consumption.	The process of taking part in health research can improve participants' health, independent of any intended intervention	Low

									Estimates larger for women of higher education		
52	Rampersad, 2013 [80]	Pre-post-intervention observational study	Children in intensive care unit (anaesthetics)	Seattle (WA), USA	catheter associated blood stream infection	12 weeks	21 cases pre-intervention and 27 post-intervention	3 appraisers' assessments on video records (42 and 49 hours)	Changes in the clinical practices of the anaesthesia providers resulting in an increase in 'clean' behaviours	Tendency of providers to change their behaviour, trying to be compliant with whatever practice they thought was audited	Low
53	Rea, 2020 [91]	Qualitative study (Focus groups)	faculty and internal medicine residents in an outpatient clinic	Mayo Clinic, Rochester (MN) USA	Pedagogy: Perceptions of scheduled vs. unscheduled directly observed visits	ND	14 faculty and 14 resident participants	Thematic analysis	Unscheduled observations were felt to be more authentic than scheduled observations and allowed for increased numbers of observations permitting more frequent formative assessments. Preference of remote video observation compared to in-room observation.	a change in behavior in response to observation and assessment… while learners are observed during patient care as their behavior may be consciously or subconsciously altered.	ND
54	Rezk, 2019 [81]	Observational pre-post study	Groin surgical site infections in vascular surgery	Jönköping County Hospital, Sweden	Antibiotic prophylaxis with Trimethoprim/ Sulfamethoxazole vs. Cloxacillin/ Cefotaxime	3 years vs.2 years	122 Cloxacillin/ Cefotaxime group vs. 67 Trimethoprim/ Sulfamethoxazole group	clinical examination and microbiological results, severity: Szilagyi classification	The change in antibiotic prophylaxis from Cloxacillin/ Cefotaxime to Trimethoprim/ Sulfamethoxazole was associated with an increased	The personal staff and operating vascular surgeons, in particular, in the study center was well aware of the problems with the high SSI rate, which have led to an individual change in behavior and a number of modifications of surgical technique,	Low

									rate of inguinal SSI	consciously or unconsciously, in order to reduce the SSI rate	
55	Rezk, 2021 [92]	Qualitative study (focus groups)	Health care professionals (surgeons, nurses, assistant nurses) in a vascular surgery department	Jönköping County Hospital, Sweden	how HCPs perceive being observed when following hygiene routines	ND	44 health care professionals	qualitative inductive content analysis approach	Compliance is affected by many factors, not least a lack of communication between different groups of health care professionals	The HE is a type of observer effect, and is often cited as a source of bias in observed behavioural changes among study participants, or due to infection control interventions. There is considerable inconsistency concerning the description and definition of the phenomenon… the size and direction of the change in behaviour depend on the total time the participant is aware of being observed… it is a change in behaviour as a motivational response to the interest, care, or attention received through observation and assessment.	ND
56	Robles-García, 2015 [36]	Randomized controlled trial	Patients with Parkinson Disease	A Coruña, Spain	Neurology Parkinson disease	ND	15 Parkinson disease, 15 healthy	Gait pattern under overt and covert evaluation	Gait pattern modified under covert evaluation in both groups	Behaviour change in patients in an experimental environment even under covert observation	Moderate
57	Rosenberg, 2018 [67]	Observational study	Young women	Bush-buckridge (Mpuma-langa), South-Africa	HIV infection prevention	48 months	3889 young women	School enrolment	Cash transfers conditional on school enrolment did not influence HIV acquisition	Differences in school enrolment status were already apparent at the beginning of the study and grew larger as the trial progressed, diminishing the differences between study arms	Low
58	Sánchez-Carrillo, 2016 [82]	3 phase pre-post-intervention observational study	Healthcare workers in a haemodialysis unit	Monterrey (Nuevo León) Mexico	Hand Hygiene	4 months	5403 Hand hygiene opportunities	WHO guidance	Direct observation might be inferior to video monitoring for evaluating hand hygiene	Direct observation underestimates hand hygiene opportunities and health care workers are more compliant during direct observation study periods	Low

									compliance, related to bias in health worker and observer		
59	Shaafi Kabiri, 2020 [83]	Pre-post intervention	young healthy adult males with normal vision	Boston (MA), USA	Neuropathology	7 minutes	30 patients	Spontaneous eye-blink rate	transitory impact on blink count during the first and third minute of a passive image-viewing task that occurred immediately after subjects were informed of their eye blinks being counted	research participants who are aware they are being observed change their behavior, potentially biasing the outcome being measured	Low
60	Smith, 2015 [37]	Randomised controlled trial	patients in emergency departments with pain from traumatic injuries	Five hospitals in England	Pain control	29 months	200 patients	total pain experienced captured by visual analogue pain rating scale	Slightly (but not statistically significantly) lower total pain in the PCA group (mean difference 2.7, 95% confidence interval −2.4 to 7.8).	The nurses who were looking after the patients in the routine care group; they knew that they were being observed, so their review of the patients' analgesic requirements may have been influenced by this.	Low
61	Smith, 2017 [38]	Randomized controlled trial	University students, usual drinkers	Sidney and Wollongong NSW (Australia)	Alcohol addiction	ND	114 regular drinkers	Alcohol use after 3 different brief alcohol interventions	Reduction of alcohol use whatever the intervention or without intervention	Effect of simple assessment requiring an important statistical power to show small effects of interventions	Moderate
62	Spector, 2012 [84]	Pre-post-intervention observational study	Healthcare workers	Bangalore (Karnataka) India	childbirth-associated mortality	6 months	499 childbirth before intervention, 794 after	Use of the WHO Safe Childbirth Checklist program 29-item checklist	Marked increase in delivery of essential childbirth practices linked with improved	Subjects' behaviour is influenced by an awareness of being observed; minimized by employing the same observers and observing in the same way in both phases	Low

									maternal, foetal, and new-born outcomes		
63	Srigley, 2014 [68]	Observational study	Healthcare workers	Toronto (Ontario) Canada	Hand Hygiene	14 weeks	562 304 ABHR dispenses and 218 473 soap dispenses	WHO guidance	The hand hygiene event rate in soap and ABHR dispensers visible to auditors was significantly higher than in dispensers not visible	Observer bias, selection bias and tendency of people to change their behaviour when they are aware of an observer	Low
64	Steward, 2020 [69]	program implementation study (cohort study)	people living with HIV in Primary Care	Nationwide USA	Provision of HIV service delivery	6 months	14 demonstration project sites 15,738 clients	To Characterize the practice transformations that were ultimately implemented by the initiative's demonstration projects and to examine the association of the transformations with retention in HIV care, ART prescription levels, and viral suppression	practice transformations are apotential strategy for addressing anticipated workforce challenges among those providing care to people living with HIV	clinical personnel who knew that they were under study were more motivated to make their projects a success	Medium
65	van Wyk, 2020 [44]	Nested study in RCT	Pregnant women with fetal growth	The Netherlands	Obstetrics (comparison of labor induction	ND	1116 women, 650 randomized, 466 declined randomization	1) assessing whether and how baseline characteristics	Nonparticipants in the DIGITAT have a worse outcome than the	Characteristics of people who consent to participate in clinical trials often differ from patients who decline	Medium

			restriction at term		with expectant monitoring) Comparison of participants and non-participants			of nonparticipants differed from participants 2) comparing study outcomes of the 2 groups.	participants, despite the fact that these women were healthier at baseline. Most nonparticipants preferred expectant management and prolonged the possible undernourished fetal environment. Could explain the less favorable outcomes in these women	participation… socioeconomic status, and less educated women are often less willing to participate… participating in a clinical trial may have an effect on the behavior both of doctors and patients…adhere more strictly to protocols, perhaps leading to earlier or other interventions that could improve outcome. Patients may be more aware of risk factors because of the fact that they may be better informed regarding their condition owing to the study information provided before the trial. They may also feel that they are being watched	
66	Vickers, 2017 [70]	Deception observational study	Individuals with and without chronic low back pain	Gainesville (FL), USA	Gait assessment	ND	30 healthy persons, 25 with chronic low back pain	Gait assessment walking on a 8.4 m gait mat; Beck Depression Inventory (BDI)	The higher the BDI score, the greater the change in walking speed when overtly observed	Patients may alter their normal gait patterns when they are aware of observation. Symptoms of anxiety and depression contribute to gait modifications during observation	Low
67	Wainberg, 2020 [48]	Appraisal of a RCT	adult psychiatric patients	Brazil	HIV risk reduction	4 years	464 (233: increased information to HIV risk behaviors, enhance skills and motivation, 231: information about common chronic medical conditions)	Sexual Risk Behavior Assessment Schedule	HIV Prevention participants showed significant improvement in Information-Motivation-Behavioral domains: behavioral intentions were associated with	asking patients detailed questions about their sex lives did not result in increased risk behavior, as has often been feared, and it might be speculated that repeatedly asking detailed questions about sex and risk might have contributed to risk-reduction in both intervention groups	Medium

									significantly fewer unprotected sex occasions. Reduction of unprotected sex occasions was similar in controls.		
68	Wander, 2014 [85]	Pre-per-post-intervention (DART trial) observational cohort study	Adults with non-traumatic out-of-hospital cardiac arrest	Seattle (WA) USA	Cardio-pulmonary resuscitation (CPR)	156 months	8,626	Bystander CPR with or without dispatcher assistance	Compared to the before period, odds of dispatcher assisted CPR were higher during DART but no different after	The trial may influence dispatcher behaviour increasing arrest identification, provision of CPR instruction, and the proportion who received bystander CPR	Low
69	White, 2021 [86]	Pre-post intervention	none	Barts Health NHS Trust clinical transplantation laboratory (UK)	Improvement project identifying current Turnaround time performance and sources of delay.	ND	ND	Mean sample turnaround time and percentage completed within 5 days (KP2)	Performance on this control also increased comparably, but then fell away after our project finished, while it did not for B27/B57	the improvement in TaT could be due to increased staff attention during the QI… the Hawthorne effect may have impacted performance during the PDSA cycles, but it is not responsible for (all) our new performance level for B27/B57.	Low
70	Wolff, 2014 [39]	Randomized controlled trial	Primary care patients	Cleveland (OH) USA	Medication reconciliation	7 months	367 patients, 20 family Physicians	Agreement between medication lists	Neither intervention improved medication lists agreement	Baseline agreement much higher than expected	High
71	Wong, 2020 [49]	Retrospective analysis of a RCT	Females with breast cancer in Ontario	Toronto (ON) Canada	Adjuvant breast cancer radiotherapy	3 months	346 patients declining participation in RCT compared to 349 patients enrolled in a RCT	compare the incidence of high-grade skin reactions	Lower pain score in the trial group compared to non-trial for conventional or hypofractionated radiotherapy.	closer follow-up, better patient adherence, more health aware patients have, or reaction to observation… known observation by researchers may alter behavior of participants due to awareness of being observed or having	Low

										assumptions about the researcher expectations	
72	Wu, 2018 [54]	Prospective cohort observational study	Healthcare workers	Kaohsiung City, Taiwan	Hand Hygiene	15 months	31,522 hand hygiene opportunities	WHO guidance	Heterogeneity of the HE Nurses > Physicians Outpatients clinics > Intensive care units	Behaviour change in healthcare professionals under observation, heterogeneity depending on status and environmental factors	Low
73	Yin, 2014 [71]	Observational study	Healthcare workers	Multi-centre USA	Hand Hygiene	26 months	11,444 hand hygiene opportunities	WHO guidance	14 minutes for the appearance of the HE, increasing further after 50 minutes. Depending on baseline complying rates and targeted improvement	Behaviour change in healthcare professionals under observation, heterogeneity depending on time and difference between baseline rates and targeted improvement	Low
74	Zhang-Rutledge, 2017 [87]	Pre-per-post-4 phases-intervention observational study	Pregnant women at childbirth	Houston (TX), USA	Episiotomy at childbirth	60 months	16,441	Episiotomy rate	Reduction in the episiotomy rate without a reduction in the rate of operative vaginal delivery or an increase in the rate of third- and fourth-degree lacerations	Behaviour change under observation, disappearing gradually in time	Low

Keys: COPD: Chronic obstructive pulmonary disease; **HH**: hand hygiene; **ND**: missing data; **NSW**: New South Wales; **NZL**: New Zealand; **RCT**: randomized controlled trial; **UTI:** urinary tract infection; **UK**: United Kingdom; **USA**: United States of America; **WHO**: World Health Organization

Table 6: synthesis of reports used to quantify the Hawthorne effect in primary care, outpatient clinics and healthy persons.

#	Article	Study-characteristic	Population	Setting	Field	Duration	Number of inclusions	Main Outcome	Comparison	Results	Level of evidence
1	Abujudeh, 2014 [72]	Pre-post-intervention observational study	Department of radiology	Boston (MA) USA	Outpatients falls	78 weeks	327 falls in 5,080,512 radiology examinations	Fall rate, fall reports	Retrospective study comparing pre and post intervention time spans	An Increase, a plateau, and a decrease in incident reports	Low
2	Barbaroux 2021 [94]	Post-hoc analysis of a RCT	General practice residents	Nice, France	Influenza vaccination	2 months	161 healthy residents	Influenza vaccination	Control group of the RCT compared to a non-exposed group	No increase in vaccination uptake	Moderate
3	Cizza, 2014 [28]	RCT	Obese outpatients	Bethesda (MD) USA	Sleep extension	81 + 121 days	125 subjects	Sleep parameters	Comparison of parameters between inclusion and randomization	Improvement between inclusion and randomization	High
4	Fernald, 2012 [30]	Quasi-experimental RCT	Primary care physicians	Texas, North-Carolina USA	Skin and soft tissue infections	7 months	91 family physicians (14 intervention, 77 control)	Antibiotic selection and prescription for abscesses	Randomly selected clinicians who participated in follow-up case reviews versus clinicians who did not	No difference between clinicians who participated in follow-up case reviews and 77 clinicians who did not	Moderate
5	Henry, 2015 [45]	Post-hoc analysis of a RCT	Depressive patients in primary care	San Francisco (CA) USA	Physician patient relation	ND	135 investigators 867 subjects	Acceptance of video-recording	Clinicians consenting video-recording compared to clinicians non consenting	Selection in investigators and subjects. No change induced by video recording	Moderate
6	Leonard, 2017 [77]	Pre-post-intervention observational study	Primary health care clinicians	Tanzania	Protocol adherence	Intervent .10 weeks Assess. 18 month	96 clinicians 4512 patients interviews	4 measures of protocol adherence and 3 feedback visits	Comparison of protocol adherence parameters in clinicians exposed to repeated measurements at 3 successive periods	Being part of a project that encouraged quality, clinicians increased the quality of care in the short, medium and long-(18 months) term	Low
7	Leurent, 2016 [33]	RCT	Healthcare workers	Tanzania	Management of anti-malarial drug prescriptions	24 months	19,579 patients in 18 facilities	Performance of a rapid diagnostic test and prescription of	Comparison of days when exit surveys were conducted with other days	Improvement of the performance of tests and lower prescription of anti-malarial drugs in negative tests	Moderate

								an anti-malarial drug			
8	Liebert, 2021 [51]	Pilot study for a RCT	Outpatients with Parkinson's disease	South Australia	Effectiveness of photobiomodulation to mitigate clinical signs of PD	12 months	12 participants: 6 immediately treated and 6 waitlisted	Time up and go measure of mobility	Comparison of selection and baseline data in waitlisted patients	Improvement of time up and go measure between enrolment and treatment, and after 4 weeks of treatment	Low
9	McCambridge 2018 [96]	3 arm online RCT	Students	Newcastle (NSW) Australia	Alcohol consumption	4 weeks	4,583 students	Self-reported alcohol consumption	Students aware of an online survey compared to students aware that the survey is about alcohol consumption + AUDIT questionnaire	No evidence of any Hawthorne effect	Moderate
10	Miller, 2015 [64]	Observational study	Community health workers in primary care	Oromia region, Ethiopia	Childhood illness	2 months	137 health workers, 790 children	WHO Health Facility Survey tool (quality of care)	Comparison of register review data of children observed by the survey team during examination by community health workers and children not observed	Differences between the two estimates relatively small for most of the indicators and borderline significant for only one indicator	Low
11	Nothnagel, 2019 [43]	Feasibility study for RCT	Chronic neck pain patients	Jena, Germany	Assessment of pain intensity between enrolment and baseline	ND	42	Average pain intensity (VAS)	Comparison or neck pain intensity between enrolment and randomisation	Reduction of pain intensity between enrolment and baseline	Moderate
12	Pate, 2018 [24]	Appraisal of a RCT: Salford COPD trial	COPD patients in primary care	Stalford, UK	Management in Primary care of COPD	12 months	Comparison of 1403 patients in the usual care arm to 16758 non trial matched patients in the Clinical Practice Research Datalink (CPRD) primary care database	rate of acute exacerbations of COPD	Comparison of COPD exacerbations in trial patients and in matched non-trial patients from the primary care CPRD database.	more exacerbations recorded in trial patients and behavioural changes in patients and general practitioner coding practices	Moderate

13	Rosenberg, 2018 [67]	Observational study	Young women	Bush-buckridge (Mpuma-langa), South-Africa	HIV infection prevention	48 months	3889 young women	School enrolment	Comparison of school enrolment of young women participant vs. non participant in a HIV prevention trial	Cash transfers conditional on school enrolment did not influence HIV acquisition	Low
14	Shaafi Kabiri, 2020 [83]	Pre-post intervention	young healthy adult males with normal vision	Boston (MA), USA	Neuropathology	7 minutes	30 patients	Spontaneous eye-blink rate	Comparison of the number of eye-blinks per minute in patients first not informed and after informed about the outcome measurement	transitory impact on blink count during the first and third minute of a passive image-viewing task that occurred immediately after subjects were informed of their eye blinks being counted	Low
15	Wollny, 2021 [95]	cluster RCT	Patients with poorly controlled type 2 diabetes mellitus	Rostock, Germany	Subjective shared decision making and patient centeredness in Primary care	24 months	833 patients 435 intervention, 398 control) and 108 GPs (54 intervention, 54 control)	effect of an educational intervention on the management of patients	Subjective shared decision making questionnaire between baseline and follow-up in both groups	Decrease of subjective shared decision associated to an increased patients' demand for shared decision making and patient-centredness	Low

Keys: COPD: Chronic obstructive pulmonary disease; ND: missing data; NSW: New South Wales; RCT: randomized controlled trial; UK: United Kingdom; USA: United States of America.

Short discussion and conclusion

In line with this thesis, this review stated 1) That experimental artefacts happen in all research, and particularly in research investigating the field of health behaviour; 2) That the experimental design of our RCT was properly shaped to prevent the occurrence of a HE or of a placebo effect, but that a regression towards the mean effect was not to be ruled out. The size of a HE in primary care research on binary outcomes, like delivery vs. not delivery of a seasonal influenza vaccine, for well-designed RCTs is expected not to be significant. If the HE could mask a very small effect size, it cannot elucidate the observed difference in vaccination uptake between our cohort and public health data.

For this reason, and based on the findings of this systematic review, a new experiment had to be designed to demonstrate the ineffectiveness or at least the neglectable effect of posters and pamphlets in waiting rooms to change patients' health behaviours in line with other studies achieved in other countries (137,169–171,283,284). Further, it should elucidate the trend towards an increase in vaccination uptake in our RCT when public health data indicate a decrease.

Chapter 6: comparing the effect of a one-off intervention to continuous care

Short introduction

One of the conclusions of our review in chapter 5 was that the risk of an experimental artefact such as a Hawthorn effect (HE) was improbable in our RCT. If a HE happened, as the design was well shaped to prevent an experimental artefact, and as it was a RCT with a binary outcome, the size of the HE is expected not to be significant.
Nonetheless, there are experimental designs that allow to avoid completely a HE, or at least to evaluate a potential HE, like the constitution *a posteriori* of a control group (264). By comparing the control group of the RCT to another group that was not aware of the experimentation, where investigated outcomes were collected routinely, it is possible to measure deviations that were observed in the control group and that can be considered as experimental artefacts (195). In this verification study, we created a second control group and we enlarged the recruitment of the utilised claim database, in order to avoid any contamination by the intervention and to avoid any population selection. Further, to investigate the trend of an increase of influenza vaccination uptake, we followed the selected cohort over three years.
Finally, as there are overlap areas between the HE and the regression towards the mean (RTM) statistic phenomenon, we integrated in the analysis process of the outcomes adjustment equations in order to erase the effect of RTM.

Reanalysis of a Randomized Controlled Trial on Promoting Influenza Vaccination in General Practice Waiting Rooms: A Zelen Design

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Published in: Vaccines. 2022;10(5):826. DOI: https://doi.org/10.3390/vaccines10050826. (IF: 4.127)

Abstract

Background: In 2014–2015, we conducted a randomized controlled trial (RCT) assessing the effect of an advertising campaign for influenza vaccination using posters and pamphlets in general practitioner (GP) waiting rooms. No effect of the intervention could be demonstrated, but the immunization uptake increased in both arms of the study.
Methods: In 2019, we deepened the investigations explaining the increased uptake conducting a registry-based 4/2/1 cluster RCT designed by Zelen with two extra years of follow-up of the study cohort. The study population included 23,024 patients eligible to be vaccinated who were registered with 175 GPs. The main outcome remained the number of vaccination units delivered per study group. Data were extracted from the SNIIRAM warehouse claim database for the Lille-Douai district (northern France).
Results: No difference in vaccination uptake was found in the Zelen versus the control group of the initial RCT. Overall, the proportion of vaccinated patients increased in the cohort from 51.4% to 70.4% over the three years. Being vaccinated the previous year was a strong predictor of being vaccinated in a subsequent year. The increase in vaccination uptake, especially among people older than 65, can be explained by a cohort effect. Health promotion and the promotion of primary health care may play an important role in this increase.

Keywords: vaccination coverage; influenza; human; primary health care; health promotion; randomized controlled trials as topic

Introduction

Seasonal influenza epidemics happen yearly in France and occur generally during 5 to 13 winter weeks (e.g., in 2016–2017, from week 49/2016 to week 06/2017) and can start early in December (e.g., for 2016–2017) or start late in February (e.g., for 2014–2015). Its intensity is variable with weekly peaks floating between 410 (2013–2014) and 990 (2014–2015) occurrences per 100,000 inhabitants. The mortality excess during the seasonal epidemic was 18,300 in 2014–2015 and 21,200 in 2016–2017, mainly in persons above the age of 75 (285).

Every year, persons 65 years and older and patients with a targeted, chronic condition (e.g., COPD, asthma, and diabetes) or pregnant women receive an invitation letter in October from their mandatory insurance company to undergo seasonal influenza vaccination, including a voucher to receive a free vaccination unit delivered by their community pharmacy between October and January. If patients lose their voucher for a free vaccination or did not receive it for their chronic condition or pregnancy, their GP can deliver a new one, but we found that the occurrence of this contingency was negligible (155). At the same time, a nationwide vaccination campaign is broadcasted on TV and radio stations, in journals and newspapers, and in the offices of health professionals through posters and pamphlets in waiting rooms. Vaccination injections can be given by general practitioners (GPs), pharmacists, nurses, and midwives. The national vaccination uptake percentage of 45.7% in 2014–2015 placed France in the upper range of the European mean coverage of the target population (63,286).

Unless they are affected by a chronic condition, infants and children are not targeted for seasonal influenza vaccination in France.

During winter 2014–2015, we conducted a randomized controlled trial (RCT) to assess the effect of the annual influenza vaccination campaign in GP waiting rooms (155). This trial compared the delivery of vaccines, counted as the number of vaccination units, in community pharmacies to patients of GPs whose waiting rooms displayed a poster and pamphlets promoting vaccination (intervention) and to patients of other GPs where the waiting rooms was as per their usual state (control group). Routinely collected data from the "*Système Informationnel de l'Assurance Maladie-Erasme"* (SIAM-ERASME), the main mandatory health insurance company covering about 75% of the population of the urban area of Lille-Douai in northern France, were used to compare both groups (156). No difference was found between these groups, strengthening the evidence that exposure to posters and pamphlets in GP waiting rooms does not result in different health behaviors (180).

However, two interesting outcomes emerged: (1) In the case of previous vaccination in 2013–2014, the vaccination uptake probability in 2014–2015 was 5.63 times higher (95% confidence interval [5.21; 6.10]), and (2) the vaccination uptake increased by 3% in both arms of the research group from 46% [45.23–47.13] to 49% [48.04–49.95]. Contemporaneously, according to national public health data, the seasonal influenza vaccination uptake in this area decreased by 2.4% from 52.7% to 50.3% and on a national level by 2.8% from 48.9% to 46.1% (68). Indeed, the vaccination uptake gradually decreased every year from 2009–2010 (60.2%: influenza A1N1 pandemic) to 2014–2015 (45.7%), after which it stagnated until 2019–2020 and rebounded in 2020–2021 during the COVID-19 pandemic (55.8%) (68). The increase in vaccination uptake in the RCT could have been due to a Hawthorne effect (HE). A systematic review of an updated definition of the HE and its determining factors concluded that an HE was unlikely to explain an increase of more than 5% of vaccination uptake (287).

Another reason for the increase may be a cohort effect. This cohort effect may be driven by a growing awareness triggered by the educational influence of patients' GPs or other sources of public health promotion (288). A cohort effect may also be driven by a perceived decline in health due to aging (289).

The main objective of this study was to assess the possibility of an HE, through comparison of the vaccination rate in the control group of the RCT to a third group of patients enlisted with GPs who were not aware of the RCT at the time the study was conducted. The secondary objective was to access the possibility of a cohort effect in this particular RCT. To investigate this, we followed our three cohorts during the two following years. As the seasonal influenza vaccination uptake was more or less stable, according to a time series analysis of the whole targeted population based on public health data, it was of interest to compare this trend with the trend in our cohort managed in primary health care (68).

Materials and Methods

We conducted a reanalysis of a cluster randomized RCT, with two arms, adding a third arm conforming to a Zelen design with retrospectively collected data. Data were extracted in 2019 from a routinely collected claim database at the patient level from 2014 to 2017. Clusters were constituted by patients aged 16 years or over registered with one of the participating 175 GPs from the Lille-Douai Health Insurance district (northern France) totalizing 155,025 patients.

The initial trial was a single-blinded 2/1 registry-based RCT carried out in the same area in 2014–2015 (155). From the 75 GPs recruited in the trial, 25 were allocated to the intervention group and 50 to the control group using a computerized random draw. The design to achieve the first objective of the current study was described by Marvin Zelen in 1979 (179,290). For this reason, we chose to call the third group of patients with retrospectively collected data the "Zelen group". The recruitment of the 100 GPs of the Zelen group was conducted in 2019 and followed the order of a randomized list of GPs not approached during the recruitment for the original trial from the same insurance district. This Zelen-designed trial was thus a 4/2/1 registry-based cluster randomized trial, with the Zelen group not being aware or contaminated by the trial's intervention, avoiding all risk of experimental artefact. To assess a potential cohort effect, the three groups were followed up during the two subsequent vaccination campaigns (2015–2016 and 2016–2017).

GPs had to practice actively in private practices, which could be single-handed, in group practices, or in primary care interprofessional units. Primary health care was their main activity, excluding those where complementary medicine (e.g., homeopathy, acupuncture) or other practice (e.g., sonography, aesthetic medicine, angiology…) was their principal activity. Group practices from which one or more GPs had been involved in the original trial were excluded from enrolment in the Zelen group.

In the original trial, data were collected from the SIAM-ERASME claim database of the main mandatory health insurance fund covering about 75% of the insured population. For this reanalysis, data were collected from the "*Système National d'Information Inter Régimes de l'Assurance Maladie—Entrepôt*" (SNIIRAM-Warehouse) claim database, merging irreversibly anonymized data at the insurance beneficiary level from all French mandatory health insurance regimes. This larger database enhances the external validity of our results, as it includes certain professional categories like teachers or farmers, which were not included in the first trial database.

To be included in the study, participants had to be 16 years or over and registered by their health insurance regime in the Lille-Douai Health Insurance district with one of the 175 participating GPs. Registration on a GP's patient list is not mandatory before the age of 16. For this reason, data regarding children are not reliable in French health insurance claim databases. Clusters were defined as all patients registered with a single GP.

The target population was defined as the patients who benefit from free access to the seasonal influenza vaccination, including patients aged 65 years or over and patients with a chronic condition requiring influenza vaccination coverage. Patients were informed about the anonymous use of their data and could refuse to participate. As research classified MR-004 by the French authorities, no informed consent for the use of individual data was required for each anonymized subject as data were routinely collected before the implementation of the European General Data Protection Regulation (GDPR), and all data were irrevocably anonymous (Ethics Committee of the Lille University Hospital (CPP Nord Ouest IV, advice #: HP 14/51) and the National Electronic Data and Liberty Commission (CNIL, advice 2019513)). The study was registered on ClinicalTrials.gov (registration #: NCT03239795).
The cohort was followed for three years after baseline. Patients without a chronic condition reaching the age of 65 during the four years of the follow-up and patients with a first chronic condition occurring during this period were not included. Patients who died or were lost to follow-up were not excluded.
The intervention consisted of withdrawing all informative material from GP waiting rooms (apart from mandatory information such as service fees), exposing only the 2014–2015 official Health Insurance poster promoting seasonal influenza vaccination and 135 official pamphlets. In the control group, the waiting rooms were left in their usual state. GPs from both groups knew that the seasonal influenza vaccination uptake of their patients would be measured, but GPs from the control group were not aware of the intervention. As written above, the 100 GPs from the Zelen group were unaware of the trial or the intervention. Their outcomes for the two-year time span of the trial were collected retrospectively.
It was not possible to measure the actual number of injections of seasonal influenza vaccination fulfilled by GPs and other medical specialists, self-employed nurses, midwifes, or community pharmacists. For this reason, the usual surrogate endpoint to measure influenza vaccination coverage in France was used: the main outcome was the number of vaccination units dispensed by community pharmacies for which payment appears in the claim databases of the health insurance companies under the name of the insurance beneficiary.
Data on patients encompassed their gender and age, the occurrence of a chronic condition, the date of delivery of the vaccination unit, and their mandatory insurance fund. Data on GPs encompassed their gender and age, the number of patients on their patient list by year of interest, the number of patients aged 65 years and over, and the number of patients with a chronic condition of interest. In instances where patients lost their free vaccination voucher or when patients were not registered with a chronic condition of interest by the health insurance company, their GPs could prescribe a vaccination unit. The number of vaccination units prescribed by the GPs were taken into account for the published trial but appeared to be negligible. In this study, vaccination units prescribed by GPs were not considered.
The variables of interest to be extracted from the SNIIRAM-Warehouse database were transmitted to the data management center of the information processing department of the National Health Insurance Fund. A first extraction was unexploitable as no link was made possible between the anonymized patient lists and their referring GPs. A second extraction assigned a GP to each patient. Despite repeated requests, the data management center did not communicate the query algorithm in digital language as recommended by the CONSORT ROUTINE guidance (156).
A potential clustering of the outcome for patients treated by the same GP was considered. To correct this bias in computing the number of GPs needed for the trial with binary outcomes, an intracluster correlation coefficient of 0.02 was used, for $\alpha = 0.05$ and $\beta = 0.20$ (165). To find a difference of 5% between groups with a target size of 400 patients per GP, 75 GPs had to be enrolled (50 controls and

25 in the intervention group) (157). As the maximal expectable HE was 5%, 100 GPs had to be enrolled in the Zelen group to be compared to the 50 in the control group.

The 75 GPs included in the original trial were enrolled between July 2014 and September 2015 following the order of a computerized random draw of 810 private practitioners registered as GPs by the health insurance fund. Another computerized random draw was used to allocate GPs to each group: 25 in the intervention group and 50 in the control group. To include the 100 GPs for the Zelen group, the continuation of the randomized list of the GPs from the Lille-Douai insurance district who had not been not approached when enrolling GPs in the original trial was used. Telephone calls were made between May and October 2017 to recruit these GPs, verify their eligibility, and obtain their agreement for participation, following the order of the list. Written consent of the eligible GPs was mandatory for inclusion.

Both the random allocation sequences were generated by the Public Health Department of Lille University Hospital. The participants in the original trial were enrolled by A.W.B. and S.Z.-M.M., co-authors of the study. The 100 participants in the Zelen group were enrolled by M.B.

Baseline characteristics of patients in the three groups are presented using a univariate analysis. Quantitative variables are expressed as a mean with a 95% confidence interval (95% CI) of the mean. Categorical variables are expressed as percentages and 95% CI of the percentage. The clustering variable "GP" was taken into account through the "*svydesign"* function of the package "*survey"* in R (166).

To assess the association between the vaccination status (dependent variable) and group (intervention/control/Zelen) membership, a generalized estimating equation (GEE) Poisson regression with an exchangeable working correlation matrix was used, resulting in risk ratios (167). We adjusted for sex, age, having a chronic condition, and clustering by GP at baseline. To interpret the intervention effect, an interaction effect between time and intervention was included. Based on the assumed nature of the effect, we deemed the use of an interaction effect more accurate than the analysis of covariance (ANCOVA), which was used in the previous analysis of the trial (155,291,292). To analyze the effect of being vaccinated the previous year on being vaccinated the consecutive year, we used a stationary first-order autoregressive transition model with being vaccinated the previous year included as a covariate (293). To analyze the differences in the evolution of vaccination over time among age groups, point estimates and related confidence intervals, corrected for clustering by GP, were calculated and displayed after stratification per every five years of age. Analyses were carried out in R using packages "*geepack"*, *"survey",* and *"ggplot2"* (166,294,295).

So far as possible, the reporting of this trial was implemented in accordance with the CONSORT extension for the reporting of randomized controlled trials conducted using cohorts and routinely collected data (CONSORT-ROUTINE) (156).

Results

The data at baseline were collected from 155,025 patients, and 23,024 patients were included in the analysis. Patients include those aged < 65 and with a chronic condition (*n* = 6,354), patients aged ≥ 65 with a chronic condition (*n* = 10,961), and aged ≥ 65 without a chronic condition (*n* = 5709). The intervention group consisted of 3,430 patients, the control group of 6,620, and the Zelen group of 12,974.

The three groups did not differ at baseline in terms of age, gender, proportion of those aged ≥ 65 years, or the existence of a chronic condition. (Table 9)

Table 9. Baseline characteristics.

Characteristics	Category	Intervention Group	Control Group	Zelen Group	P (i-c) adj	P (z-c) adj	P (z-i) adj
		(*n* = 3,430)	(*n* = 6,620)	(*n* = 12,974)			
		mean or % [95% CI]	mean or % [95% CI]	mean or % [95% CI]			
Age	years	70.3 [68.7; 71.9]	69.9 [68.9; 70.8]	69.7 [68.9; 70.5]	0.687	0.751	0.524
Gender	male	44.9% [42.2; 47.5]	43.7% [42.2; 45.3]	44.7% [43.4; 45.9]	0.465	0.353	0.889
Age ≥ 65	yes	76.0% [71.9; 80.0]	76.0% [73.5; 78.6]	75.1% [72.7; 77.4]	0.979	0.58	0.704
Chronic condition	yes	74.0 [70.9; 77.1]	74.7 [72.7; 76.8]	75.8 [74.3; 77.2]	0.700	0.413	0.314

Legend: CI = Confidence Interval, adjusted for clustering by general practitioner.

Main Outcome

The vaccination uptake in the three groups did not differ at baseline and after intervention (Table 10).

Table 10. Influenza vaccination uptake in the three groups during three years after baseline

Category	Intervention	Control	Zelen	P (i-c)	P (z-c)	P (z-i)
	(*n* = 3,430)	(*n* = 6,620)	(*n* = 12,974)			
	% [95% CI]	% [95% CI]	% [95% CI]			
2013–2014 (baseline)	49.8% [45.9; 53.7]	50.0% [47.8;52.3]	52.5% [50.3; 54.7]	0.904	0.131	0.241
2014–2015 (intervention)	55.7% [52.6; 58.8]	54.1% [51.0;56.3]	55.1% [53.6; 56.7]	0.408	0.444	0.748
2015–2016	64.0% [60.7; 67.2]	67.3% [65.6;69.1]	67.4% [65.8; 68.9]	0.078	0.989	0.067
2016–2017	70.9% [66.9; 74.9]	70.0% [65.7; 74.3]	70.5% [68.1; 72.9]	0.763	0.851	0.856

Legend: CI = Confidence Interval, adjusted for clustering by general practitioner.

Comparing the three groups in a multivariable model, no difference was found between the control group and the intervention group despite a larger database and a more accurate analysis, supporting our previous findings. No difference was found between the control group and the Zelen group, acknowledging our hypothesis of a very weak or inexistant HE in our study. Comparing the intervention group and the Zelen group, we found a statistically significant difference (Table 11). However, this difference needs to be interpreted with caution as the baseline point estimate of the Zelen group was higher than the baseline point estimate of the intervention group; this may have elicited a regression to the mean (RTM) effect (295). We therefore decided to perform a sensitivity analysis using analysis of covariance, which is known to adjust for a potential RTM effect (295). This resulted in a nonsignificant intervention effect: RR 1.019 (95% confidence interval 0.986; 1.052).

Table 11. Comparison of the three groups after intervention

Comparison	Estimate (RR)	95% CI	*p*
Intervention vs. Zelen	1.065	[1.020; 1.113]	**0.0043**
Intervention vs. control	1.037	[0.988; 1.087]	0.141
Control vs. Zelen	1.029	[0.995; 1.064]	0.09943

Legend: RR = Relative Risk; CI = Confidence Interval.

Secondary Outcomes

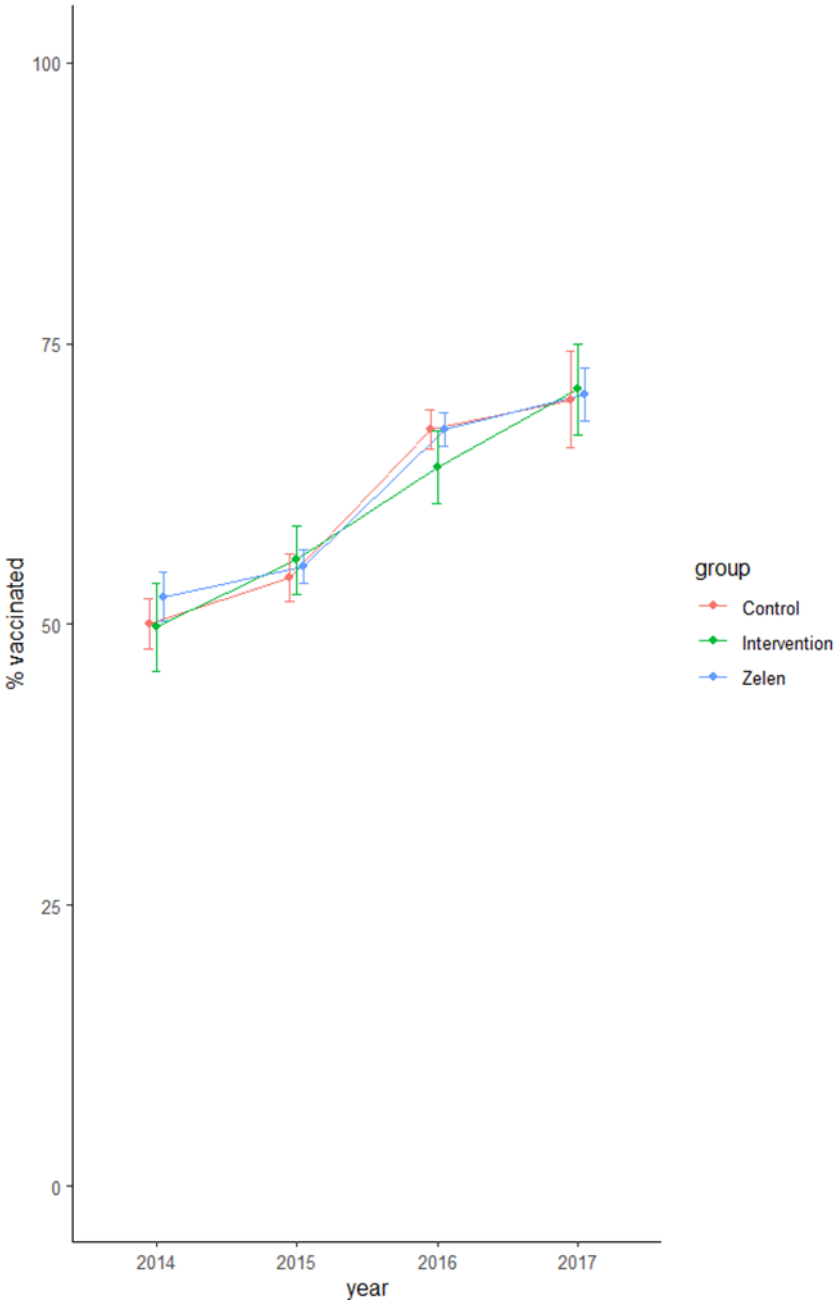
Each subsequent year, vaccination uptake increased. Considering the point estimates, the increase was higher between the first year of follow-up (2015–2016) and the second year of follow-up (2016–2017) (Table 10 and Figure 5).

Over the whole period, patients vaccinated in the preceding year showed a 250% increase in the odds of being vaccinated in the subsequent year, or the odds of someone being vaccinated who was vaccinated in the previous year were 3.5 times the odds of someone who was not (Table 12).

Since age showed a significant effect on the evolution of vaccination over time (Table 12), we assessed yearly vaccination uptake for the different age strata and per risk category.

The three groups at risk showed an increasing trend in terms of the percentage vaccinated at baseline per increasing age groups (see Figures 6–8 and Tables 13–15). Within most groups, we saw an increasing trend in the percentage vaccinated during the three years of the study. For the group above 65 years of age, this increasing trend became less prominent for the older strata to finally reverse for the oldest stratum. For the group under 65, the increase within the group remained more stable over the different age strata. The percentage vaccinated at baseline in this group was relatively low, especially among the younger strata.

At baseline, the subjects with the highest vaccination uptake were patients ≥ 65 years with a chronic condition, with 51.9% in the 65–69-year-olds, rising gradually to 70.3% in the 94–105-year-olds. However, the higher the value at baseline, the less it increased, reaching 75.6% to 71.0% in 2017 for the 65–79-year-olds and decreasing in the ≥85-year-olds. The major increase of 23.7% was observed in the most represented age group of 65–69-year-olds (Table 13 and Figure 6).



Legend: Estimate and 95% CI of the percent vaccinated per year and different study arms.

Figure 5. Vaccination uptake in the three groups.

Table 12. Factors associated with increased vaccination

Characteristic	Estimate (OR)	95% CI	*p*
Vaccination in the previous year	3.50	[3.28; 3.73]	<0.001
Characteristic	**<65 (with chronic condition)**	**≥ 65 (without chronic condition)**	**≥ 65 (with chronic condition)**
	RR [95% CI]	RR [95% CI]	RR [95% CI]
Age	1.002 [1.001; 1.004]	0.996 [0.994; 0.997]	0.993 [0.992; 0.994]
Gender	1.021 [0.998; 1.045]	0.948 [0.928; 0.970]	0.990 [0.976; 1.004]

Table 13. Influenza vaccination uptake by age at baseline ≥ 65 group (with chronic condition)

Age Category (Baseline)	*n* (Baseline)	2013–2014 (Baseline) % [95% CI]	2014–2015 % [95% CI]	2015–2016 % [95% CI]	2016–2017 % [95% CI]
[65, 69]	2672	51.9 [49.5; 54.4]	57.7 [55.6; 59.8]	73.7 [71.7; 75.7]	75.6 [72.5; 78.7]
[70, 74]	1922	57.3 [54.6; 60.1]	62.3 [59.7; 64.9]	74.3 [72.2; 76.5]	74.3 [71.5; 77.1]
[75, 79]	2266	58.1 [55.6; 60.5]	60.6 [58.2; 63.0]	74.2 [72.1; 76.3]	71.0 [68.5; 73.5]
[80, 84]	2045	59.9 [57.2; 62.6]	61.2 [58.8; 63.7]	69.4 [67.0; 71.8]	67.8 [65.4; 70.3]
[85, 89]	1378	59.7 [56.5; 62.9]	59.6 [56.4; 62.8]	61.6 [58.8; 64.5]	57.8 [54.7; 61.0]
[90, 94]	604	61.6 [57.7; 65.5]	55.6 [51.2; 60.0]	54.5 [49.7; 59.2]	47.8 [43.5; 52.2]
[95, 105]	74	70.3 [58.9; 81.6]	51.4 [41.6; 61.1]	37.8 [27.6; 48.0]	21.6 [11.9; 31.3]

Legend: CI = Confidence Interval, adjusted for clustering by general practitioner.

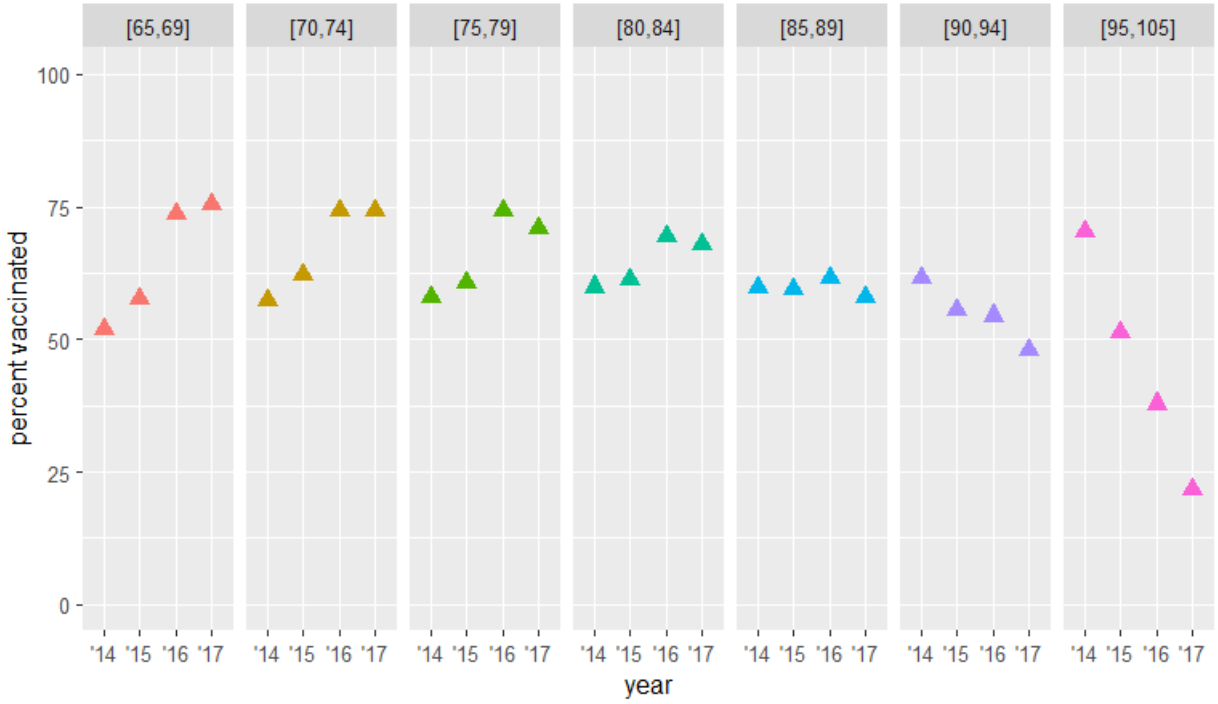


Figure 6. Influenza vaccination uptake by age at baseline ≥ 65 group (with chronic condition)

In the group of patients ≥ 65 years of age without a chronic condition, the baseline percentage of vaccination uptake was lower, rising from 46.3% in the 65–70-year-olds to 69.2% in the 95–105-year-olds. However, this group showed the greatest increase reaching levels between 75.7% and 79.5% in the 65–84-year-old strata. A major increase of +29.4% was observed in the 65–69-year-old stratum. A decrease in the ≥90 strata was also observed (Table 13 and Figure 7).

Table 6. Influenza vaccination uptake by age at baseline ≥ 65 group (without chronic condition).

Age Category (Baseline)	*n* (Baseline)	2013–2014 (Baseline) % [95% CI]	2014–2015 % [95% CI]	2015–2016 % [95% CI]	2016–2017 % [95% CI]
[65, 69]	1770	46.3 [43.4; 49.1]	52.7 [50.3; 55.1]	66.7 [64.2; 69.2]	75.7 [73.2; 78.2]
[70, 74]	1092	51.2 [47.7; 54.7]	58.1 [55.0; 61.1]	72.1 [69.0; 75.2]	79.5 [76.0; 83.0]
[75, 79]	1156	54.0 [50.7; 57.2]	59.7 [56.6; 62.8]	73.6 [70.8; 76.5]	77.7 [74.0; 81.3]
[80, 84]	880	55.1 [51.1; 59.1]	57.6 [54.3; 60.9]	68.8 [65.3; 72.2]	78.2 [75.0; 81.4]
[85, 89]	542	57.6 [53.0; 62.2]	57.7 [53.2; 62.3]	63.8 [59.8; 67.9]	69.4 [65.6; 73.1]
[90, 94]	230	53.5 [45.8; 61.1]	46.5 [41.0; 52.0]	57.8 [52.2; 63.4]	54.3 [47.1; 61.6]
[95, 105]	39	69.2 [54.6; 83.9]	43.6 [27.4; 59.8]	43.6 [29.2; 57.9]	35.9 [20.3; 51.5]

Legend: CI = Confidence Interval, adjusted for clustering by general practitioner.

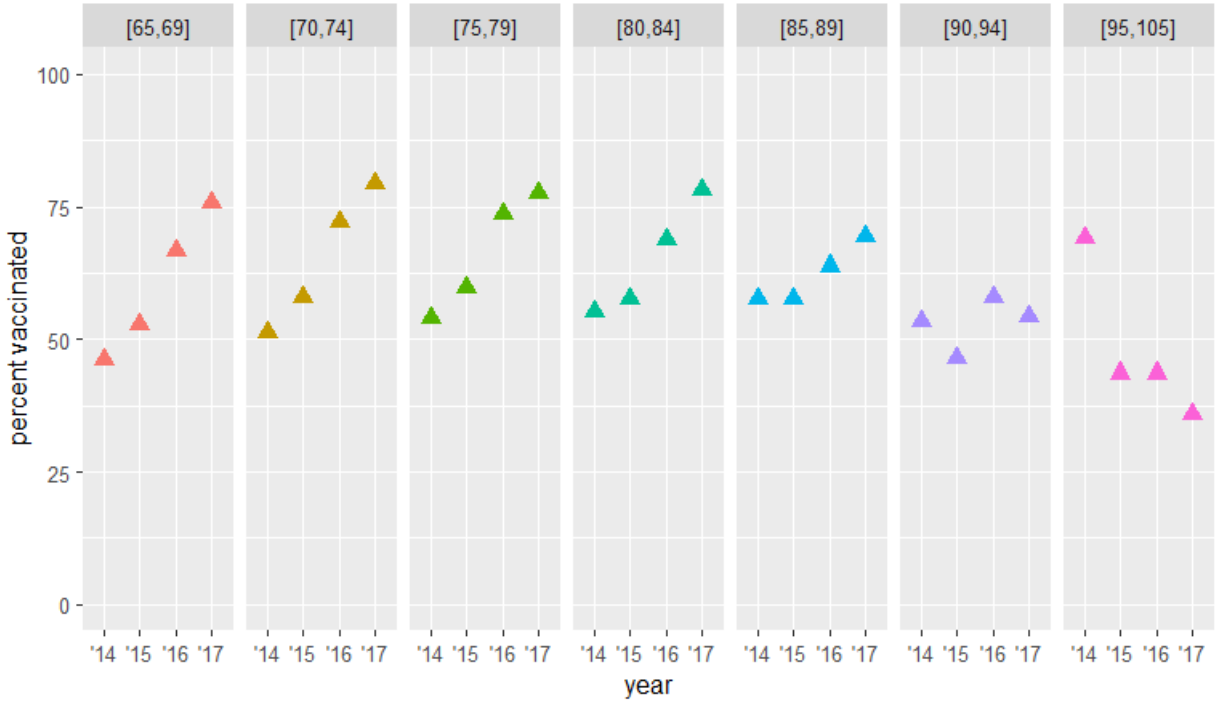


Figure 7. Influenza vaccination uptake by age at baseline ≥ 65 group (without chronic condition)

In the group of patients < 65 years of age with a chronic condition, the baseline vaccination uptake percentages were rather low, with a baseline figure in the 16–39-year-olds of between 26% and 34%, and in the 40–64-year-old strata between 40% and 46%. The increase was gradual from 9.7% in the 16–24-year-old stratum to 35.7% in the 60–64-year-old stratum, reaching a main vaccination uptake of 74.9% in the latter (Table 15 and Figure 8).

Table 15. Influenza vaccination uptake by age at baseline < 65 group (with chronic condition)

Age Category (Baseline)	*n* (Baseline)	2013–2014 (Baseline) % [95% CI]	2014–2015 % [95% CI]	2015–2016 % [95% CI]	2016–2017 % [95% CI]
[16, 24]	166	33.7 [26.2; 41.2]	38.0 [30.3; 45.6]	41.0 [33.2; 48.7]	43.4 [35.8; 51.0]
[25, 29]	175	26.3 [19.6; 33.0]	32.6 [25.7; 39.5]	39.4 [32.3; 46.6]	50.9 [43.4; 58.3]
[30, 34]	189	32.3 [26.0; 38.5]	32.3 [25.9; 38.7]	45.5 [37.7; 53.3]	50.3 [43.2; 57.3]
[35, 39]	270	33.3 [27.4; 39.2]	37.8 [31.6; 44.0]	47.0 [40.7; 53.4]	57.0 [50.2; 63.8]
[40, 44]	385	40.0 [34.4; 45.6]	42.9 [37.7; 48.0]	50.4 [45.6; 55.2	62.6 [57.1; 68.1
[45, 49]	595	43.2 [38.8; 47.6]	46.6 [42.5; 50.6]	54.6 [50.7; 58.5]	65.9 [62.2; 69.5]
[50, 54]	922	44.0 [40.7; 47.4]	45.0 [41.6; 48.4]	58.9 [55.8; 62.0]	68.9 [65.7; 72.1]
[55, 59]	1365	46.4 [43.1; 49.6]	47.8 [45.1; 50.6]	65.0 [62.2; 67.7]	70.6 [67.4; 73.8]
[60, 64]	2287	39.2 [36.9; 41.5]	47.9 [46.0; 49.8]	64.1 [61.8; 66.4]	74.9 [72.1; 77.7]

Legend: CI = Confidence Interval, adjusted for clustering by general practitioner.

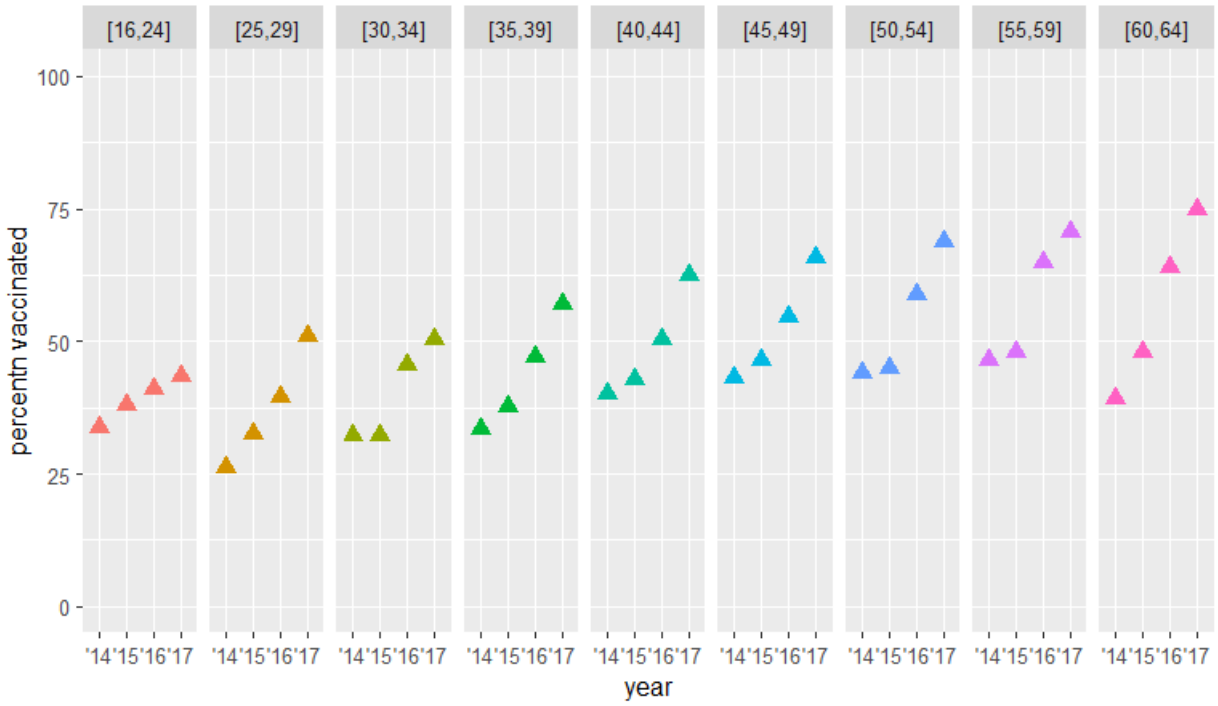


Figure 8. Influenza vaccination uptake by age at baseline < 65 group (with chronic condition)

In the end, the largest age group of 59–69-year-olds (*n* = 6,729; 29.2%) in our population was also the group where the vaccination uptake increase was the highest. On the other hand, the vaccination uptake was diminishing or stable in the smaller group of patients (*n* = 2,364; 10.3%) with a chronic condition and who were over 85 years of age, or without a chronic disease and over 90 years of age.

Discussion

Regarding the main outcome, no difference was found in the seasonal influenza vaccination units dispensed in community pharmacies between the control group and the Zelen group at baseline (winter 2013–2014) and after the intervention (winter 2014–2015). This rules out the hypothesis of an HE to explain the 4% to 5% increase in the vaccination uptake in the two groups of the RCT, while the uptake was diminishing by 2.5% in public health data on a time series analysis in the whole targeted

population (68). Initially, a difference was found between the intervention group and the Zelen group, but this difference disappeared after adjusting for RTM effect.

Our secondary objective was to explore a possible cohort effect to explain the increase in seasonal vaccination uptake in the study groups. Over the total three years of follow-up, we computed an increase of 19.0% from 51.4% to 70.4% in this cohort, nearly reaching the vaccination coverage of 75% recommended by the World Health Organization (65). Vaccination uptake was strongly associated with being vaccinated the previous year in line with findings from other studies (296). The increase in vaccination was determined by age, not by gender. Analyzing the three risk groups separately showed that the most substantial increase was observed in the two largest groups: the 2,287 patients aged 60 to 64 years with a chronic condition (+23.7%) and the 1,770 patients aged 65 to 69 years without a chronic condition (+29.4%). This increase was balanced by a decrease in vaccination uptake in the oldest stratum that we explain by uncensored mortality.

The reanalysis of our RCT published in 2018 confirmed that hanging posters and making pamphlets available in the waiting rooms to promote seasonal influenza vaccination did not increase the vaccination uptake between the two groups of the trial. This supports the evidence also noted by Li that posters and pamphlets can enhance patient knowledge, but they have limited educational impact to change patient behavior compared to encounters with doctors or nurses (297).

Our study has limitations. In our cohort, data from deceased patients were not censored, but assimilated to unvaccinated ones. This is our best explanation of a decrease in vaccination uptake in patients ≥ 95 years of age without a chronic condition or ≥ 90 years with a chronic condition.

The query algorithm in digital language to form our database from the SNIIRAM-Warehouse was not communicated by the health insurance company. For this reason, we are not able to discuss limitations that may have appeared during this process. However, the SNIIRAM is a powerful tool, a rather trusted claim database used by French public health authorities, encompassing almost the whole French population, and the engineers running the database are also experienced in running such data queries.

In the control and Zelen groups, no intervention in the waiting room was implemented. However, it is possible that posters or pamphlets from the influenza campaign might have appeared as our trial was implemented in real-life conditions. Based on our expertise and experience, we assumed that the presence of such promotional material would have been limited. Many public health campaigns are simultaneously implemented by posters and pamphlets in GP waiting rooms and are displayed for a long time, limiting the visibility of each of them. Maskell counted on average 72 posters covering 23 topics and 53 leaflets covering 24 topics with many outdated and poorly presented materials of limited accessibility (112). For this reason, in the intervention group, we only displayed the material of the influenza campaign, withdrawing the material of all the others to enhance exposure.

To determine the seasonal influenza vaccination uptake, like public health authorities do and like we did in the original trial, we used a surrogate endpoint: the number of vaccination units delivered in community pharmacies (157,298). It is uncertain whether all the delivered units were dispensed, as it is not known if patients had their vaccination units delivered by another path other than community pharmacies. However, the same limitation is applicable to all three arms of our study and should be without consequence for the final comparisons.

Our cohort only included persons who are registered with a GP. It is known that patients not registered with a GP in France have a lower vaccination coverage than registered ones (298). As many GPs from the baby boom generation are going into retirement without a replacement, a growing number of patients (5.4 million in 2019), including older patients with a chronic condition (600 thousand in 2019)

have not found a new GP agreeing to register them on their patient lists (299). Our findings may not apply to these patients.

As noted above, in this fixed cohort of patients managed by a GP, the vaccination uptake for seasonal influenza globally increased by 19% over three years. This increase, not noted in public health data from a time series analysis of the targeted population (68), can be characterized as follows: Firstly, the most prominent increase in seasonal influenza vaccination uptake happened among sexagenarians, between 60 and 69 with a chronic condition and between 65 and 69 without a chronic condition, representing one third of the total population targeted to be vaccinated. Secondly, the increase in vaccination uptake was generally lower in the younger age strata diagnosed with a chronic condition (diabetes, COPD…). Younger patients with a chronic condition diagnosed during the three years of follow-up were not included in the cohort, and hence their coverage rate did not influence our results. It is possible that the remarkable rise in most of these age strata can be partly attributed to the influence of the GPs or other primary care staff. Based on a cross-sectional online questionnaire, Dexter identified seven independent factors that may result in an increase in vaccination uptake up to 7% (288). However, these factors were analyzed in the context of the Quality and Outcomes Framework implemented in England, and hence are not fully transferable to France (there are no written reports to review influenza vaccine uptake rates in French primary care structures to earn quality rewards). Having a lead member of staff for planning the practice's influenza vaccination campaign was identified as a key factor to promote vaccination in patients. In French surveys, the influenza vaccination uptake appears to be low among healthcare personnel in hospitals: the level is highest in personnel working in geriatric wards with 31% among nurses and 48% among physicians) (300). In contrast, 77% of GPs declare to be vaccinated, 78% are promoting vaccination with their patients, and 93% are mentioning completed vaccinations in their medical record (301). GPs in France may therefore function as an adequate lead member to plan influenza vaccinations. Further, Dexter indicates that sending a personal invitation to all eligible patients has a significant effect. All French patients targeted to be vaccinated receive such an invitation from their mandatory insurance company between the second half of September and the first half of October. This invitation favors the conversation about influenza vaccination initiated by the patient, by the GP, or by the community pharmacist who delivers the vaccination units (297). Once convinced, patients usually find no barrier to access vaccination as they can receive it from their GP, midwife, community pharmacist, or nurse. This finding also elucidates the shortfall of vaccination uptake in populations not registered a GP though noticed in cross-sectional studies (298).

It is of interest to note that the vaccination uptake increases in older adults though immune responses generally decline with age. Consequently a decline in vaccination efficacy can be expected, but data from RCTs searching influenza vaccine efficacy in older adults are contradictory (302). The increase in vaccination uptake can be explained by the free vaccination of persons with a chronic condition and aged 65 years and over and by the incitation by authorities. It can also be explained by a growing perception of vulnerability in elderly patients who also may experience serious influenza infections with prolonged and sometimes incomplete recovery in themselves or in relatives (303). This hypothesis is supported by the earlier increase in vaccination uptake in the population with a higher level of frailty related to a chronic condition. Separating efficacy and effectiveness of vaccination in persons ≥ 60 (304), GPs contribute to fostering influenza vaccination in elderly patients to prevent hospital admission due to influenza, to reduce primary care encounters for influenza-like illnesses, and to reduce influenza imputable mortality. However, observational studies considering all the confounding

factors when evaluating vaccination effectiveness (with the most important confounding factor being the matching of vaccines to the circulating strains) remain contradictory (302).

Conclusions

The Hawthorne effect does not explain the rise in vaccination uptake in the two groups of the original RCT. Posters and pamphlets promoting seasonal influenza vaccination in GP waiting rooms have no influence on seasonal influenza vaccination uptake. In contrast, among patients registered with a GP, we saw an increase each year in follow-up in most of the age strata and more among the sexagenarians. This increase may be attributed to health promotion by primary care, nearly reaching the vaccination coverage recommended by the WHO.

Short discussion and conclusion

Public health authorities are using the SNIIRAM warehouse database and the number of influenza vaccination units dispensed by community pharmacists to assess influenza vaccination coverage in France. In this new analysis or our RCT, we used the same database and the same main outcome. Public health authorities recover their data from the generalist beneficiaries sample, while we followed a cohort of patients managed during a total of 4 years by the same sample of 175 GPs, selected at random in the health insurance district of Lille-Douai. Following the findings of our systematic review regarding experimental artefacts (287), we adjusted our results for the regression towards the mean effect. The main finding of this reanalysis is that where vaccination uptake stagnated nationwide in public health indicators between 2013 and 2017 between 48.9% and 45.7% (68), it increased during the same period from 51.4% to 70.4% in our sample.

As the intervention showed no efficacy of posters and pamphlets in GPs' waiting rooms, and as we demonstrated that the same increase was observed in the three arms of our trial, we cannot point to the efficacy of a one-off intervention to explain this increase. We already knew that being vaccinated the previous year increased markedly the probability to be vaccinated the next year. However, this indication alone cannot be sufficient to explain the increase of vaccination uptake in our sample.

It is of note that even at baseline the difference was 2.5% in favour of our sample, gathering only patients registered on a GP's patient list. The literature is in favour of better vaccination uptake in patients managed by a primary care team (305,306), without a clear evidence of the causal imputation: motivational interventions from the team or a greater concern for their health of registered patients. This last trial tends to allege that interventions are of few effect as it appears in the *Vann et al.* review (305) and that the continuous relationship with the primary health team with a growing motivation of patients for their health appears to be essential (307).

In our study, the rise in influenza vaccination uptake is not to be assigned to an experimental artefact or to the advertising campaign by posters and pamphlets in GPs' waiting rooms. It voices a greater concern and trust in vaccination in populations interacting with primary care teams promoting vaccination as an efficient prevention. Sexagenarians exposed to more frequent health problems for themselves and among their relatives appear to be more motivated to initiate vaccination. Their probability to continue vaccination the following years after the first shot is more than threefold compared to those never vaccinated.

Chapter 7: General discussion

Main results

The main results are presented as responses to the research questions from the general introduction.

The overall aim of this thesis is to test posters and pamphlets as the most common patient education tools in GPs' waiting rooms to change patients' health behaviours using the influenza vaccination campaign as a model, and to clarify the reasons why our findings differ from public health data: experimental artefact or cohort effect?

Using two different databases and two different designs of randomized controlled trials conducted in cohorts and routinely collected data (156,308), we couldn't demonstrate any effect of the influenza vaccination campaign based on posters and pamphlets in GPs' waiting rooms in Northern France. The rise of vaccination uptake that was noted in the intervention group and equally in the two control groups was not due to an experimental artefact but to a cohort effect and led to major increase in vaccination uptake in sexagenarians.

1) *To identify, describe and appraise studies that have investigated the effects of audio-visual aids on health promotion in primary healthcare waiting rooms and to determine which factors influence this impact (Chapter 3).*

We identified many different media used in primary care waiting rooms to broadcast health messages intending to educate attending patients.
The most common were posters and pamphlets that are in use in almost all waiting rooms. Many public health campaigns are implemented simultaneously and are displayed for such a long time that much are outdated, limiting the visibility and interest of each of them (112). In the literature, no effect was clearly demonstrated on interest, knowledge or health behaviour regarding posters and pamphlets.
Video recordings or slideshows shown on TV screens or tablets in waiting rooms appeared to raise more concern about the broadcasted messages. There is an acceptable evidence level on the effect of increase in knowledge, but insufficient evidence to demonstrate a change in health behaviour (140–142,174,309,310). The feasibility of implementing this type of education tool in primary care waiting rooms seems good (164,311,312), however, some consider the waiting room as a place for rest and relaxation before consulting, rather than being bombarded with health promotion messages (160).

Computer software has not demonstrated their efficacy. Interventions were mainly implemented in populations with low literacy, for instance not necessarily sensitized in playing serious games. The more extensive use of computers and smartphones require an update of our review regarding these education media. However, it seems that the use of a smartphone in waiting rooms is more dedicated to recreation games or social networks than to health education activities (313). Health apps on smartphones are more devoted to patients with specific conditions requiring medications or medical devices than to undifferentiated patients spending time in waiting rooms (314). These applications are often developed by pharma industry and with the risk of a promotional approach.

2) *To evaluate the effect of an advertising campaign using posters and pamphlets in GPs' waiting rooms on the number of influenza vaccination units delivered in community pharmacies, and to determine predictors of individual vaccination (Chapter 4).*

Based on our studies in France, there is a high level of evidence to rule out the efficacy of posters and pamphlets on seasonal influenza vaccination uptake in GPs' waiting rooms, even when only one public health message was dispensed at a time during the limited period of the seasonal influenza vaccination campaign. A Cochrane review from 2018 about interventions to increase influenza vaccination rates of those 60 years and older in the community couldn't demonstrate any efficacy of posters and pamphlets (283). From a behavioural change perspective, we can state with a reasonable risk of error that posters and pamphlets in primary care waiting rooms do not change any health behaviour and consequently do not reduce health inequities related to education and health literacy. A recent RCT evaluating the use of different pamphlets showed similar results (313). The only significant predictor for individual vaccination that we were able to highlight was being vaccinated the previous year, with an OR of 5.63 [5.21; 6.10] over two consecutive years.
However, during the study trial, the rising uptake of vaccination in both arms was surprising, while in public health statistics this uptake decreased contemporaneously. Public health statisticians were using another claim database encompassing all different mandatory Health Insurance regimes, while in this trial we used the claim database of the only main Health Insurance regime. The cohort used by public health statisticians was the generalist beneficiary sample (55) while we were using a cohort of patients registered on GPs' patients lists, the patients of each GP forming a cluster. Public health statisticians use data from patients whose GPs are not aware of any intervention aiming at enhancing seasonal influenza vaccination, and whose consent is not requested and actively given to participate in a study. For these reasons two new questions arose: was there an experimental artefact like a Hawthorne effect that biased the outcomes of our RCT? And was there a cohort effect related to the population difference in our RCT compared to the general beneficiary sample?

3) *To refine the definition of the Hawthorne effect (HE) and outline the progress of research on the HE in terms of its existence and characteristics, to estimate the size of the effect in primary care studies and to estimate the risk of a HE in our research (Chapter 5).*

We noticed that researchers are not unanimous regarding the existence of the HE and that there was considerable inconsistency concerning the description and definition of the phenomenon. The point is not a denial of an experimental artefact which is unanimously agreed. The dissension relates to the description of what happened at the Hawthorne plant. Rather than calling this artefact 'participant reactivity' as suggested by some authors we chose to keep the folkloric name of "Hawthorne effect" as it is growingly and commonly used in healthcare research.

We defined the Hawthorne effect (HE) as an aware or unconscious complex behavioural change in a study environment, related to the interaction of four biases affecting the study subjects and investigators: selection bias, commitment and congruence bias, conformity and social desirability bias, and observation and measurement bias. Its size varies in time and depends on the education and professional position of the investigators and subjects, the study environment, and the outcome, conferring a considerable heterogeneity. In primary care, outpatient clinics and healthy subjects, we computed an OR of 1.41 [1.13;1.75], with two major limitations: first, binary outcomes cannot exemplify a complex system and second, the whole variance in the HE can be explained by heterogeneity. In sensitivity analysis, we noticed that the significance of the HE disappeared in well-designed studies and in studies with a good level of evidence for binary outcome measures. There are overlap areas between the HE, placebo effect and regression towards the mean, as discussed in chapter 5.
Assessing our RCT in light of our findings, we believed that a risk of a HE was minimal. However, to rule out any risk of a HE, we decided to reanalyse our trial comparing the control group in the trial to a new control group composed *a posteriori*.

4) *To assess the possibility of an HE, through comparison of the vaccination rate in the control group of the RCT to a third group of patients enlisted with GPs who were not aware of the RCT at the time the study was conducted and to assess the possibility of a cohort effect in this particular RCT (Chapter 6).*

No difference was found comparing the influenza vaccination uptake between the control group of the original trial and the new controls (called by us, the Zelen group), ruling out a HE in our RCT. In the original trial, our data were extracted from the SIAM-Erasme database of the general scheme mandatory health insurance and we acknowledged a limitation related to the fact that the SIAM-Erasme database encompasses only 80% of the French population, missing for example teachers and farmers. In this study, we could rule out the HE extracting our data from the SNIIRAM-Warehouse database, a larger claim database encompassing all different French mandatory Health Insurance regimes, the same database and the same main outcome than the ones used for Public Health assessments of influenza vaccination uptake, though with a different population. Instead of recovering data from the generalist beneficiaries sample (55), we collected our data from a cohort of patients registered on GPs' patients lists, the patient of each GP forming a cluster, analyses being implemented on patient level. We also analysed our data adjusting for a regression towards the mean effect.
We confirmed the absence of effect on influenza vaccination uptake of the promotion campaign using posters and pamphlets in GP waiting rooms and ruled out any HE on our main outcome by comparing our three cohorts at the time of the trial without any significant difference between the three groups. During the three years of follow up of our cohort, we computed an increase from 51.4% to 70.4% in the vaccination uptake, nearly reaching the vaccination coverage of 75% recommended by the WHO. The increase in vaccination was determined by age but not by gender. Analysing by age strata and by disease characteristics our cohort, we showed that the most substantial increase was observed in the two largest groups: the 2287 patients aged 60 to 64 years with a chronic condition (+23.7%) and the 1770 patients aged 65 to 69 years without a chronic condition (+29.4%).
We could also recompute over the three years of follow-up the probability to be vaccinated in patients having been vaccinated in the previous year. The OR was of 3.50 [3.28; 3.73], thus smaller than when we analysed only the year of the trial vs. baseline, though still highly significant.

Limitations

This research has limitations. The first one is contextual. This study was conducted in France, an occidental democratic country with good social protection of its inhabitants, where no major sanction is enforced against people who refuse to be vaccinated. During the COVID-19 outbreak, France was one of the countries where vaccination against the SARS-CoV2 strain was mandatory for health care professionals, but no other sanction other than the impediment to work in a health centre was taken against health care professionals who refused vaccination. At the time of the study, seasonal influenza vaccination was recommended and free of charge in persons having chronic diseases increasing the risk related to influenza, in pregnant women and in persons over 65 years of age, but was not mandatory. The countries where similar studies were conducted had more common points with France then differences (i.e. UK, USA, Canada, the Netherlands). For these reasons, the findings of this thesis do not apply in non-democratic countries where vaccination of persons can be performed without the agreement of the party. They do not apply in countries without good social protection or in countries were the supply of vaccines is not ensured whatever the reason (i.e. war, logistics organisation, poverty).

The second limitation is related to the seasonal influenza campaign itself. The great majority of primary health care professionals encourage the vaccination of the target population and the vaccination coverage in GPs is 77%. Vaccine units are easily available in community pharmacies and vaccine injections can be performed by the community pharmacist himself, by nurses, midwifes and GPs without prescription. The targeted population receives from its' mandatory insurance company a personalised letter with a voucher for the delivery of a free vaccine unit at the community pharmacy. There is an important mass-media campaign (including TV) promoting vaccination in the target population. All these elements, identified as highly effective to promote vaccination, and that France is one of the European countries were influenza vaccination uptake is the highest with over 50% of the target population vaccinated (over 60% in persons over 65 years of age), might make the effect of posters and pamphlets negligible and not statistically significant. Most of the other studies regarding the impact of posters and pamphlets in primary care waiting rooms lead to the same conclusions, but here again, these are countries with more factors in common with France than differences in their primary health care management. Our results might have been different in a country without other efficient incentives than posters and pamphlets in waiting-rooms and with much lower vaccination coverage in the targeted populations.

Regarding other vaccinations, the case of HPV vaccination in France, with one of the lowest vaccination coverage rates in Europe (<30%) makes it difficult to generalize our findings regarding a high vaccination uptake like influenza to HPV vaccination. Besides, target populations to vaccinate are not the same. France is preparing a large vaccination catch-up campaign in mass-media, in schools and in primary care professionals. However, posters and pamphlets in primary care waiting rooms are not an option.

Comparison to literature

This comparison will encompass three domains that are slotted like Russian dolls: 1) the ability of posters and pamphlets in primary care waiting rooms to increase influenza vaccination uptake and further change in health behaviour; 2) the ability of one-off interventions in primary care to

demonstrate behaviour changes in patients vs. sustained relationship between patients and primary health professionals; 3) indications for future research on health behaviour change in primary care.

The ability of posters and pamphlets in primary care waiting rooms

This research will not change at least one fact: there are still going to be posters and pamphlets in primary care waiting rooms advertising public health promotion campaigns or for local health events. Primary care centres, with a lot of patients passing daily through their waiting rooms, will always remain places to promote health related actions. This research stated that messages, spread by these posters and pamphlets, are not consciously noted by patients, and don't modify patients' health behaviour. However, it does not mean that patients do not subconsciously integrate the messages they carry, with their doctor's advice to be vaccinated (315). In a way to integrate subconsciously the message of a poster, the latter needs to be noticed, even in a short unconscious glance. This means the improvement of observation acuity that is so important in the education of GPs and is related to deeply rooted education factors (316). Are persons that were educated in their childhood to observe the world around them and capture the particulars more sensitive to messages conveyed by posters? Since the COVID-19 outbreak, the use of Quick-Response Codes (QR-Codes) technology has been widespread, mainly to confirm that vaccinations had been achieved (317). New literature is appearing about the use of these QR-Codes on posters or on pamphlets or cards for diverse health uses in primary care: access to an online survey (318), self-screening for atrial fibrillation (319), or access to a website providing information about non-alcoholic fatty liver disease (NAFLD) (320). Our interest goes to study the use of a poster presenting a QR-Code in primary care waiting rooms to screen for intimate partner violence accessing the validated WAST 8-questions scale.

The ability of one-off interventions in primary care to demonstrate behaviour changes in patients vs. sustained relationship between patients and primary health professionals

We noticed in Chapter 6 that we could emphasize about the ineffectiveness of a one-off intervention using posters and pamphlets in primary care waiting rooms to promote seasonal influenza uptake. However, though the intervention was ineffective, the increase in vaccination uptake was observed in all three groups: intervention group, control group and Zelen group. We demonstrated that this was not related to experimental artefacts. The outcome was not equally fulfilled in all age groups and for all conditions. In patients with a chronic condition, the rise of uptake was maximal between 50 and 65 years of age, reaching the level of 75% after 3 years of follow up. In patients without a chronic condition, in which vaccination is recommended from the age of 65 with access to free vaccination (receiving a voucher sent by their mandatory Health Insurance fund) the rise in uptake was maximal between 65 and 75 years of age, reaching levels even over 75% (79.5 [76.0; 83.0]). On the opposite side, in younger patients with a chronic condition, the increase was much smaller: in the 16-20 years age group the increase was limited to 10%, hardly reaching 43.4% [35.8; 51.0] after 3 years.

This leads to three reflections.
1) The intervention we conducted might not have been effective because other concomitant incentives were much more efficient and the effect of our intervention negligible, or at least completely crushed in statistics by the effect of the other incentives. It is notable that counselling by primary care professionals, the influenza vaccination campaign on TV and the sending of a nominative voucher for

a free vaccination probably had much more promotion impact than posters in the waiting room (283,288,321,322). Besides, access to care regarding influenza vaccination benefits of many facilitators of ubiquitarian efficiency: free vaccine units dispensed by community pharmacies and free injections performed by pharmacists, community nurses, nurse practitioners, midwifes and GPs (323).

2) The motivation of health professionals and their proactivity to promote health behaviour changes with their patients has an important impact, but this needs at least the adherence and readiness of their patients (324,325). The motivation level of field GPs and their time spent as investigators in research projects is limited. I couldn't find any article tackling this point, but by my own experience conducting RCTs in primary care and sharing experiences with colleagues is enlightening. In the QR-Code study to screen for intimate partner violence in women (not yet published), we noted that in a population of field GP investigators where contracts were signed with the promotor and training was completed, one third did not include any patient, one sixth included many patients, and they all needed a relaunch every three months from the study team to support motivation (326). After three to six months, depending on the energy deployed by the team management, any further incentive seems vain. GPs are subject to too many stimuli originating from many different fields of their practice (motivation to change their patients' health behaviour for diverse chronic conditions (327), A and B grade screening for 49 conditions (328), diverse guidelines issued by international, national and professional health authorities, etc.) and it is difficult to keep the focus of their interest on one area for a long time. This might be an issue in the time related depreciation of the Hawthorne effect and is an explanation of the absence of sustainability of one-off interventions over time when financial incentives are removed (329).

3) The readiness and the adherence of patients is essential. Patients concerned about their own health and a healthy lifestyle are motivated to be registered on a GP practice patient-list and to implement affordable behaviour changes. These patients are open to advice from their primary healthcare worker to participate in health promotion projects. When their GP implements a one-off intervention to change their behaviour and they accept to participate, there is a substantial chance that they sustain this change, like being vaccinated the next year when they underwent the vaccination the year before. This is true, whatever the intervention, as for instance in the field of type 2 diabetes (330). We can hypothesize that the increase in vaccination that we observed in our cohort and that differs from the observations in the general beneficiary sample, is linked to the eligibility criteria of being enrolled on a GP practice patient list and with an over-representation of sexagenarians who were more concerned and motivated to undergo influenza vaccination. There might be a form of *hidden curriculum* among patients that are registered on a GP practice patient-list responsible for a change of behaviour to stick to the image of being a "good patient". In this perspective, being vaccinated for seasonal influenza can be seen as a necessary rite of the good patient's identity (331). It is notable that our cohort does not represent the general population, but the population managed by a GP over time. In this cohort, a combined effect of patients being mindful of their health and of primary care practitioners performing the role of trusted experts to accompany their patients along their health pathway leads to the 75% of vaccination uptake in the most involved patients.
If there is a spontaneous tide for 3 patients out of 4 who are registered on a GP practice patient-list to change their health behaviours so as to meet a healthier lifestyle, it has little interest in research to focus on this population. It is notable that not registered patients mainly those with a low level of health literacy are less vaccinated (84,332). They should be the target of interventions in primary care

research to influence their health behaviour. We can also consider the remaining 25% of patients registered on GPs' patients lists and who are not going to be vaccinated.

Indication for future research on health behaviour change in primary care

The outcomes of this thesis have an interest for both effectiveness research and implementation research in primary health care.

Effectiveness research

In order to avoid a Hawthorne effect (HE), effectiveness research has to eliminate cross sectional surveys based on questionnaires. The latter tick all the boxes of the HE: selection of investigators and patients, commitment and congruence of the patients agreeing to answer the questions, conformity and social desirability of the patients who will give the answers that they think the researcher expects, and observation and measurement bias that will encourage answers to be in line with the social norm. This leaves one alternative: reuse of data collected in routine or classical RCTs.

The secondary analysis of data collected in routine databases (like we did for our two RCTs) is interesting as neither investigators or patients have the feeling of being part of an experimental framework. If the intervention has a low impact on the daily life of patients and the working habits of the health practitioner, there is a low chance that it will influence their behaviour for experimental reasons. Self-efficacy is defined by Albert Bandura as the sense a person has of their level of ability to achieve a given task. People with a poor level of literacy miss this feeling of self-efficacy and tend to adopt a passive behaviour, or even quit (333). If the patients undergo the research in a passive way, their degree of self-efficacy won't influence their motivation to participate. Besides, there is little difference in the feeling of being observed between those in the intervention group and those in the control group. Reuse of data can be easily extended in time and is not prone to a deficiency of the motivation of the investigators. For these reasons, the observation period of the study groups can easily be extended in time which is very useful in primary care where the duration of the relationship between the patient and the primary health team appears to be so important. The only important point to be considered is the regression towards the mean (RTM) that has to be integrated in the analysis of the data.

Classical RCTs can also be implemented in primary care with a small risk that the HE will affect the external validity of the experiment if the tested effect size is not too small. However, if the HE affects the experiment, it happens equally in both arms of the trial, interventional and control, with little influence on binary outcomes (268). This is also what was noted in the sensitivity analysis of our meta-analysis in Chapter 5. The real problem will be to motivate and empower GP investigators to enrol patients in the RCT, the first inclusions being the most difficult to implement as they mean a change in routine, and then to sustain the motivation of the investigators if the RCT is expected to last more than 3 months. To reduce the HE and the RTM effect in RCTs, we can suggest a delay by at least 3 weeks between the enrolment of patients in RCTs and their randomization. This strengthens the risk of demotivation of the investigators and needs a permanent support of the research team.

This delay was implemented in a beautiful recent Belgian RCT investigating the use of blended care to discontinue benzodiazepine receptor agonists (BZRA) for chronic insomnia (334). Between enrolment and randomization, that is before starting the intervention, 8% of patients had discontinued their BZRA use. However, as usual in addiction medicine, one third of these were tested positive at 12 months, main outcome of the study (335).

Implementation research

Effectiveness research is of no interest to primary care without implementation research, mainly regarding the daily clinical relationship between patients and the primary care team. There is often a broad gap between what should be done (effectiveness) and what is affordable to do (implementation) related to the complexity of situations in real life. This was very clear regarding the COVID-19 vaccination in France. Implementation research can use more methods, quantitative to measure implementation outcomes or qualitative to understand or explain implementation strategies.

Qualitative research will have the ability to understand or to elucidate the gaps between science and real life. Qualitative research will sometimes start from a postpositivist paradigm, assuming that there is a single, objective reality and that the study is designed to describe this reality. However, this simplistic paradigm will sooner or later be confronted with the complexity of practical needs when it comes to the moment that concurrent needs have to be addressed. In these cases, the paradigm for more complex situations might be constructivist or interpretivist, assuming multiple, subjective realities and the study will be designed to describe these multiple realities, with no attempt to merge or reconcile these realities. The approach will usually be a general inductive approach or going more in depth into a phenomenography approach (282). Going into complexity, a tool like the consolidated framework for implementation research (CFIR) including observational field notes and semi-structured interviews with primary care professionals to produce actionable findings, can be useful to improve implementation of effectiveness research outcomes in primary care settings (336). As seen in chapter 5, it is important that the distance between the researcher's background and the topic is as broad as possible, in way to avoid a contamination of the interpretative analysis by researcher's a priori, and it is important that no identification process or hierarchic relationship occurs between the researcher and his/her research field, as was noted regarding Dickson during the Hawthorne experiments (183).

Cross sectional or cohort studies will be prone to the Hawthorne effect, but knowing that it will appear, the effect can be used to explain or measure underlying beliefs or attitudes that influence the implementation of findings from the effectiveness research. Social desirability and conformism will reveal underlying social norms that drive behaviours, and commitment and congruence will underline the reasons for people to continue behaviours in order to avoid cognitive dissonance. The most formidable effect to avoid, and investigators should be aware of it and trained to prevent it, is selection bias, that eliminates persons with low health literacy, causing blind spots in research as described below.

Health literacy, is defined as the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions (337). Persons with a low level of literacy are mainly persons who were not in state to access school education or to complete their education curriculum. They have lower skills of observation, experience problems understanding health messages, and accessing and benefiting from health services (338). As noted in chapter 5 as a selection bias contributing to the HE, their poor understanding of study instructions and their difficulties giving informed consent keeps them away from decision making procedures and from research protocols (339).

If we take the example of smoking as a paradigm of adverse health behaviour, we note a growing link over time between smoking and literacy in France. In the generation 1941-1955, smoking was not perceived as an avoidable risk factor for cancer, cardiovascular and respiratory diseases. It was most prevalent and was a poor social marker in males: about 50% at 25 years of age whatever the education

level. In females it appeared to be an emancipation symbol with a predominance of educated women amongst smoking ones (30% vs. 20%). In the generation 1956-1970, educated males were aware of the risks and the difference in smoking between the most and the less educated males was of 20% (60% vs. 40%). In females, the smoking percentage in educated women did not diminish (30%) but it notably increased in the less educated women, raising from 20% to 40%, outreaching the percentage in educated women. In the generation 1971-1985, the difference related to education appeared to be even more emphasized. In males at the age of 25, 60% were smoking in the less educated population, while less than 30% were smoking in the most educated population, and at the age of 40, still 60% were smoking in the less educated vs. 15% in the most educated. In females, at the age of 25, the percentage of smoking women had increased to 50% in the less educated population while it remained stable in the most educated (about 25-30%) (340).

To summarize this point regarding health behaviour, health literacy and research: People with a low level of literacy have improper health behaviours, experience problems accessing and benefiting from health services as their common expectations are the relief of symptoms, have difficulties understanding health messages, are not enrolled in medical research studies and have a shorter life expectancy in good health. These last years, the health gap between educated persons and those with a low level of literacy is widening. For all these reasons, they have to be a priority target for health behaviour interventions.

The composition of their population is identified, but they are known to be difficult to approach in primary care and to include in interventions: they dwell in deprived communities (341), they are at risk of developing chronic conditions or their complications, they are prefrail or frail aging persons (342), and they are young people not in education, employment or training (NEET) (343,344). The best solution to implement interventions in this population is related to complex health interventions (CHI) (345): 1) to attract them in primary health care settings, 2) to enrol them in a health pathway, 3) to motivate them to change one behaviour at the time in a list of shared defined objectives, 4) to develop multilevel interventions aiming at achieving these objectives surpassing the boundaries or their lack of self-efficacy, and 5) to assess these interventions (see table 16 summarizing the diverse steps)

Table 16: research fields for implementation research

<table>
<tr><td>Deprived populations
Move towards in the community
- Tracking/mediation
- Enrolment/outreach
- Community health workers</td><td>Immigrants
Low literacy
Sexual minorities
Mental disabled persons
Addicts, marginalized</td><td>Objectives
- Solve sheltering problems
- Enhance health literacy
- Adapt health behavior
- Improve quality of life
- Improve life expectancy</td></tr>
<tr><td colspan="3">Multilevel interventions
- Housing outcomes
- Education/empowerment/increased self-management workshops
- Coordination of medical/social workforce/dentistry
- Enhanced mobility
- Screening (cancers: breast, cervix, bowel, lungs, throat)</td></tr>
</table>

<table>
<tr><td>Patients with chronic disease
Move towards in the community
- Tracking/mediation
- Enrolment/outreach
- Improved access to health services
- Community health workers</td><td>Obesity
Cardiovascular diseases
Respiratory diseases
Diabetes</td><td>Objectives
- Change health behavior
➢ Sedentariness
➢ nutrition
- Prevent increasing medication and iatrogenic
- Prevent hospitalization
- Improve quality of life
- Improve life expectancy</td></tr>
<tr><td colspan="3">Multilevel interventions
- Prevention in younger populations (Children)
- Education/empowerment/increased self-management workshops
- Coordination of health practitioners
➢ Primary care level/secondary care level
➢ Practice nurses/nurses/physiotherapists
➢ Pharmacist
- Adapted physical activity</td></tr>
<tr><td>Aging persons
Move towards in the community
- Tracking/mediation
- Enrolment/outreach
- Improved access to HS
- Community health workers</td><td>Prefrail
Frail
Dependent</td><td>Objectives
- Prevent dependance
- Avoid hospitalizations
- Improve quality of life
- Improve life expectancy
➢ In good health
➢ In line with their lifegoals</td></tr>
<tr><td colspan="3">Multilevel interventions
- Prevention in younger populations (55 – 65 years of age)
- Housing outcomes/institutionalization
- Education/empowerment/increased self-management workshops
- Enhanced mobility/Adapted physical activity</td></tr>
<tr><td>Post-scholar population (NEET)
Move towards in the community
- Tracking/mediation
- School coordination
- Enrolment/outreach</td><td>Leaving school
➢ Without diploma
➢ Without employment
➢ Without training</td><td>Objectives
- Prevent addictions/marginalization
- Enhance health literacy/behavior
- Improve quality of life
- Improve life expectancy</td></tr>
<tr><td colspan="3">Multilevel interventions
- Housing outcomes
- Education/empowerment/increased self-management workshops
- Social prescribing/coordination with vocational training</td></tr>
</table>

As it is difficult to include these populations in classical observational or interventional studies, assessment could be based on the follow-up of routinely collected data like we did in our RCTs. This has the advantage to induce a low Hawthorne effect as neither patients nor investigators are conscious of being observed, repeated research measures are avoided, and assessment of the issues are completed without direct involvement of the health professionals or of the patients.

These data can be collected from electronic medical records or from claim databases where not registered patients can be sorted out, participants being selected before pseudonymization of the database. However, since 2018, the implementation of the General Data Protection Regulation (GDPR) tends to complicate the use of in routine collected data, patients having to be aware and give their consent to the reuse of their health data.

Regarding the research in sexual minorities, and in particular their vaccination to prevent STDs, social networks can be a good medium to reach them as these minorities are very active in these networks (346).

Regarding the implementation of future vaccination campaigns, since the publication of our first RCT (Chapter 4) French authorities and Health insurance funds stopped asking primary healthcare workers to hang posters and hand out pamphlets in their waiting rooms. In 2022, the vaccination campaign has mainly been broadcasted on mass media and social networks, coupling vaccination for the 4-valent seasonal influenza vaccine and the 2nd booster for COVID-19 vaccination with a bivalent vaccine including the classical and the omicron strains.

Conclusion

All primary care practitioners use a waiting room in their settings to inform patients by posters or pamphlets about public health recommendations. Some use messages dispensed on TV screens or on tablets. If the messages broadcasted on screens seem to enhance patients' knowledge, there is no evidence that they change patients' behaviour. The efficacy of posters and pamphlets on any behavioural change appears to be negligible. They might be unconsciously glanced at by patients with their educated and developed sense of observation and they influence subconscious behaviours, but the latter are not the focused targets for health behaviour change. They might be a booster for vaccination campaigns broadcasted by mass-media, but as many posters and pamphlets for many different campaigns, often totally outdated, coexist in the same waiting-room, even this hypothesis seems to be weak.

In a cohort of patients registered on GP practice patient-lists, an unique campaign with posters and pamphlets avoiding message contamination through other information in the waiting room, the vaccination uptake was not enhanced in this exposed population compared to usual waiting rooms in controls. Patients vaccinated the previous year had a five-fold higher chance to be vaccinated the next year, and a trend to increased vaccination uptake was noted in both intervention and control groups. This phenomenon could be explained by an experimental bias like a Hawthorne effect or a cohort effect.

The definition of the Hawthorne effect as an artefact assigned to the fact of being observed in an experimental environment appeared to be conflicting. However, the term is still more used in health science research as an experimental artefact in general, far from its initial meaning related to the Hawthorne experiments. From the different meanings and explanations found in recent literature, we refined the definition as an aware or unconscious complex behavioural change in a study environment that diminishes the generalizability of studies, related to the complex interaction of four biases affecting the study subjects and investigators: selection bias, commitment and congruence bias, conformity and social desirability bias, and observation and measurement bias. The size and influence of the HE depends on the population being studied, the educational level and the social position of the investigators and subjects, the mental health status of the investigators and subjects, the studied variable, its initial value and its expected variation, and the duration of the experiment. Its combined OR for binary outcomes can be carefully (due to heterogeneity) estimated at 1.41 (95%CI: [1.13;1.75]) when considering studies conducted in outpatient clinics and with healthy persons. In RCTs and quasi-experimental studies or studies with a high level of evidence, its value is not significant anymore, but the binary variable cannot be an example of a complex system of biases. There are important overlap areas with the regression towards the mean and the placebo effect. The increase of the vaccination uptake in both arms of our RCT could not be possibly imputed to the Hawthorne effect.

Following the research cohort during three years using a larger and more accurate claim database, and forming a third group of control patients *a posteriori*, thus not aware of the RCT, we confirmed 1) the absence of an effect of posters and pamphlets in the waiting rooms to enhance seasonal influenza uptake and 2) the absence of a Hawthorne effect. We found a continuous increase of the seasonal influenza uptake in our cohort reaching 70% over 3 years, or even 75% in sexagenarians. We imputed this finding to a cohort effect due to an overrepresentation of sexagenarians, the most prone to undergo vaccination, and to the fact that our cohort only encompassed patients registered on GPs patient lists. Knowing that the vaccination uptake is much lower in populations with a low level of literacy and not registered on patients lists, their absence in our cohort could explain the discrepancy

observed with public health data. The hypothesis of the motivation of enlisted patients to be vaccinated is that these patients have a higher level of health literacy, a better feeling of self-efficacy making them more proactive, and a hidden curriculum to be considered as “good patients”. The major role of the primary care teams is to strengthen their beliefs to adapt their health behaviour to their health outcomes.

If these enlisted patients spontaneously evolve towards better health behaviours, research should concentrate on people with poor health literacy or not registered on patients lists who are usually excluded from implementation research as they are difficult to reach, to motivate in participating in research programs, and to make them understand the instructions contained in the research protocol.

Summary

The general purpose of this thesis was the study of tools to enhance health behaviour with patients in primary care waiting rooms. The time patients spent in the waiting room was used as an opportunity for a moment of health education. A systematic review on educative efficiency of audio-visual aids in primary care waiting rooms learned that audio-visual aids broadcasting messages using screens (TVs, computers, tablets, smartphones with Bluetooth® pairing) probably enhance patients' knowledge, but a change in health behaviour remains controversial. In a second phase the thesis focused on the annual advertisement campaign by posters and pamphlets in general practice (GP) waiting rooms to promote seasonal influenza vaccination as a paradigm to measure the efficacy of posters and pamphlets with a randomized controlled trial (RCT). It is notable that the validity of studies in the field of changes in health behaviour is often invalidated by experimental artefacts, in particular, the so-called Hawthorne effect (HE), related to behavioural changes in patients and in investigators caused by the experimental environment. The thesis sought to update and refine the definition of the HE in medical research and more specifically in primary care. Following our refined definition, the probability of a HE in the RCT was scarce, but no indisputable evidence was strengthening our conclusions. We redesigned our RCT bypassing the limitations of the first and followed over two years our research cohort to obtain an insight of the natural evolution of seasonal influenza vaccination uptake in GPs' customer base.

Health promotion and patients' health education are an important part of a GP's commitments as patients' health behaviours are crucial factors in life expectancy and good health. Most waiting-rooms have therefore been implemented with audio-visual aids (posters, pamphlets or screens) for health promotion purposes. Posters and pamphlets are present in practically all primary care practices. Few studies have assessed the effect of audio-visual aids in primary care.

Our first objectives, as to scan this research field, was to identify, describe and appraise studies that had investigated the effects of audio-visual aids on health promotion in primary health care waiting-rooms and to identify which factors influence their effect through a systematic literature review.

Databases were searched by two independent researchers using predefined keywords. Additional records were extracted from the reference lists of the selected articles. The selection of the reports was performed on the title and abstract, followed by complete reading and assessment. Bias and level of evidence were analysed.

We collected 909 records. Most of them were not in primary care settings. Fourteen peer-reviewed reports fully meeting the inclusion criteria were retained for analysis. Good quality studies were scarce as it appeared difficult to distinguish the specific effect of the aids from the motivation of investigators. Eight of these articles using videos or slideshows on TV screens or tablets indicated effects: three of them showed a significant improvement of patient knowledge with acceptable evidence and three on health behaviour with surrogate endpoints didn't show a clear association with the studied outcome. Audio-visual aids seemed to be used or noticed by patients and could induce conversations with physicians. The relevant factors that might influence these effects (duration of exposure, conception quality, theme, target population and time spent in the waiting-room) were insufficiently investigated. Finally, if audio-visual aids broadcasting messages using screens might enhance patients' knowledge, no effect of posters and pamphlets in waiting rooms was demonstrated. A change in health behaviour remained controversial.

As most GPs use advertising with posters and pamphlets in their waiting rooms for patient's education purposes without clear evidence of their use, we sought to demonstrate the effect of an advertising campaign using these two media. Patients vaccinated against seasonal influenza have been gradually lessening between 2009 and 2014, and mandatory health insurance companies have implemented in France an advertising campaign using posters and pamphlets displayed in primary care waiting rooms to promote seasonal influenza vaccination uptake, together with incentives in mass-media.
We designed a trial with the objective of assessing the effect of this advertising campaign for influenza vaccination using posters and pamphlets in GPs' waiting rooms.
This registry based 2/1 cluster randomized controlled trial (RCT), a cluster gathering the enlisted patients aged over 16 years, of 75 GPs, run during the 2014-2015 influenza vaccination campaign. It compared patient's awareness in 50 GPs' standard waiting rooms exposed to a lot of information (control group) versus that of patients, spending their time in waiting rooms from 25 GPs, who had received and displayed (in addition to mandatory information) only those pamphlets and one poster about the influenza vaccination campaign (intervention group). The main outcome was the number of vaccination units delivered in community pharmacies. Data were extracted from the SIAM-ERASME claim database of the main mandatory Health Insurance Fund of Lille-Douai (France). The association between the intervention (yes/no) and the main outcome was assessed through a generalized estimating equation.
Seventy-five GPs enrolled 10,597 patients of 65 years and over, or of 16 years and over suffering from long lasting diseases (intervention/control as of 3781/6816 patients) from October 15, 2014 to February 28, 2015. No difference was found regarding the number of influenza vaccination units delivered in community pharmacies (Relative Risk =1.01; 95% Confidence interval: 0.97 to 1.05; *p=0.561*). A vaccination performed on the previous year increased revaccination probability (RR=5.63; 95%CI: [5.21 to 6.10] p<0.001). Effects of the monothematic campaign promoting vaccination against influenza using a poster and pamphlets displayed in GPs' waiting rooms could not be demonstrated.
Unexpected, vaccination uptake rose by 3% in both arms of the RCT whereas public health data based on the "generalist sample of beneficiaries" and the SNIIRAM warehouse database indicated a simultaneous decrease of 2%. We wondered if the design of the trial had led to a Hawthorne effect (HE). Searching the literature, we noticed that the definition of the HE was unclear. In medical sciences, the meaning of the HE was drifting towards the interaction of artefacts in an experimental environment. In social sciences, and mainly in psychology, it was more closely bound to the Hawthorne experiments conducted from 1924 to 1933 and the definition given in 1953 by Festinger; for these reasons, its existence was disputed.
Our objectives were 1) to refine a definition of the HE in medical sciences and for primary care and 2) to evaluate its size and to draw consequences for primary care research.
We designed a PRISMA 2020 review and meta-analysis between January 2012 and March 2022. We included original reports defining the HE and reports measuring it without setting limitations. Definitions of the HE were collected and summarized. Main published outcomes were extracted and measures were analysed to evaluate odds ratios (OR) in primary care and close circumstances.
The search led to 180 records, reduced after review on title and abstract and on full reading of the remaining reports to 74 on definition and 15 on quantification. Our refined definition of HE is "an aware or unconscious complex behaviour change in a study environment, related to the complex interaction of four biases affecting the study subjects and investigators: selection bias, commitment and congruence bias, conformity and social desirability bias and observation and measurement bias". Its size varies in time and depends on the education and professional position of the investigators and

subjects, the study environment, and the outcome. There are overlap areas between the HE, placebo effect and regression towards the mean. In binary outcomes, the overall OR of the HE computed in primary care was 1.41 (95% CI: [1.13;1.75]; I^2=97%), but the significance of the HE disappears in well-designed studies.

We concluded that the HE results from a complex system of interacting phenomena and appears to some degree in all experimental research. Its size can considerably be reduced by refining study designs, for instance by the submission of research projects to registry platforms. Further, the chance that the increase of the vaccination uptake in both arms of the RCT was related to a HE appeared to be negligible.

As noted above, to conduct our RCT, we used a different database than the SNIIRAM warehouse claim database to collect our data. The SNIIRAM warehouse database merges data from all different mandatory French Health Insurance regimes and is used for public health surveys. By the time of the trial, there was a sufficient number of GPs left on our randomisation list to recruit 100 more GPs that were naïve to the RCT, and thus completely exempt of influence that might lead to a HE. Searching for an explanation of the rise in influenza vaccination uptake, it was possible to follow our trial cohort during three years using the SNIIRAM warehouse database and to constitute *a posteriori* a second control group, naïve to the trial, as described by Zelen in 1979.

So, in 2019 we deepened the investigations explaining the increased uptake, conducting a registry-based 4/2/1 cluster RCT designed by Zelen with two extra years of follow-up of the study cohort. The study population included 23,024 patients, registered with 175 GPs, eligible to benefit from a free influenza vaccination, that is, aged 65 years and over or 16 years and over with a chronic condition. The main outcome remained the number of vaccination units delivered in community pharmacies per study group. Data were extracted from the SNIIRAM warehouse claim database for the Lille-Douai district (Northern France).

No difference in vaccination uptake was found in the Zelen versus the control group of the initial RCT, closing the debate about the usefulness of posters and pamphlets as health promotion vectors in primary care waiting rooms. Overall, the proportion of vaccinated patients increased in the cohort from 51.4% to 70.4% over the three years. Being vaccinated the previous year was a strong predictor of being vaccinated in a subsequent year. The increase in vaccination uptake can be explained by a cohort effect, especially among people of 65 years and older, reaching 75% of influenza vaccination coverage as determined by the WHO. Health promotion and the promotion of primary health care may play an important role in this increase. However, if promoting health behaviour of patients matches with the commitment and congruence, and conformity and social desirability expected from general practitioners and primary care teams, to reach their objectives these teams also have to meet the expectations of patients who feel concerned by their health outcomes, like sexagenarians regarding the prevention of influenza.

The limitation of this health promotion approach in primary care is the population, mainly represented by persons with a low level of health literacy, whose life priorities don’t meet their health outcomes. This population, roughly representing one quarter of the global population, is difficult to reach by primary health teams, generally shares a low life expectancy in good health, is barely participating in primary healthcare research projects and not represented in routine collected databases (claim databases or databases collecting data in primary care electronic medical records), constituting a research blind spot. One of the most important challenges for the next years in primary healthcare

practice and research will be to reach these populations and integrate them in health pathways meeting their expectations: deprived communities, patients at risk of developing chronic conditions or their complications, prefrail or frail aging persons, or young persons not in education, employment or training (NEET).

Samenvatting

Het algemene doel van dit proefschrift was de studie van hulpmiddelen om gezondheidsgedrag bij patiënten in de eerste lijn te verbeteren. De tijd die patiënten in de wachtkamer doorbrachten, werd gebruikt als gelegenheid voor gezondheidseducatie. Een systematische review naar de educatieve efficiëntie van audiovisuele hulpmiddelen in wachtkamers in de eerstelijnszorg leerde dat audiovisuele hulpmiddelen die berichten uitzenden via schermen (tv's, computers, tablets, smartphones met Bluetooth®-koppeling) waarschijnlijk de kennis van patiënten vergroten, maar dat een verandering in de gezondheidsgedrag controversieel blijft. In een tweede fase concentreerde het proefschrift zich op de jaarlijkse promotiecampagne via posters en folders in de wachtkamers van huisartsen voor de seizoensgriep vaccinatie, als paradigma om de werkzaamheid van posters en folders te meten met een gerandomiseerde gecontroleerde trial (RCT). Opmerkelijk is dat de validiteit van studies op het gebied van gedragsveranderingen vaak wordt ontkracht door experimentele artefacten, in het bijzonder het zogenaamde Hawthorne-effect (HE), die verband houden met gedragsveranderingen bij patiënten en onderzoekers veroorzaakt door de experimentele omgeving. Het proefschrift trachtte de definitie van de HE in medisch onderzoek en meer specifiek in de eerste lijn te actualiseren en te verfijnen. Volgens onze verfijnde definitie was de waarschijnlijkheid van een HE in de RCT schaars, maar er was geen onweerlegbaar bewijs dat onze conclusies versterkte. We herontworpen onze RCT waarbij we de beperkingen van het eerste rapport omzeilden en volgden ons onderzoekscohort gedurende twee jaar om inzicht te krijgen in de natuurlijke evolutie van het gebruik van seizoensgriep vaccinaties bij patiënten in de huisartspraktijk.

Gezondheidsbevordering en gezondheidsvoorlichting van patiënten vormen een belangrijk onderdeel van de inzet van huisartsen, aangezien het gezondheidsgedrag van patiënten een cruciale factor is voor een levensverwachting in goede gezondheid. De meeste wachtkamers zijn dan ook voorzien van audiovisuele hulpmiddelen (posters, folders of schermen) in het kader van gezondheidsbevordering. In vrijwel alle eerstelijnspraktijken zijn posters en folders aanwezig. Weinig studies hebben het effect van audiovisuele hulpmiddelen in de eerstelijnszorg onderzocht.

Onze eerste doelstellingen bij het doorzoeken van dit onderzoeksveld waren het identificeren, beschrijven en beoordelen van studies die de effecten van audiovisuele hulpmiddelen op gezondheidsbevordering in wachtkamers in de eerstelijnsgezondheidszorg hadden onderzocht en om te identificeren welke factoren hun effect beïnvloeden door middel van een systematisch literatuuronderzoek.

Databases werden doorzocht aan de hand van vooraf gedefinieerde trefwoorden door twee onderzoekers onafhankelijk van elkaar. Aanvullende records werden geëxtraheerd uit de referentielijsten van de geselecteerde artikelen. De selectie van de rapporten gebeurde op titel en abstract, gevolgd door volledige lezing en beoordeling. De kans op bias en het niveau van bewijs werden geanalyseerd.

We hebben 909 records verzameld. De meesten kwamen niet vanuit de eerstelijnszorg. Veertien peer-reviewed rapporten die volledig voldeden aan de inclusiecriteria werden behouden voor verdere analyse. Studies van goede kwaliteit waren schaars omdat het moeilijk bleek om het specifieke effect

van de hulpmiddelen te onderscheiden van de motivatie van onderzoekers. Acht van deze artikelen die video's of diavoorstellingen op tv-schermen of tablets gebruikten, wezen op effecten: drie van hen toonden een significante verbetering van de patiëntenkennis met acceptabel bewijs en drie over gezondheidsgedrag met surrogaateindpunten vertoonden geen duidelijk verband met de bestudeerde uitkomst. Audiovisuele hulpmiddelen leken te worden gebruikt of opgemerkt door patiënten en konden gesprekken met artsen op gang brengen. De relevante factoren die deze effecten zouden kunnen beïnvloeden (blootstellingsduur, conceptiekwaliteit, thema, doelpopulatie en tijd doorgebracht in de wachtkamer) waren onvoldoende onderzocht. Audiovisuele hulpmiddelen die berichten uitzenden via schermen vergoten misschien de kennis van patiënten maar daarentegen een effect van posters en folders in wachtkamers werd niet aangetoond. Een verandering in gezondheidsgedrag bleef controversieel.

Aangezien de meeste huisartsen promotie met posters en folders in hun wachtkamers gebruiken voor patiëntenvoorlichting zonder duidelijk bewezen effectiviteit, probeerden we het effect aan te tonen van een promotiecampagne met behulp van deze twee media. Het aantal patiënten dat tegen seizoensgriep werd gevaccineerd, is tussen 2009 en 2014 geleidelijk afgenomen, en verplichte ziekteverzekeringsmaatschappijen hebben in Frankrijk een promotiecampagne gevoerd met posters en folders die in wachtkamers van eerstelijnspraktijken zijn opgehangen om het gebruik van seizoensgriep vaccinatie te promoten, samen met stimulansen in de massamedia.

We hebben een onderzoek ontworpen met als doel het effect te beoordelen van deze promotiecampagne voor griepvaccinatie met behulp van posters en folders in de wachtkamers van huisartsen.

Deze 2/1 cluster gerandomiseerde gecontroleerde studie (RCT), werd uitgevoerd tijdens de griepvaccinatiecampagne 2014-2015, en baseerde zich op clusters van ingeschreven patiënten ouder dan 16 jaar bij 75 huisartsen. Het vergeleek het effect bij patiënten in de wachtkamers van 50 huisartsen die aan veel informatie werden blootgesteld (controlegroep) met dat van patiënten die hun tijd doorbrachten in wachtkamers van 25 huisartsen, die (naast de verplichte informatie) enkel folders over de griepvaccinatiecampagne hadden ontvangen en hierover ook een poster in de wachtzaal hadden gezien (interventiegroep). De hoofduitkomstmaat was het aantal afgeleverde vaccinatie-eenheden in openbare apotheken. De gegevens zijn afkomstig uit de SIAM-ERASME-claimdatabase van het belangrijkste verplichte ziekenfonds van Lille-Douai (Frankrijk). De associatie tussen de interventie (ja/nee) en de hoofduitkomstmaat werd beoordeeld door middel van een marginaal model (generalized estimating equation of GEE) .

Van 15 oktober 2014 tot 28 februari 2015 includeerden 75 huisartsen in totaal 10.597 patiënten van 65 jaar en ouder of van 16 jaar en ouder met langdurige ziekten (interventie/controle: 3781/6816 patiënten). Er werd geen verschil gevonden voor het aantal afgeleverde griepvaccinatie-eenheden in openbare apotheken (Relatief risico = 1,01; 95% betrouwbaarheidsinterval: 0,97 tot 1,05; p = 0,561). Een vaccinatie uitgevoerd in het voorgaande jaar verhoogde de kans op hervaccinatie (RR=5,63; 95%CI: [5,21 tot 6,10] p<0,001). Er kan geen effect worden aangetoond van deze monothematische campagne ter bevordering van vaccinatie tegen griep door middel van posters en folders in de wachtkamers van huisartsen.

Onverwacht steeg de vaccinatieopname met 3% in beide takken van de RCT, terwijl volksgezondheidsgegevens op basis van de "algemene steekproef van begunstigden" en de SNIIRAM-

magazijndatabase een gelijktijdige daling van 2% aangaven. We vroegen ons af of het ontwerp van de onderzoek had geleid tot een Hawthorne-effect (HE). Zoekend in de literatuur merkten we dat de definitie van de HE onduidelijk was. In de medische wetenschappen verschoof de betekenis van het HE naar de interactie van artefacten in een experimentele omgeving. In de sociale wetenschappen, en vooral in de psychologie, was het nauwer verbonden met de Hawthorne-experimenten die van 1924 tot 1933 werden uitgevoerd en de definitie die Festinger in 1953 gaf; om deze redenen werd het bestaan ervan in twijfel getrokken.

Onze doelstellingen waren 1) het verfijnen van een definitie van de HE in de medische wetenschappen en voor eerstelijnszorg en 2) het evalueren van de omvang ervan en de gevolgen ervan te bepalen voor eerstelijnsonderzoek.

We hebben een systematisch literatuuronderzoek met meta-analyse uitgevoerd, volgens het PRISMA 2020 protocol, naar referenties tussen januari 2012 en maart 2022. We hebben originele rapporten toegevoegd die de HE definiëren en rapporten die deze meten, zonder beperkingen op te leggen. Definities van de HE werden verzameld en samengevat. De belangrijkste gepubliceerde resultaten werden geëxtraheerd en maatregelen om odds ratio's (OR) in de eerstelijnszorg en nabije omstandigheden te evalueren, werden geanalyseerd.

Dit literatuuronderzoek leidde tot 180 records, die na bestudering van titel en samenvatting en na volledige lezing van de resterende rapporten werden teruggebracht tot 74 m.b.t. definitie van HE en 15 m.b.t. kwantificering van het HE. Een verfijnde definitie werd geformuleerd: HE is “een bewuste of onbewuste complexe gedragsverandering in een studieomgeving, gerelateerd aan de complexe interactie van vier biases die de proefpersonen en onderzoekers beïnvloeden: selectiebias, inzet en congruentiebias, conformiteits- en sociale wenselijkheid bias en observatie- en meetbias”. De omvang varieert in de tijd en is afhankelijk van de opleiding en professionele positie van de onderzoekers en proefpersonen, de studieomgeving en de uitkomst. Er zijn overlapsgebieden tussen HE, placebo-effect en regressie naar het gemiddelde. Bij binaire uitkomsten was de totale OR van het HE berekend in de eerste lijn 1,41 (95%-BI: [1,13;1,75]; I^2=97%), maar de betekenis van het HE verdwijnt in goed opgezette studies.

We concludeerden dat het HE het resultaat is van een complex systeem van op elkaar inwerkende fenomenen en tot op zekere hoogte voorkomt in elk experimenteel onderzoek. De omvang kan aanzienlijk worden verkleind door het onderzoeksopzet te verfijnen, bijvoorbeeld door onderzoeksprojecten in te dienen bij registratieplatforms. Verder leek de kans verwaarloosbaar dat de stijging van die vaccinatiegraad in beide armen van de RCT verband hield met een HE.

Zoals hierboven vermeld, hebben we voor het uitvoeren van onze RCT een andere database gebruikt dan de SNIIRAM-magazijnclaimdatabase om onze gegevens te verzamelen. De SNIIRAM-magazijndatabase voegt gegevens samen van alle verschillende verplichte Franse ziekte-verzekeringsregimes en wordt gebruikt voor volksgezondheidsenquêtes. Op het moment van de onderzoek bleven er voldoende huisartsen over op onze randomisatielijst om 100 extra huisartsen te rekruteren die naïef waren ten opzichte van de RCT en dus volledig waren vrijgesteld van invloed die zou kunnen leiden tot een HE. Op zoek naar een verklaring voor de toename van het gebruik van griepvaccinaties, was het mogelijk om ons proefcohort gedurende drie jaar te volgen met behulp van de SNIIRAM-magazijndatabase en a posteriori een tweede controlegroep te vormen, naïef voor de proef, zoals beschreven door Zelen in 1979.

Daarom deden we in 2019 een verder diepgaand onderzoek om de toegenomen griepvaccinatie opname verklaren , door een op een register gebaseerde 4/2/1 cluster RCT, ontworpen door Zelen, uit te voeren met twee extra jaren follow-up van het studiecohort. De onderzoekspopulatie omvatte 23.024 patiënten, geregistreerd bij 175 huisartsen, die in aanmerking kwamen voor een gratis griepvaccinatie, dat wil zeggen 65 jaar en ouder of 16 jaar en ouder met een chronische aandoening. De hoofduitkomst bleef het aantal afgeleverde vaccinatie-eenheden in openbare apotheken per studiegroep. Gegevens werden geëxtraheerd uit de SNIIRAM-magazijnclaimdatabase voor het district Lille-Douai (Noord-Frankrijk).

Er werd geen verschil in vaccinatieopname gevonden in de Zelen versus de controlegroep van de initiële RCT, waarmee het debat over het verwaarloosbare nut van posters en folders als vectoren voor gezondheidsbevordering in wachtkamers in de eerste lijn werd afgesloten. Over het algemeen nam het aandeel gevaccineerde patiënten in het cohort toe van 51,4% tot 70,4% over de drie jaar. Gevaccineerd zijn in het voorgaande jaar was een sterke voorspeller van gevaccineerd worden in een volgend jaar. De toename van de vaccinatieopname kan worden verklaard door een cohorteffect, vooral onder mensen van 65 jaar en ouder, waarbij de 75% van de griepvaccinatieopname wordt bereikt, zoals vastgesteld door de WHO. Gezondheidspromotie en bevordering van de eerstelijnsgezondheidszorg kunnen bij deze toename een belangrijke rol hebben gespeeld. Als het bevorderen van gezondheidsgedrag van patiënten echter overeenkomt met de inzet en congruentie, conformiteit en sociale wenselijkheid die van huisartsen en eerstelijnszorgteams worden verwacht, moeten deze teams, om hun doelstellingen te bereiken, ook voldoen aan de verwachtingen van patiënten die zich betrokken voelen bij hun gezondheidsresultaten, zoals zestigplussers over de preventie van griep.

Deze benadering van gezondheidspromotie in de eerste lijn heeft een belangrijke beperking m.b.t. de bevolkingsgroep van personen met een laag niveau van gezondheidsvaardigheden, van wie de levensprioriteiten niet overeenkomen met hun gezondheidsresultaten. Deze populatie, die ruwweg een kwart van de totale bevolking vertegenwoordigt, is moeilijk te bereiken door eerstelijnsgezondheidszorgteams, heeft over het algemeen een lage levensverwachting in goede gezondheid, neemt nauwelijks deel aan onderzoeksprojecten in de eerstelijnsgezondheidszorg en is niet vertegenwoordigd in routinematig verzamelde databases (claim databases of databases die gegevens verzamelen in elektronische medische dossiers in de eerstelijnszorg), en vormt dus een blinde vlek voor onderzoek. Een van de belangrijkste uitdagingen voor de komende jaren in de praktijk en het onderzoek in de eerstelijnsgezondheidszorg zal zijn om deze bevolkingsgroepen te bereiken en te integreren in gezondheidstrajecten die aan hun verwachtingen voldoen: achtergestelde gemeenschappen, patiënten die het risico lopen chronische aandoeningen te ontwikkelen of hun complicaties, prefragiel of fragiel verouderende personen, of jongeren die geen onderwijs, werk of opleiding volgen (NEET).

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