Do we over- or underestimate the overall cost burden of infectious diseases in ageing adults?

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Abstract

Background

arithmetic average values about disease burden across ageing adults are often used, which assumes homogeneity in group characteristics such as age, sex, disease frequency (incidence rates), and cost distributions. The question arises about how much outcome results such as overall cost obtained under this homogeneity assumption deviate from real-world population data that may manifest non-homogeneous distributions.

Methods

the method explores the amount of deviation measured between homogeneity versus non-homogeneity for overall infection costs in ageing adults as the outcome measure to assess. Population modelling is used with an extended sensitivity analysis plan (ESAP) that simulates non-homogeneous, age-specific distributional spread for demography, infectious disease, and its severity in people aged > 65 years old over a 1-year period in univariant and multivariant assessments. Costs are adjusted for 3 severity levels with increased difference between them using multiplication factors.

Results

the assumed full homogenous dataset systematically overestimates up to 10% the overall cost in ageing adults when compared with a group simulated with non-homogeneous distributions for age, infection, severity, and cost, mainly due to the demographic age-composition. Overall cost of a proposed homogeneous condition tends to underestimate the spending of non-homogeneous conditions when the reference case has a partial homogeneous set-up or when the demographic change in the non-homogeneous condition evolves towards age-demographic homogeneity (same number of people with increasing age), a likely evolution in the coming 10 to 20 years.

Conclusion

assessing the current cost burden of infectious diseases in ageing adults must consider exact age-composition of demography, infection spread with severity levels and their cost differences to avoid unrealistic cost estimates when assuming homogeneous group conditions.

Background

When assessing disease burden in children or young adults, the structural and distributional composition of the group is often considered to be homogeneous for age, sex, and health conditions related to co-morbidities [1]. The assumption of homogeneity facilitates the evaluation of summary estimates of the group. Calculating arithmetic average values is sufficient for obtaining credible overall results. However, homogeneity is not always present in all population groups studied [2, 3]. Ageing adult people above 65 years (y) are not homogeneous in many ways differing in composition by age, sex, health condition, and place of residence [4]. Moreover, these characteristics evolve over time, as dynamic population features, such as living a longer life, which may lead to smaller sex differences and more healthy years overall [5]. Non-homogeneity in the distribution of variables could have consequences for the economic analyses expressed in summary outcome results, such as the overall cost of the disease burden, when arithmetic average values, assuming homogeneity, are used instead [6, 7]. When reviewing the literature on assessing the burden of infectious disease in ageing adults, concerns about non-homogeneity in the data are often raised, but no clear answers are given on how to adequately address that issue [8]. It leaves researchers with questions about the size of the problem caused by non-homogeneity, and how to adjust following which approach [9]. For instance, data on infection spread of aging adults in hospital care illustrate that the stay and duration are strongly non-homogeneously distributed by age, sex, co-morbidities, and ward selection [10]. Consequently, the overall real management cost of infectious diseases could be heavily skewed due to the multiplication of treatment decision processes followed, and the specific disease evolution patterns seen, such as more nosocomial infections in certain sub-groups leading to longer hospital stays that could heavily impact the assumption of homogeneity.

We like to present new evaluation methods of data related to ageing adults that better investigate the duality between homogeneous versus non-homogenous datasets and finding out how big the difference in summary outcome measures can be. The approach should improve our understanding and knowledge of the issue of homogeneity versus non-homogeneity in economic evaluation, indicating the variable distributions in the target population that result in most marked differences when compared with the assumption of homogeneity and what may cause a change in evolution over time. It should therefore allow more precise evaluations of the disease burden, whether the results based on the homogeneity assumption represent an over- or an under-estimation of the real burden in ageing adults. It may inform the approach to be taken in the research performed by the European consortium group that evaluates the whole burden of infectious disease in ageing adults, presented as an Innovative Medicines Initiatives (IMI)-project called VITAL (**V**accines and **I**nfec**t**ious diseases in the **A**geing popu**l**ation) [11].

Methods

Aim

The objective of this study is to demonstrate that, in the absence of having easy access to good real-life data, it is possible to explore the amount of outcome difference in the infectious disease cost burden, influenced by variables that have known non-homogeneous spreads, when compared with the assumption of homogeneity in the same group, using the extended sensitivity analysis plan (ESAP).

Baseline reference model

The analysis uses a simple, hypothetical population structured model to start with, evaluated over one year, called the homogeneous X_1 model. It estimates the overall disease management cost for the group exposed to infectious diseases with standard treatment. The data input for this basic homogeneous model is reported in Table 1, presented as a fully homogeneous condition (X_{1a}) or a partial homogeneous condition (X_{1b}). In X_{1a} the categories for 3 different severity levels by age-group have the same proportion of 33.33%. In X_{1b} those categories have an adjusted proportional distribution of 60% for low, 30% for medium, and 10% for high severity. The analysis, using these data, gives the overall cost estimate, equivalent in using arithmetic averages for the population under study. The outcome result is the baseline reference value for the comparison and the calculation of the cost-difference with simulated non-homogeneous model conditions. Details of the data calculation of X_{1a} are presented in Appendix 1.

Table 1
Data input to populate the basic homogeneous model of X_{1a} (fully homogeneous) and X_{1b} (partially homogeneous)

Variable	Values for X_{1a}	Values for X_{1b}
Population number (N)	1000	
Age-range	65–100 years	
Age-groups (A_n)	10 equal age-groups of 3.5 years each	
Rate of infection in each age-group (I_n)	15%	
Levels of disease severity (I_s)	low, medium, high (33.33% for each)	60% low, 30% medium, 10% high
Cost of treatment (C_T)	Average cost for any severity level of 20€ 33.33%*10€+33.33%*20€+33.33%*30€	Average cost for any severity level of 15€ 60%*10€+30%*20€+10%*30€
Time assessment	1 year	

Extended Sensitivity Analysis Plan (ESAP)

The basic population model (X_1) is now progressively adjusted, adding discrete variable spread changes in a new model, called X_2, using the technique of sensitivity analysis. By having those changes in the model, X_2 is by nature heterogenous in its composition as compared with X_1. Deviations from the overall cost outcome of the homogeneous condition, related to these changes, are quantified, and compared.

The whole sensitivity analysis is developed within a framework of an ESAP (Table 2). The plan encloses a list of basic, known explanatory variables for the outcome measure of overall cost about demography and infection tested with different levels of uncertainties. This is happening in a multistep approach with links present between the different steps. Subsequent analyses combine some of the variable changes together (two- and three-way sensitivity analysis). The following assumptions are introduced in model X_2 [12]:

- -total number of individuals in the population and total number of disease episodes assessed are the same in each model of X_1 and X_2 except in the demographic change of the combination analysis, X_{2b};
- -disease rate (I_n) exponentially increases with older age-groups (A_n);
- -increasing age has a higher proportion of severe disease episodes (I_{sn}) compared with younger ages;
- -cost level of managing a disease episode (C_T) depends on its severity level: severe disease episodes have a higher cost compared with medium severity episodes, and medium severity cases have a higher treatment cost than low severity cases.

The values used for disease rates by age-group and for the severity levels by age-group in model X_2 are presented with the cost for each severity level (C_{Tm}) in Appendix 2.

Table 2 Extended sensitivity analysis plan (ESAP) to assess the outcome of overall cost in a homogeneous condition X_{1a} and X_{1b} and in a non-homogeneous condition of X_{2a} and X_{2b}

Type	Steps	Model	Homogeneous/ Non homogenous	Domain									Figure #
				Demography	Infection								
				Age-distribution	Disease rate distribution	Severity level			Cost				
Multistep Variation	Step 1	X1a	Full-homogeneous	Equivalent across age-groups	Equivalent across age-groups	Equivalent across age-groups			Equivalent across age-groups				Figure 2
		X2a	Non-Homogeneous	**Realistic Belgian age-distribution**	Equivalent across age-groups	Equivalent across age-groups			Equivalent across age-groups				
	Step 2	X1a	Full-homogeneous	Equivalent across age-groups	Equivalent across age-groups	Equivalent across age-groups			Equivalent across age-groups				Figure 3
		X2a	Non-Homogeneous	**Realistic Belgian age-distribution**	**Exponential**	Equivalent across age-groups			Equivalent across age-groups				
	Step 3	X1a	Full-homogeneous	Equivalent across age-groups	Equivalent across age-groups	Equivalent across age-groups			Equivalent across age-groups				Figure 4
		X2a	Non-Homogeneous	**Realistic Belgian age-distribution**	**Exponential**	**Low**	**Medium**	**High**	Equivalent across age-groups				
	Step 4	X1a	Full-homogeneous	Equivalent across age-groups	Equivalent across age-groups	Equivalent across age-groups			Equivalent across age-groups				Figure 5
		X2a	Non-Homogeneous	**Realistic Belgian age-distribution**	**Exponential**	**Low**	**Medium**	**High**	**Low**	**Medium**	**High**		
	Step 5	**X1b**	*Partial Homogeneous*	Equivalent across age-groups	Equivalent across age-groups	*Low (60%)*	*Medium (30%)*	*High (10%)*	Equivalent across age-groups				Figure 6
		X2a	Non-Homogeneous	Realistic Belgian age-distribution	Exponential	Low	Medium	High	Low	Medium	High		
	Step 6	X1a	Full Homogeneous	Equivalent across age-groups	Equivalent across age-groups	Equivalent across age-groups			Equivalent across age-groups				Figure 7
		X2a	Non-Homogeneous	*Equivalent across age-groups*	Linear	Exponential	Extreme	Low	Medium	High	Low	Medium	High
Combination multivariate	3-way sensitivity analysis 1	X1a	Full Homogeneous	Equivalent across age-groups	Equivalent across age-groups	Equivalent across age-groups			Equivalent across age-groups				Figure 8-9
		X2a	Non-Homogeneous	Realistic Belgian age-distribution	**Exponential (Move)**	**Low to high (Grade)**			Low	Medium	High		
	3-way sensitivity analysis 2	X1a	Full Homogeneous	Equivalent across age-groups	Equivalent across age-groups	Equivalent across age-groups			Equivalent across age-groups				Figure 10-11
		X2a	Non-Homogeneous	Realistic Belgian age-distribution	**Exponential (Move)**	**Low to high (Grade)**			**Low to high (MF)**				
	3-way sensitivity analysis 3	X1a	Full Homogeneous	Equivalent across age-groups	Equivalent across age-groups	Equivalent across age-groups			Equivalent across age-groups				Figure 12-13
		X2b	Non-Homogeneous	**Proportional demographic increase**	Exponential (Move)	Low to high (Grade)			Low to high (MF)				

MF: Multiplication Factor

Yellow cells: new in multistep variation; light green cells: progressive change in X_2 in multistep variation; dark green cells: progressive change in X_2 in combination multivariate

Multistep analysis

In the multistep analysis, extreme frontiers in variable spread for age and infection rate distribution are explored. The relevance of their values related to the outcome result of overall costs is evaluated and tested at their minimally and maximally allowed levels. The multistep analysis plan further comprises six Steps, comparing the 2 models of X_{1a} or X_{1b} with X_{2a} in separate changes of the baseline-values. In Step 1 the condition X_{2a} assesses the effect of applying the current age distribution of the ageing population in Belgium [13] (see Appendix 2). Step 2 has only the variation changed in the numbers in each age group (A_n) and the disease rate changes (I_n) by age-group for X_2. That distributional change follows an exponential increase marked by boundaries of 7% in the lowest age-group up to 59% in the oldest age-group. Step 3 adds in the analysis the variability of severity level (I_{sn}) by age and Step 4 includes the variability in cost (C_{Tm}) by severity level for X_{2a}. In Step 4 is challenged the full homogeneity condition, using instead a partial homogeneity condition as reference situation for X_1 (see previous paragraph). Finally, Step 5 indicates what may happen with the overall cost if the age-demographic picture in X_{2a} is equivalent to X_{1a} while the infection rate distribution in function of age may follow 3 options: linear (around the age midpoint for the group, which is 82.5 years of age (= 65 + (100 − 65)/2)); exponential ($I_n = 0.0496*e^{0.1783*An}$; A_n = age-group); extreme ($I_n = 6.224E\text{-}08*A_n^5 - 2.8E\text{-}05*A_n^4 + 0.005*A_n^3 - 0.4378*A_n^2 + 18.835*A_n - 319.58$). This exercise explores the effect of non-homogeneous distribution of disease spread (higher disease rates at higher ages) applied to a homogeneous age distribution, which represents the likely further evolution of the population structure at older ages (see also age-demographic changes in the combination analysis) as shown in the next Fig. 1.

Combination analysis

Subsequent evaluations combine different non-homogeneous variable distributions (disease rate (I) with severity level (I_s)) in an integrated sensitivity analysis to identify the amount of overall cost change when compared with X_{1a}. In the 3-way sensitivity analysis1 the changes shift a higher disease rate (I) -called Move- with an increased severity level (Is) -called Grade- towards the older age-groups. It is the direction expected to be observed in real life [14–16]. Appendix 3 provides the details of that process. The cost variables (C_{Tm}) are assessed in a separate sensitivity analysis (3-way sensitivity analysis 2) to demonstrate their specific effect on condition X_{1a} and X_{2a}. Multiplication factors (MF) are used for the cost of each severity level of Medium and High separately with a

different maximum MF range of 10 for Medium and 20 for High. However, it is assumed that unit costs do not individually change by disease severity level when the non-homogeneous distributions of the variables, disease rate and severity level, change by age.

The final 3-way sensitivity analysis 3 concerns the simulation of age-demographic changes. One analysis is a progressive change in the demographic age-curve towards the more homogenous age-structure (see Fig. 1) as assumed in the full homogeneous data analysis of X_{1a}. It is expected to observe a point in the change of the age-demographic curve where the overall cost is equivalent between the two models compared of full homogeneity with the heterogeneity construction in which all the other variables are maintained in their heterogeneous conditions of X_{2b}. That point is interesting to measure as it may indicate by when it is expected that the overall cost will be underestimated when using the full homogeneous model. The other demographic analysis is the change of moving the demographic curve to the right in X_{2b}, thereby increasing the number of people in older age groups living longer. The overall cost of that simulation is compared with X_{1a} and X_{2a} when no demographic change is made.

Summary evaluation

The overall cost results of the different sensitivity analyses performed are presented in a summary table that compares the relative value differences with the reference case (X_{1a} and X_{1b}). This summary table helps indicating the data that would be most valuable to collect in a formal analysis of the group that is solely composed of ageing adults.

Results

Multistep results

The next graphical presentation of Step 1 and 2 (Fig. 2) visually demonstrates how changes from the reference full homogeneous case (left side, X_{1a}) may occur when adding in two steps firstly, the adjustment of the population demography to match the current age distribution in Belgium, and secondly the increased rate of infection with age, while keeping the disease severities across the ages and the cost per severity level constant (X_{2a}). The overall number of people (n = 1000), disease events (n = 150), and the overall cost (3,000 €) are the same left and right. The average cost for the group (3000/1000 = 3€) is also the same, left and right, because the population group and the number of events are the same in each constellation. The net difference of the sum of the overall cost between X_{1a} and X_{2a} is zero (0% relative change). The shift of the cost curve in the heterogeneous group (X_{2a}) into a bell shape distribution is the consequence of the demographic population movement decreasing the numbers from high to low with increasing age, combined with the number of events increasing with increasing age from low to high. If there was no increase of the infection rate with increasing age, the shape of the cost results would be like the age-distribution. These distribution shifts are important to note regarding the expectations about where the bulk of the disease burden is likely to be observed in function of age in real life.

In Step 3 shifts in severity level distribution by age are added in X_{2a}. Meanwhile, because the cost per severity level remains the same in this step, the overall cost will again be the same as in the reference full homogeneous group. Figure 3 illustrates that process of adding disease severity levels.

Calculating the overall cost difference between the homogeneous and the heterogeneous condition is obtained through the measurement of the areas between the summary curves as shown in Fig. 4. The line-up of the accumulated cost area of the homogeneous condition (blue line) splits the figure into a negative side (area under the blue line) and a positive side (area above the blue line). Superimposed on the line of the overall homogeneous costs is the spread of the line figure of the heterogeneous costs (orange line) that has two parts at the extremes (left and right) in the negative area (green colour) and a middle part that is designed in the positive area of the figure (orange colour). The sum of the positive and negative areas between the two curves indicates if there is a higher (sum is positive) or lower (sum is negative) overall cost for the heterogeneous versus the homogeneous cost spread in function of age. The result of that exercise, as shown in Fig. 3 for the difference between the two cost graphs of Figs. 1 and 2, has a zero-sum cost result as mentioned earlier.

In Step 5 is now added the specific grade distribution of the severity level by age with the cost differentiation by severity level. However, the mean cost calculation of an event, whether it is a low (10€), medium (20€), or high severity (30€) level, is equivalent to the mean cost used in the homogeneous condition ((10€+20€+30€)/3 = 20€). Figure 5 first reports the distribution of the severity levels by age, followed by the cost distribution, and the net cost calculation as the areas between the curves. A small cost difference is measured between X_{1a} and X_{2a} full line with a -4.2% lower cost for the non-homogeneous spread (€2,875-€3,000 = -€125; -€125/€3,000 = -4.2%). The dotted line represents the cost-line of X_{2a} of Fig. 4.

Step 5, with the introduction of the partial homogeneity distributions in X_1, is presented in Fig. 6. The blue dotted straight line shows the cost result for the partial homogeneous reference case (X_{1b}) with a mean cost per age group that decreases from €300 (X1a) to €225 because of the change in the proportional distributions of the severity levels by age-group. When the overall cost of X_{2a} (orange line) is then compared with the overall cost of X_{1b}, the relative cost difference suddenly jumps to an extra cost of + 27.78% (€2,875 - €2,250 = € 625). The negative area between the curves is now much smaller while the positive area has much increased. This analysis indicates the importance of selecting well the homogeneous composition of the reference comparator in X_1 (full or partial).

Figure 7 presents the results of Step 6, showing the overall cost distribution by age group with the homogeneous condition of the demographic age distribution retained of X_{1a} while all the changes in the other variables (disease, severity, cost) occur following the specific constraints of extreme and exponential disease distribution. The overall cost may increase to + 11.73% for the extreme distribution because of the high number of severe cases in the oldest people (€3,352 - €3,000 = €352) (Fig. 7C). The exponential distribution ends at an overall cost increase of 9% (€3,258 - €3,000 = €258) (Fig. 7B). The latter is the same type of change as observed in Step 2 but now the number of ageing adults is equivalent to the younger age groups. The linear regression distribution has an overall cost difference of 0%, equivalent to the base-case analysis in Step 1. It is a forced analysis as it is developed using the fixed

population with the fixed number of infections with cost results that are in balance across the age groups around the mean age (82.5 years), that is equivalent to the median age of the group. This is not the case for the other distributions that have an unbalanced distribution of disease cases and their severity level across ages in relation to the age midpoint (Fig. 7A) causing therefore a positive net cost difference.

Combination analysis

Move and Grade

The next analysis combines changes in disease spread (Move) with changes in disease severity level (Grade), shifting more events to the more aged group in condition X_{2a}, while keeping the population number and disease events fixed as in the previous multi-step analysis. The approach first looks at the results of the Move shift of the disease spread using an increased exponential growth as shown in Fig. 8 (left side, green line) (from 6% at the youngest age to 88% in the oldest age-group) and presents the outcome as the overall cost spread in function of age (€2875 for X_{2a} versus €2934 for X_{2a} + Move). With Move more diseases shift towards the more aged group causing an increase in overall cost (+€66). However, it still results in a negative net cost when compared with the full homogeneous condition ((€3000-€2934)/€3000= -2.2%). There is a concentration push of the overall cost in the in-between age-group of 75 to 90 years old, as can be seen in Fig. 8 (right side, green line).

Figure 9 adds to Fig. 8 now the Grade change that may happen in two different ways. One is an increase of the gradient of the linear function of the low severity level across the ages (grey line in the left graph of Fig. 9, called Grade 1). The other change, called Grade 2, induces a parallel decrease of the low severity level function (brown line in the left graph of Fig. 9) while the high severity function is increased with the same amount. Again, the outcome result is presented as the overall cost spread in function of age with a separate design for Grade 1 and Grade 2. Both are designed in addition to the Move change presented in Fig. 8.

The results of Grade 1 and Grade 2 have a different profile resulting for Garde 1 in a negative net cost sum between X_{2a} Move & Grade 1 and the full homogeneous cost result (X_{1a}) that is worse than if Move only was considered (€ 2,922-€ 3000 = -€78; -2.6%). Grade 2 in contrast causes a higher overall cost than X_{1a} that is caused by the difference in profile between low and high severity levels (€3,167-€3000 = €167; +5.6%).

Unit cost per severity level

The unit cost changes are the next evaluation (3-way sensitivity level 2). They are implemented using multiplication factors (MF) of the baseline cost value by the two severity levels Medium and High (maximum 10 times for Medium and 20 times for High severity). In the reference base-case condition of X_{1a} a uniform cost for each disease severity level is applied, calculated as the average cost for the three severity levels. Consequently, the mean cost in the full homogeneous model of X_{1a} is adjusted as soon as the unit cost is changed in the non-homogeneous constellation. Figure 10 shows in the first row the cost difference obtained when the MF for Medium severity cost is 1 while the MF for High severity cost is at the maximum level of 20.

As shown in Fig. 11, the relative overall cost difference between X_{1a} and X_{2a} under those circumstances, is 1.29% or -€407 in absolute terms (€31,093-€31,500). The second row in Fig. 10 illustrates the result when the optimal combination is achieved in MFs for Medium and High severity cost, resulting in the highest overall relative cost-difference between X_{1a} and X_{2a} (11.19% or -€1,419; €11,261 – 12,630 for MF 6 in Medium severity and 4 for High severity). One should be aware of the difference in overall costs by age-group (Y-axis) between the first and second row in Fig. 10. The result of moving to higher cost differences by disease severity level augments the overall negative relative cost difference between X_{1a} and X_{2a} (see Fig. 11). The results of this analysis show the importance of investigating the dominance of High severity cost as compared with the costs of the other severity levels of Low and Medium. With very high dominance of High severity cost (MF = 20) it is likely that the relative cost-difference between homogeneous and heterogeneous overall cost estimate is marginal, also shown in Fig. 11. Some values in Fig. 11 are not reported because they do not comply with the constraint of having a higher cost for a Higher severity level.

Demography

The last combined sensitivity analyses (3-way sensitivity analysis) for the disease burden are the demographic changes. It should be clear from previous evaluations that the current age-demographic composition of the ageing adults in Belgium induces an overestimation of the cost burden when using the full homogeneous analysis approach. It is therefore interesting to know by which level of age-demographic change, the application of the full-homogeneous analysis may result in an underestimation of the cost burden. To make this analysis straightforward, an approximation is applied to the age-demographic change using linear regression lines that calculate the angle score in the age-demographic change to be increased for reaching the zero overall net sum cost (= €3000). The slope numbers of the 2 linear regression lines in Fig. 12, left side, helps indicating the negative angle increase of the demographic age-component between the base-line Fig. 5 with an overall cost of € 2,875 and the cost neutral estimate at around €3,000. That angle increase (red arrow) is around 3.3° (110.7 °-107.4°) which means that the population increase in the oldest age-group of 98y old must increase from 0.4–1.91% or a 4 time increase in absolute numbers to get to the overall cost-neutral point.

A final disease burden analysis applies a demographic augmentation of the population in X_2 which is different from the previous exercise, matching the current demographic age distribution in Belgium. This enlargement is a likely evolution that is compared with X_1 with no demographic change. The analysis shifts the overall cost to an increase of 2.26% for a 7% population increase (Fig. 13). It could move to close a 15% cost increase if a 20% population increase in X_2 is applied which may happen over a period of 15 to 20y from now (data not shown).

Summary results

Table 3 summarizes the outcome data of all the different simulations conducted based on the ESAP of Table 2. To obtain estimates that are comparable between the different evaluations, relative cost differences are reported for X_2 compared with X_1. A big driver in the relative cost difference is the reference case selected and compared with of the homogeneous condition (Step 5). The next one is the demographic change that may cause a 15% cost increase if the population augments with 20%. Other changes go into the direction between 2–12% cost changes.

Table 3
Absolute and relative change in overall cost by each analysis step of the ESAP

Item	Disease cost burden												
	Condition	Step 1	Step 2	Step3	Step 4	Step 5	Specific	Step 6	Specific	3-way 1	Specific	3-way 2	Speci
homogeneous	X1a	€ 3,000	€ 3,000	€ 3,000	€ 3,000			€ 3,000		€ 3,000	MFH20, MFM1	€ 31,500	
											MFH4, MFM6	€ 12,680	
	X1b					€ 2,250							
non-homogeneous	X2a	€ 3,000	€ 3,000	€ 3,000	€ 2,875	€ 2,875	linear exponential extreme	€3000 €3262 €3378	Move + Grade 1 + Grade 2	€2934 €2922 €3167	MFH20, MFM1 MFH4, MFM6	€31,093 €11,261	
	X2b												1%
													7%
													20%
Difference	X2a-X1a	€ 0	€ 0	€ 0	-€ 125		linear exponential extreme	€0 €258 €352	Move + Grade 1 + Grade 2	-€66 -€78 €167	MFH20, MFM1 MFH4, MFM6	-€407 -€1,419	
	X2a-X1b					€ 625							
	X2b-X1a												1%
													7%
													20%
Relative Cost Difference	(X2a-X1a)/X1a	0.00%	0.00%	0.00%	-4.17%		linear expotential extreme	0.00% 8.60% 11.73%	Move + Grade 1 + Grade 2	-2.20% -2.60% 5.57%	MFH20, MFM1 MFH4, MFM6	-1.29% -11.19%	
	(X2a-X1b)/X1b					27.78%							
	(X2b-X1a)/X1a												1%
													7%
													20%
Figures		Figure 2	Figure 3	Figure 4	Figure 5	Figure 6	Figure 7			Figure 8 & 9	Figure 10 & 11		Figur
MFH: Multiplication factor High severity; MFM: Multiplication factor Medium severity													

Discussion

With limited accurate and detailed healthcare data that are not easily available, analyses often rely on more accessible information such as arithmetic average values for the group under study. That approach assumes group homogeneity in all characteristics for which average values are applied. If this assumption is invalid, the summary results of cost and/or Quality Adjusted Life Year (QALY) gain could then be inaccurate with the reality. Other ways are needed to look for estimate of the uncertainty in the outcome results instead of using averages. It is however often unknown whether non-homogeneity in the data causes a substantial difference in the outcome results compared with the assumed homogeneity. To explore that potential size of the difference, this analysis here shows an approach using the extended sensitivity analysis tool, called the ESAP-plan, that may better help understanding what is at stake. The variables selected and studied are known factors causing potential non-homogeneity in the group under study, such as demographic age distribution and infectious

disease spread. These points have been mentioned in the literature, but few publications have evaluated the consequences of not assessing non-homogeneity in the data analysis. Non-homogeneity could be of little concern if the variable spread is well balanced in the group, or when the numbers to evaluate are fixed – as illustrated in Step 1 and in Step 6 (linear regression). However, if some or all the variables may have unequal or unbalanced distributions, the overall summary cost estimate may be heavily skewed, as a non-homogeneous factor may become especially critical if it is linked to other unbalanced variables in the group, such as age linked to infection rate, frailty level, disease severity, and cost.

The summary Table 3 illustrates some interesting features of the complete analysis of the ESAP about issues that should be further investigated in a real-life setting. First, it is important to be clear about the reference condition of homogeneity selected for the comparison. One should define upfront whether a full (X_{1a}) or partial (X_{1b}) homogeneity condition is selected for that comparison. This selection may heavily influence the over- or under-estimation of the overall outcome measured with a non-homogeneous spread as indicated in Step 4 versus Step 5 in this exercise. Step 4 has selected a full homogeneous condition of comparison in X_{1a}, leading to a marginal negative net cost-difference (4%) for the non-homogeneous condition, whereas in Step 5 a partial homogeneous condition is selected to compare with, and suddenly the net cost-difference is largely positive (29%) for the same non-homogeneous condition. Second is to check the age-specific demographic change in the study population under study linked to the rate of infectious disease increase by age. That combination results in a bell-shaped frequency of the overall cost as shown in Figs. 2 & 3. The bell shape will be more pronounced when the age-demographic and the disease data are more non-homogeneously spread by age. The third item to consider is the link between the distribution of disease severity levels by age and the cost per severity level. If there is no much of a difference in cost by disease severity level to be expected, then limited effort should be spent to obtain more precise overall costs than the homogeneous dataset.

When the full homogeneity situation has been selected, the results of this study indicate that the range of relative value changes in the overall cost estimates for the disease management can reach a maximum of 15% in the context of extreme situations of demographic age distribution, disease rate increase with increasing age, disease severity distribution by age group, and a high multiplication factor for the high cost in severity level (data not shown in the figures). When less pronounced distributions are considered, the relative cost difference between the fully homogeneous assumption of X_1 and the non-homogeneous condition of X_2 is likely to be between 2.5–6% overall. It indicates that the level of deviation in the cost summary results is not as large as often suspected. The difference change is limited because the constraints, defined up-front for this analysis, impose strict boundaries on the evaluation. For instance, non-homogeneity of the numbers by age groups is restricted and auto-correlated in the setting defined by the values in the prior age-class and the post-age group using a smooth curve design. This seems reasonable unless catastrophic events may heavily disturb temporarily the age distribution, such as war or natural catastrophe where suddenly many people of a specific age group are lost from the population. Other interesting features, identified through this ESAP, demonstrate the complexity of the problem. Demographic and disease spread alone don't create a cost difference unless linked to disease severity levels and cost changes by disease severity levels.

An element of concern is the effect of non-homogeneous factors that are unbalanced in the opposite direction across the group, with strange consequences for the summary assessment. For example, with an ageing population the decline in numbers of individuals in progressively older age-groups, due to the increase in mortality with age, is not programmed as a gradual linear decrease with age, but instead follows an accelerated course causing a highly unbalanced age distribution in the overall study group. Infection spread moves in the opposite direction, with higher prevalence rates in the older groups because of worsening health condition with increasing age. There is a perception that ageing induces an overall healthcare cost increase [16, 17]. The example here, estimating overall healthcare costs of infectious disease management in ageing adults, indicates the opposite. It shows that overall cost may be lower when adjusted for non-homogeneity, compared with the overall cost of a study group when assumed to be fully homogeneous. This happens when the age structure is heavily unbalanced (fewer very old people), which imposes a lower absolute number of highly severe and costly treatments, despite having proportionally much more severe disease present in those older age-classes. This lower overall cost estimation may seem counterintuitive, but Fig. 6 shows it is possible. If, however, the age imbalance is marginal (Figs. 7 & 12), which is likely to be the development over time as the whole population lives longer, the problem of infectious diseases with more severe cases in the older groups could increase the overall cost above the homogeneously assumed estimates. Managing infectious disease in ageing people could therefore become a serious threat to tackle to help control healthcare cost increases over time.

Another surprising finding is that higher costs for treatment of more severe cases may not result in an obvious change in the cost difference between an assumed homogeneous evaluation and an adjusted non-homogeneity evaluation, as indicated in Fig. 10. The result could move in the opposite direction, with a higher negative cost difference with higher cost for the more severe cases, because the average cost in the homogeneous situation X_1 also increases (Fig. 11). Also, changes in demographic composition may take time before a substantially higher cost is observed when substantially more people are living longer, as Fig. 12–13 indicates [18].

Having highlighted the issues of non-homogeneity with a hypothetical example using the ESAP, the results indicate the information that would be needed for developing more accurate estimates. Detailed demographic data are usually collected by national institutes of statistics at country level. However, infectious diseases are often neglected and not monitored or registered precisely and systematically across age groups. The recent COVID-19 pandemic highlighted the importance of measuring details of infection spread among different groups.

This analysis did not include all possible factors that could have an unbalanced spread across the population group, as it would have been too complex to model non-homogeneity if all known factors had been considered. However, the following additional elements could be considered that might influence the overall cost results with their unequally distributions across the group: sex; health condition expressed as the level of co-morbidities present in numbers and severity; frailty and disability; place of living (home, nursing homes, service flats); and hospitalisation. Regarding frailty, a recent review has shown the bi-directional movement of infection influencing the frailty condition of the individual and vice versa [19]. That may complicate the correct assessment of total infectious disease cost burden and the impact estimate of new interventions on that particular health condition like vaccination [20]. It is known and reported that frailty increases exponentially with aging which may justify the exploration here done of exponential graphs for infectious diseases [21]. The better knowledge about frailty that increases with time, allows for considering more appropriate and efficient prevention programs in ageing adults [22].

Regarding hospitalisation, infectious disease costs for hospitalisation are considerable and the cost differences by type of infection in hospital care could be large. This could potentially cause a high impact on the estimates of the overall infectious disease cost if these differences are not accounted for, and this was not evaluated in this analysis [23, 24]. Finally, another point not considered in this analysis is disease seasonality. This is particularly relevant for respiratory diseases, the most important type of infection in ageing adults [25]. Seasonal effect is an important non-homogeneous factor influencing good management of hospital beds across the year. It can severely impact the quality of care in hospital disease management, as reported for infectious diseases in children [26].

Non-homogeneous analysis of the data, such as that presented here, may indicate a different assessment of importance of the cost and the need for good management of the healthcare problem of infectious disease in older adults. Infectious diseases may spread beyond the initial cases and may harm many others during a considerable period. They become a serious threat when they accumulate, particularly in costly environments such as hospital settings. It is there that they cause most damage to society, although many infections could be avoided through prevention. Non-homogeneous analysis may capture more accurate and more detailed evaluations that better help understanding the costs of infectious disease, and consequently the potential benefits of preventive interventions.

The analysis presented here has some obvious limitations, as the objective of the simple hypothetical example used was to illustrate the use of the ESAP method to indicate potential impact on the differences between homogeneous and non-homogeneous analysis types. However, economic evaluations often work with simple models. A check against real-world data may give a more nuanced picture than indicated by the present simple data analysis. Future studies may go beyond this analysis, using more sophisticated models that could also capture the effect of seasonality and other variables not considered in this analysis, and the indirect effects of new interventions such as vaccination.

It is important to choose the most appropriate data analysis to obtain the most accurate estimates of the potential health and cost gains from preventive interventions. Ultimately, the big challenge concerns the next steps after evaluating the costs of disease management, including prevention strategies to support healthy ageing[27]. Understanding how non-homogeneity in variable categories may skew reported results could potentially help researchers to provide better modelling and evaluations of the healthcare cost data, closer to the real-world situation.

Abbreviations

€: euro

A_n: Age-groups

C_T: Cost of treatment

C_{Tm}: Cost per severity level

ESAP: Extended sensitivity plan

I_n: Rate of infection in each age-group

I_s: Levels of disease severity

I_{sn}: severity level by age-group

MF: multiplication factor

MTH: multiplication factor high severity

MTM: multiplication factor medium severity

N: Population number

QALY: Quality adjusted Life Year

VITAL: Vaccines and infectious diseases in the Aageing population

X_1: basic homogenous model

X_{1a}: fully homogeneous model

X_{1b}: partial homogeneous model

X_2: non-homogenous model

X_{2a}: non-homogeneous, no demographic model

X_{2b}: non-homogenous demographic increase of the model

Declarations

Ethics approval and consent to participate

No request for participation as this is a modelling exercise

Consent for publication

No consent needed for publication as this is a modelling exercise

Availability of data and materials

Models are available on request to the first author

Competing interests

No competing interests

Funding

No funding

Authors contributions

Baudouin Standaert conceived and designed the study, developed the model, analyzed the data and drafted the manuscript.

Anne-Marie De Cock reviewed the different versions of the manuscript and included the clinical perspective of the analysis.

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Amandine Radzijwoski of Business & Decision, Brussels, Belgium, helped managing the submission.

Authors' information

Anne-Marie De Cock is head of the geriatric department of the biggest hospital in Belgium and has a huge interest in frailty measurement and in better understanding the infection problem amongst ageing adults

Baudouin Standaert is a health economist and has a huge interest in infection problems, vaccination, and ageing adults. They both worked together to investigate the infection problem in hospital care a few years ago.

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Figures

Figure 1

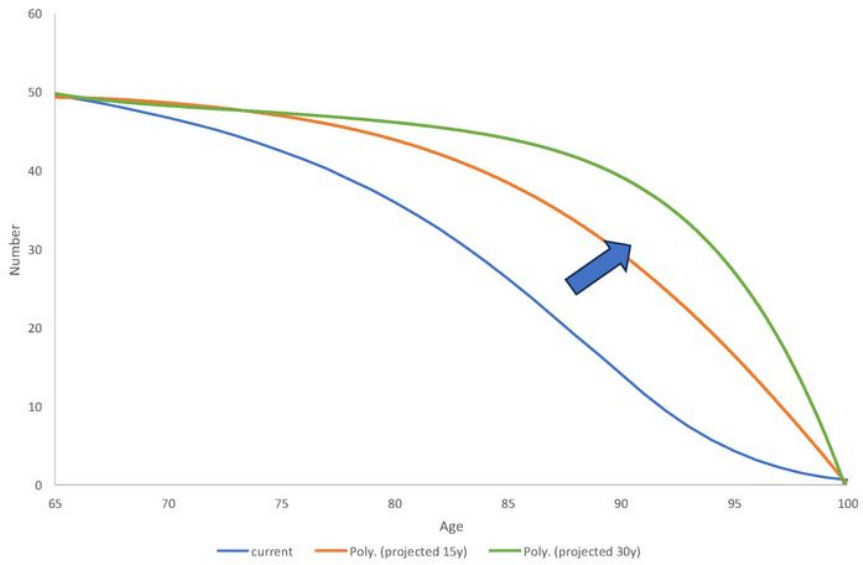

Figure 1

The likely evolution to a more age-homogeneous demographic distribution from current blue to predicted green.

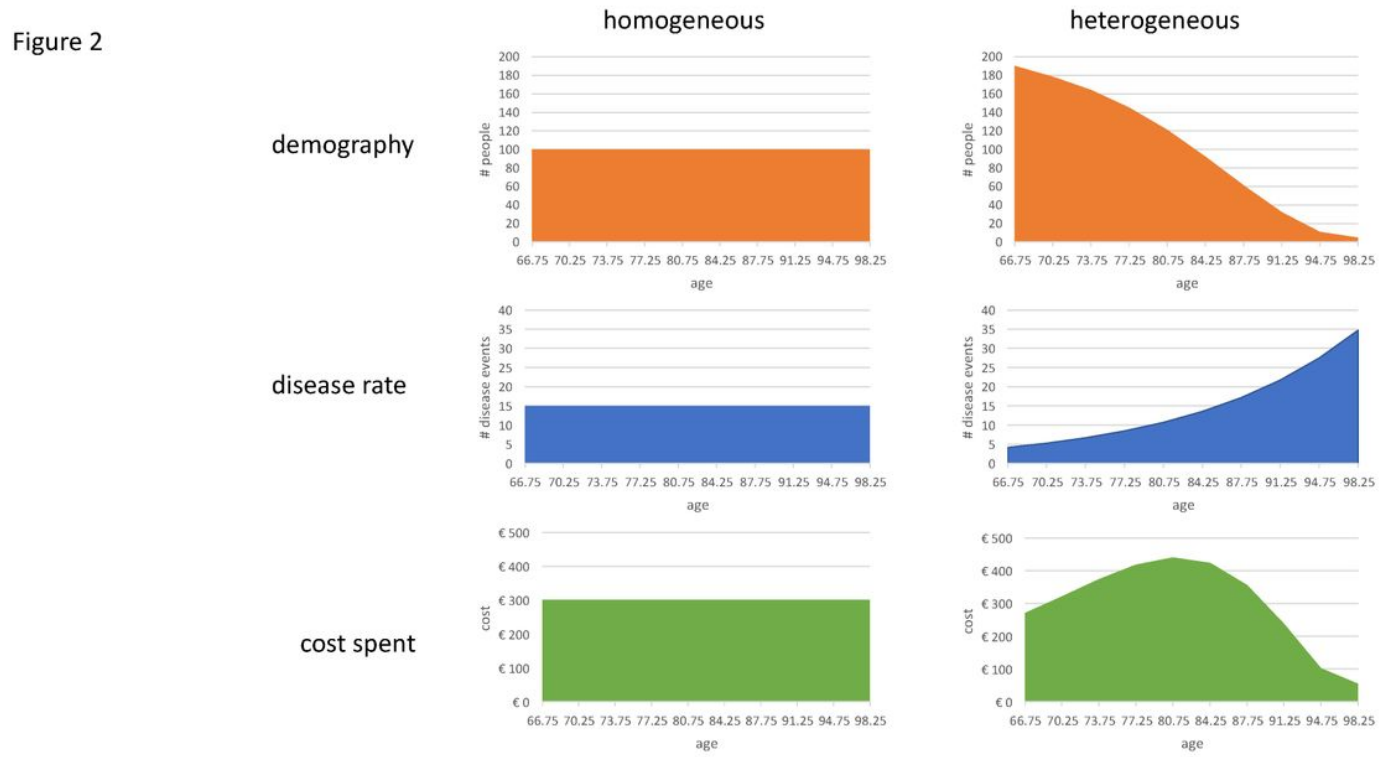

Figure 2

Presentation of the population, infection, and cost spread in function of age for a fully homogeneous group (left side) versus a heterogeneous group (right side)

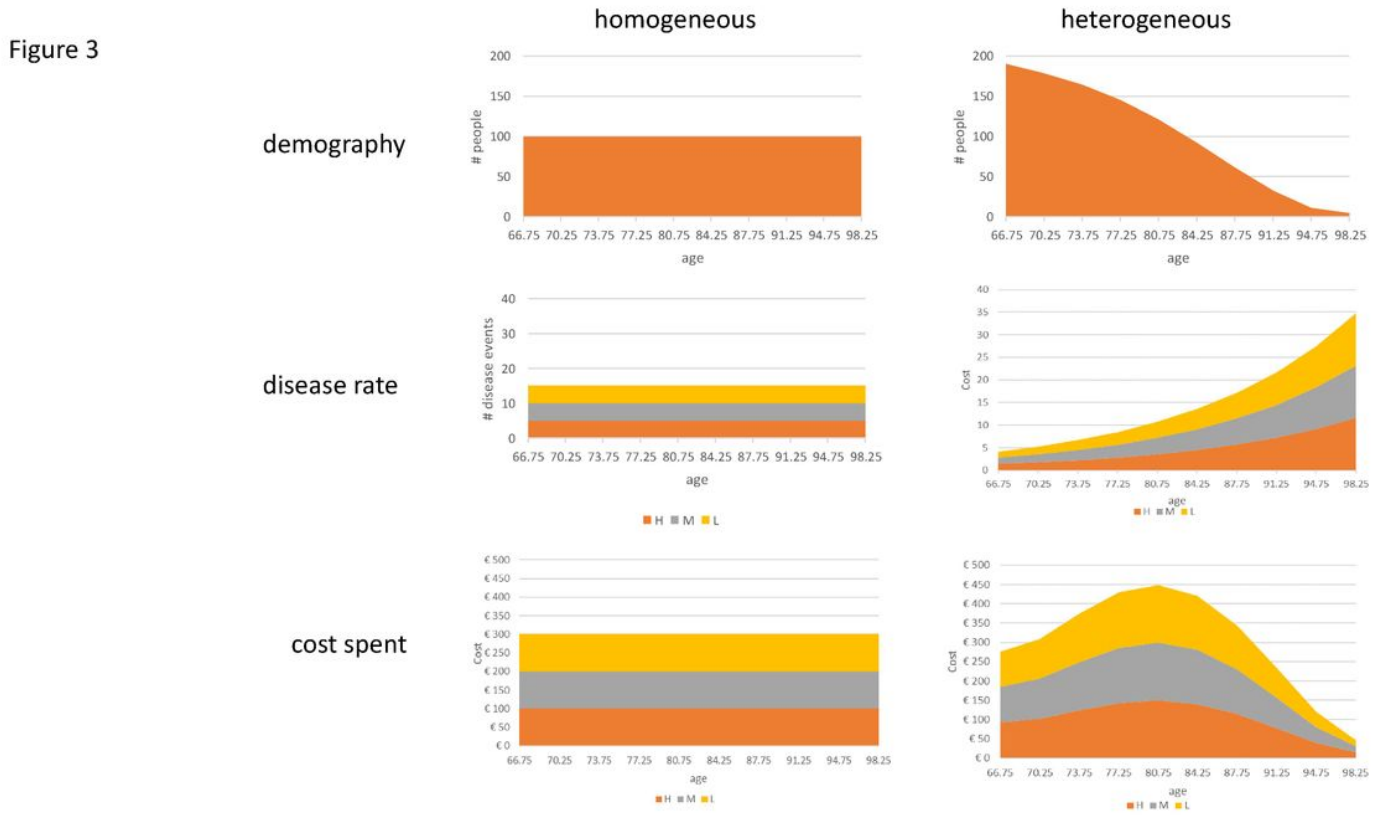

Figure 3

Presentation of the population, infection, and cost spread in function of age for a fully homogeneous group (left side) versus a heterogeneous group (right side) including equivalent disease severity levels of low (L), medium (M), and high (H)

Figure 4

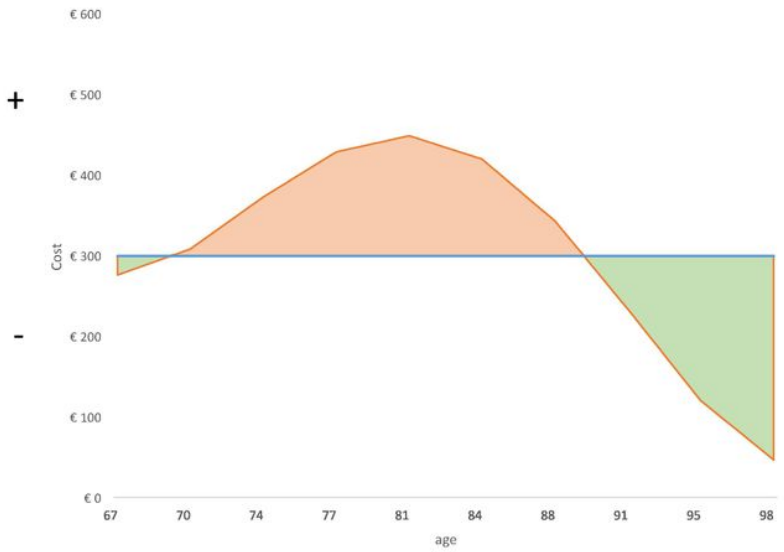

Figure 4

Calculating the areas between the curves of homogeneous versus heterogeneous cost estimates.

Figure 5

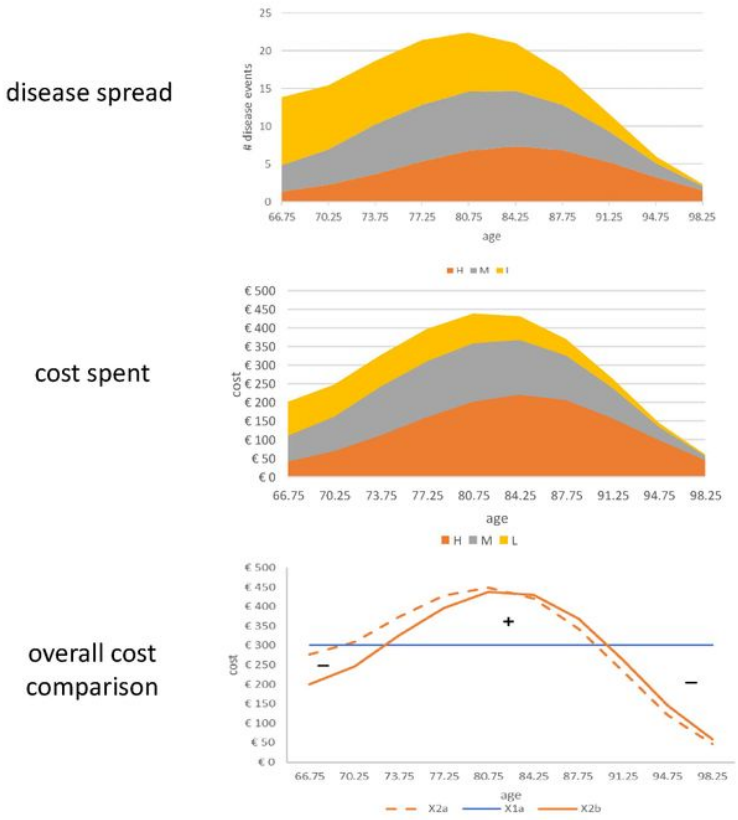

Figure 5

Illustrating first the disease severity spread of low, medium, and high by age, followed by the cost spend (X_{2b}; full line), and making the comparison with the homogeneous cost estimate (X_{1a}; blue line)) and with no cost differentiation by severity level (X_{2a}; dotted line).

Figure 6

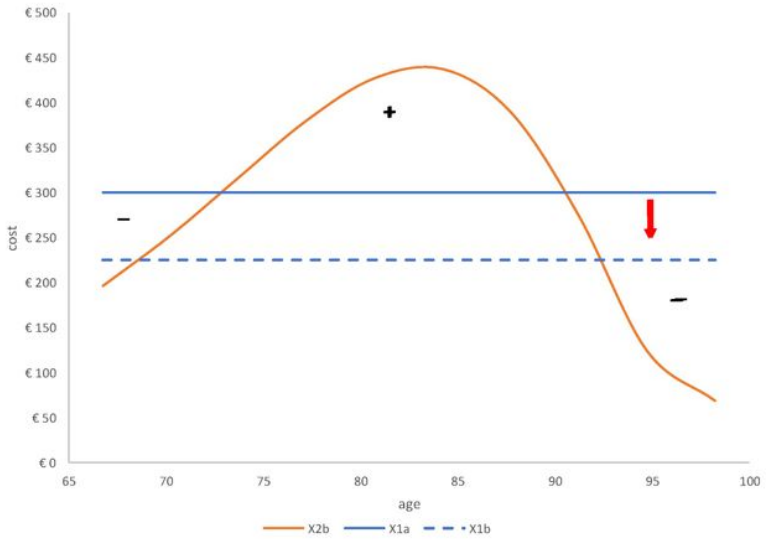

Figure 6

The distribution of overall costs by age group of condition X_{2a} with the changes in severity level and unit cost for treatment under the full homogeneous condition (X_{1a}) or the partial homogeneous condition (dotted line in X1b)

Figure 7

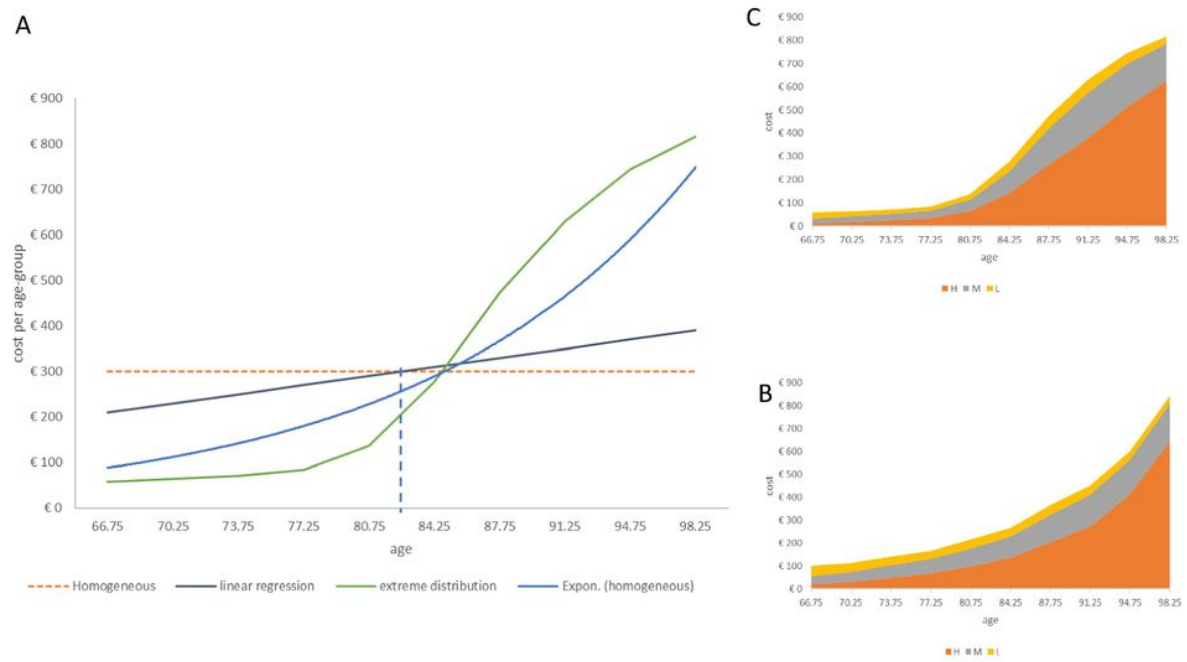

Figure 7

The distribution of overall costs by age group and age condition for a homogeneous age distribution but non-homogeneous spread in disease (A), severity, and treatment costs for exponential increase (B) and extreme condition (C)

Figure 8

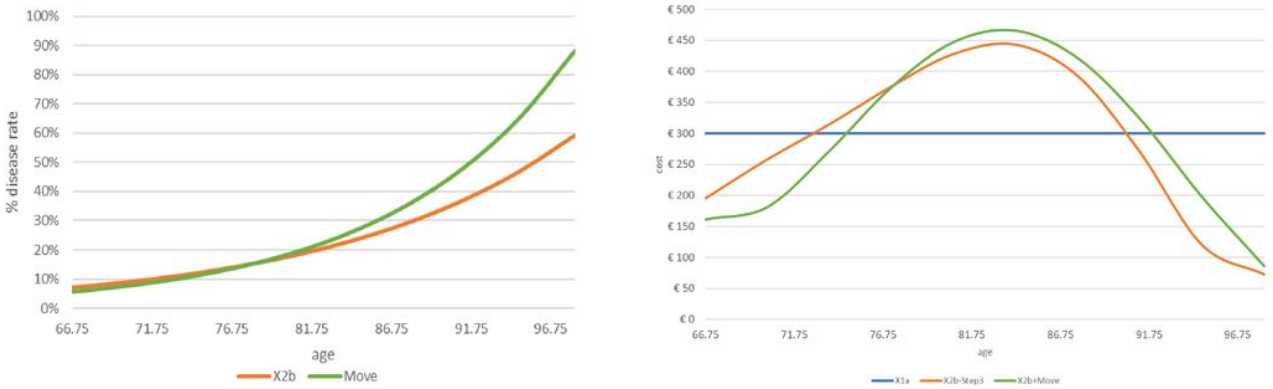

Figure 8

Showing the Move overall cost results (right) by increasing the exponential growth of infection by age (left)

Figure 9

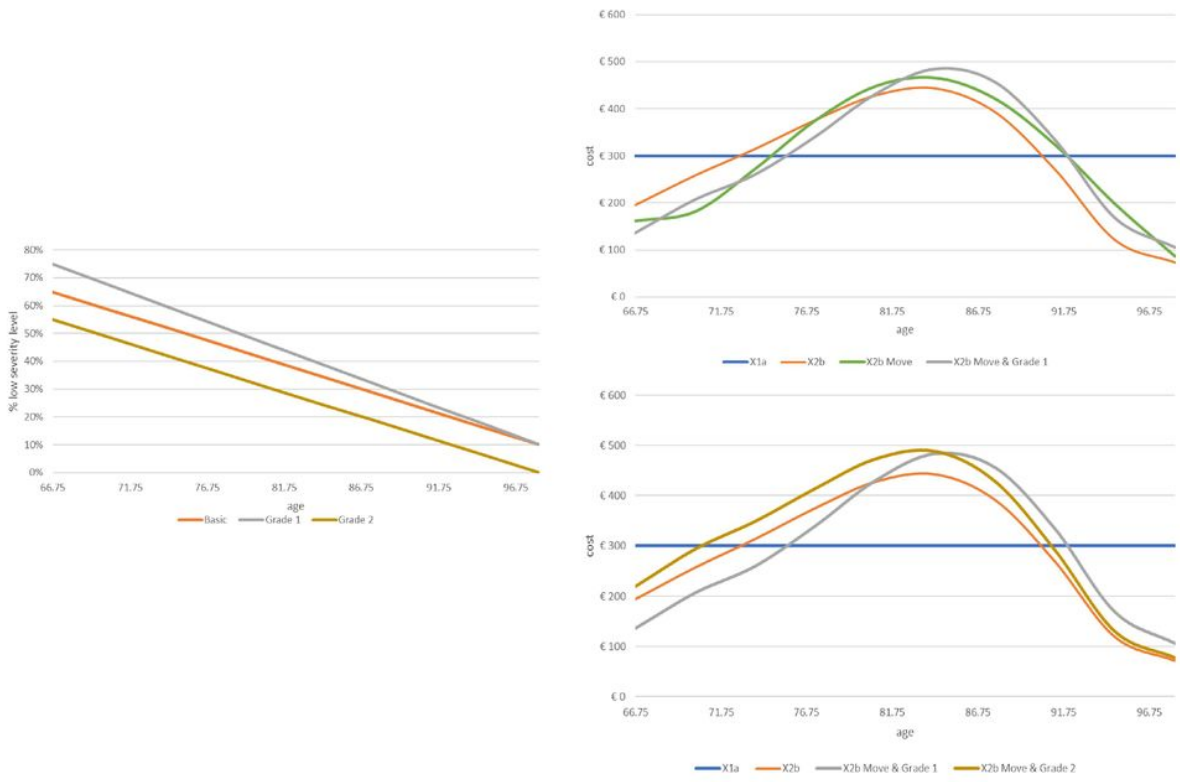

Figure 9

Showing the impact of Grade 1 (right upper graph) and Grade 2 (right lower graph) on the overall cost results by age

Figure 10

1/20

6/4

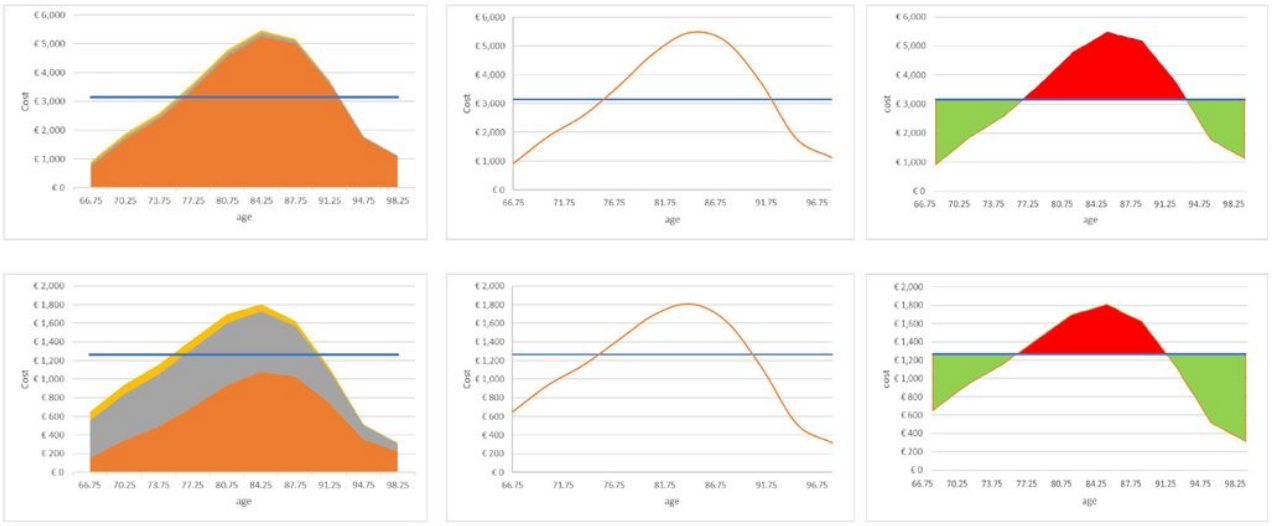

Figure 10

Changing the multiplication factor (MF) for cost of Medium severity level in the numerator and High severity level in the denominator showing the cost spread by age-group and the areas between the curves.

Figure 11

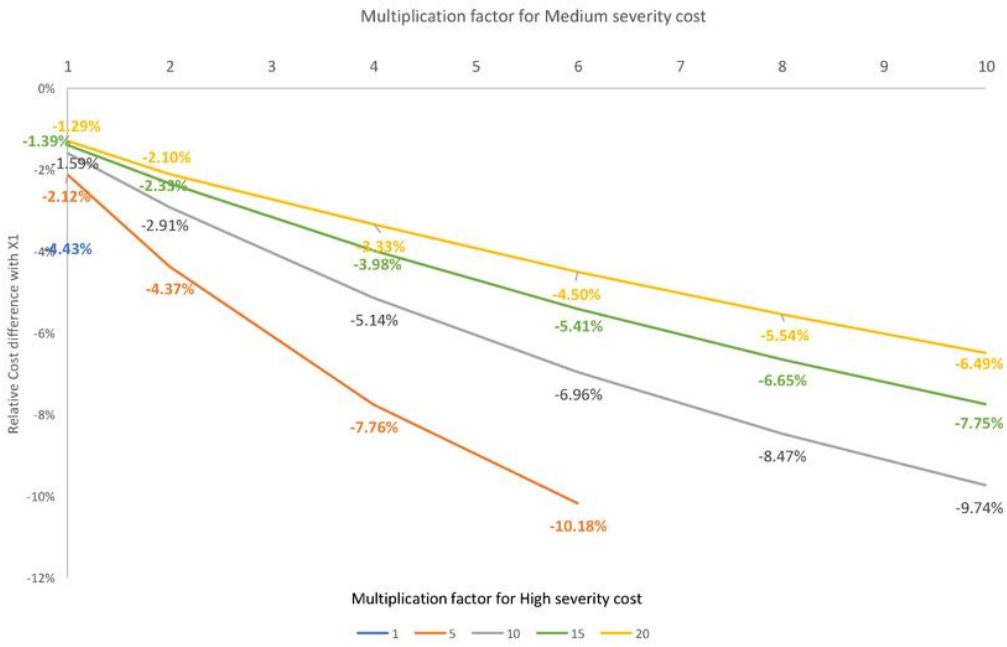

Figure 11

Multiplication Factor for Medium severity cost (1 to 10) on the X-axis for different multiplication factors of the cost of High severity level (colour index 1 to 20 in legend) expressed as a relative cost difference between X_1 and X_2 (Y-axis)

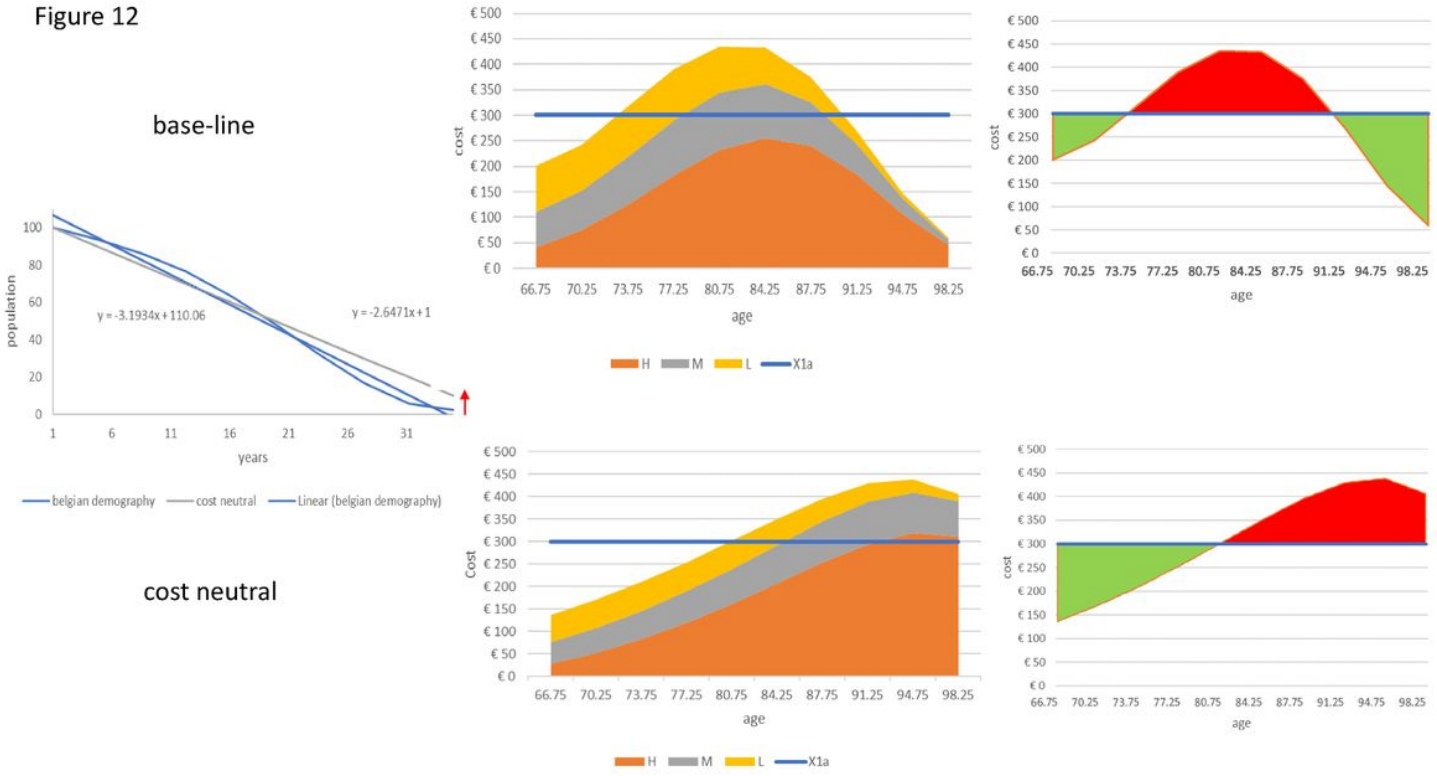

Figure 12

Estimating and visualizing the demographic increase needed to arrive to a cost-neutral estimate between X_{1a} and X_{2b}

Figure 13

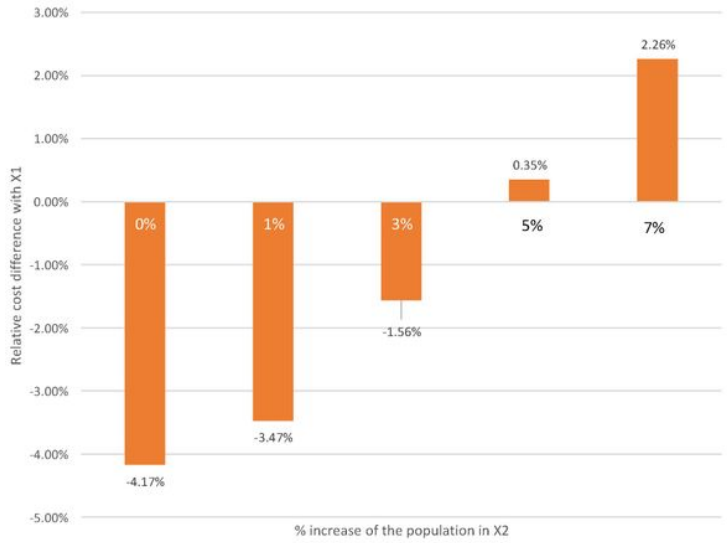

Figure 13

Effect of demographic change on the overall cost result

Supplementary Files

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- Appendix1.docx
- Appendix2.docx
- Appendix3.docx