MODELING THE IMPACT OF CHILDHOOD VACCINATION ON THE SPREADING OF PNEUMOCOCCAL DISEASES IN AUSTRIA: DIFFERENCES BETWEEN A MARKOVIAN AND ODE APPROACH.

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1 Motivation

In Austria pneumococcal bacteria cause over 25000 serious illnesses each year [6]. The most common are meningitis, septicaemia and bacteraemic pneumonia. Furthermore there are other illnesses where only a certain proportion is caused by identified serotypes (e.g. otitis media). Most infections occur among children, especially those younger than 2 years, and people older than 60 years [6, 3]. There exists a vaccine that protects against the most common 23 pneumococcal serotypes (of approximately 90) which can only be used for people over 2 years, but also a 7-valent conjugate vaccine for children which can already be used for 2-months-old babies. This vaccine is also licensed in the European Union and other developed countries [1]. This vaccine is under discussion of being introduced in Austria's child immunization program and is already in use for about 10 percent of all children, for example premature babies. The aim of the current work is to create a model to simulate the pneumococcal illnesses and estimate the possibility of preventing the disease by vaccination with the 7-valent serum and thereby get better insights in cost effectiveness influenced by factors like herd immunity and serotype replacement.

2 Methods

At first a Markovian model, which is the most common modelling strategy used in such kind of problem, has been developed because it can be compared with existing models created by health economists. These static models are usually based on decision trees created by expert panels. In the model we look at a birth cohort from birth to 10 years and estimate the incidence of pneumococcal diseases. Therefore, we look at the probability of being ill [3], evaluated in each time step, where each time step covers 6 months. Furthermore the death probability for each illness and the estimated long-term sequelae which produce further costs are examined and in case of vaccinated children the age and illness-specific efficacy of the vaccine are investigated [6, 3]. The structure of the decision tree is shown in figure 1.

In each time-step, which covers 6 months, it is checked for each child in the simulated birth cohort if it is vaccinated. Then it is decided if the child becomes ill from one of the considered illnesses. The infection rates depend on the age of the child, the considered illness and the time span since vaccination because the vaccine effectiveness decreases over time. Afterwards it is estimated if the patient will suffer from a long-term sequelae, get healthy again or die. The cases of long-term sequelae cause more costs in the future and therefore have to be included when regarding the cost-effectiveness of the vaccine.

Running the model one time with vaccination and a second time without vaccination allows estimating the costs caused by pneumococcal illnesses and, furthermore, if vaccination results in an increase of life quality for the patients or if at the same time it is cost-beneficial. However, the system is very sensitive to changing either the vaccination costs or the costs (and indirect costs) that the specific illnesses cause.

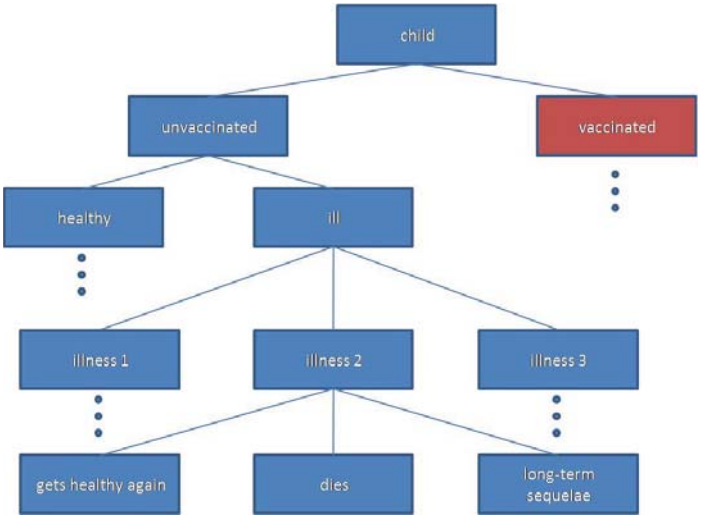

Figure 1: Organisation of the decision tree for the Markovian model. The vaccinated path has the same structure as the unvaccinated path but with different parameters.

Because the data analysis for Austria is not yet completed, Figure 2 shows the estimated illnesses for the Austrian population structure based on the infection probabilities in the United Kingdom, where we got a dataset from. In the beginning we looked at the publication of an UK study about the introduction of PCV7 and tried to reproduce the model by reverse engineering, starting with the solution graph and the basic knowledge to the method used. As result we received a Markovian model which delivered the same results quality as the corresponding result graphs of the UK study.

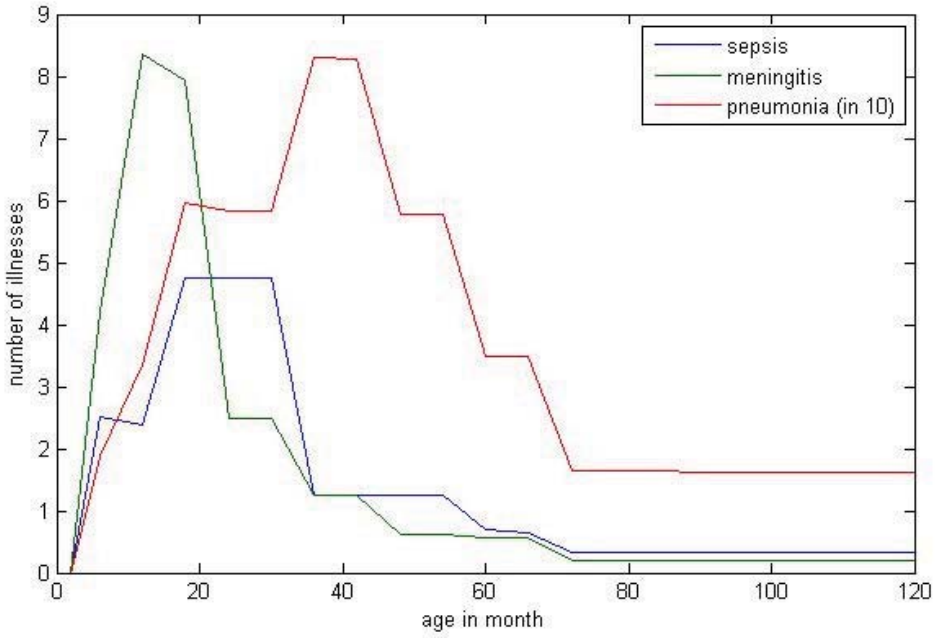

Figure 2: Number of illnesses in each time-step for sepsis, meningitis and pneumonia for children from birth to ten years calculated with the basic Makovian model

The structure of the Markovian model does not allow a deeper insight into the dynamic effects of spreading of the illnesses influenced by vaccination and dynamic feedback due to the properties of the Markovian structure. With this model it is not possible to represent dynamical nonlinear effects like herd immunity in other age groups or serotype replacement. These phenomena lead to different infection rates and thereby a different number of cases. Herd immunity is a factor observed in literature and so cannot be ignored but there are many different approaches of integrating this effect [4, 5]. The lack of studies especially concerning serotype shifting is a big problem and therefore it is questionable if it can be modelled in an appropriate way to estimate the cost-

effectiveness of vaccines. Data of different other countries lead to different conclusions either claiming that serotype shifting has no effect at all or that the eradicated serotypes are completely replaced.

Therefore a system of first order differential equations has been developed that allows estimating the number of infected people for each specific illness at any given time [2]. The model uses different parameters for each age-class where from one to ten years each year is one class and then there are classes for teenagers, adults and old people. The definition of the time span of each class is based on the distribution of cases of the three illnesses of interest. Another reason is that the outcomes of both modelling approaches have to be compared after implementation. The development of the population is estimated in each class separately based on data from Statistik Austria [7]. The development of the illnesses in the past without vaccination is known, so both, the ODE and Markovian model deliver the same results when simulating the past years without vaccination.

The structure of the ODE-System is shown in figure 3:

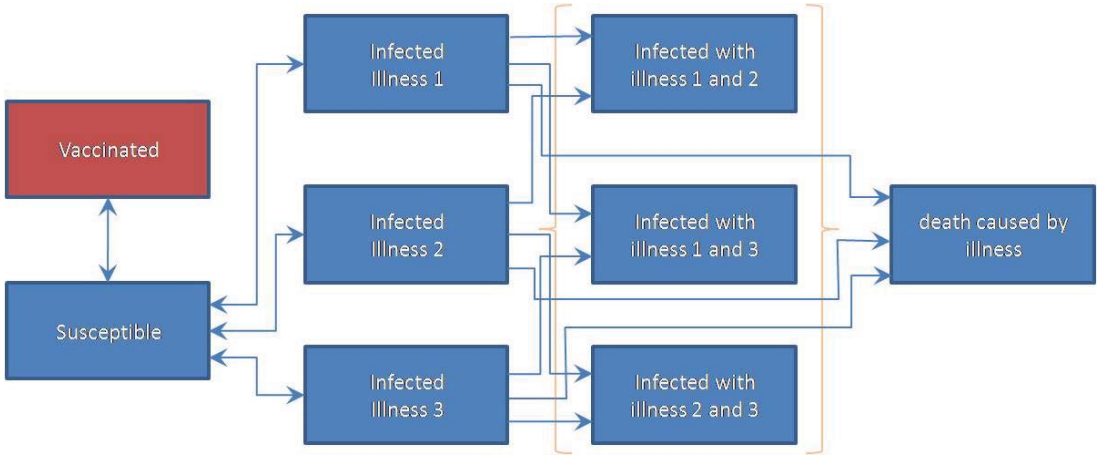

Figure 3: Organisation of the ODE-system. The arrows show the directions of possible flows, for example susceptible people can get vaccinated and vaccinated people can get susceptible. Dead people cannot return to any other class.

We now look at infected people, who are more than those people who actually suffer from the illness, because if a person gets infected with the bacteria it is still not ill but can show symptoms after the incubation time although it is infectious much longer (Considering pneumococcal illnesses, people who are vaccinated cannot carry the bacteria strains they are vaccinated.). In general only a part of the infected people show symptoms, most of them carry a strain of the bacterium in nasopharynx and loose it again after a specific time span. As can be seen in literature the carrying period seems to be quite different in European countries. It also varies depending on the age of the infected person. The proportionality factor 'infected ill' has to be agreed on by an expert panel thus it can be used for the cost evaluation. Susceptible people get infected with illness I with an infection rate β_i and get rid of the bacterium with the rate α_i. They die with the rate γ_i. The rates depend on the age of the person and the gender. Furthermore, in general people can get infected with more than one illness, but this is not common. In that case there would be more than $n!$ additional parameters, which cannot be identified.

Because we want to reduce the number of parameters we have to show that people who suffer from more than one pneumococcal illness have no impact on the results and therefore can be ignored in our model. That is why we cut the model down to two illnesses. We now simulate the model with the case that a person can actually suffer from two illnesses and use those where the probability of being infected with two at the same time is the biggest. Afterwards the results are compared to the simulation without the possibility of being infected with more than one illness at each time point. It can be seen that there is no significant difference. Even when performing a parameter variation analysis of ±80 percent of the standard parameters for the infection rates the difference remains very small. This is because the infection probabilities are very low. Now we expand the investigation on three illnesses. The highest infection probability of being infected with two illnesses is an upper border for all these cases (and of being infected with all three illnesses at the same time). When we now assess

the mistake we make when excluding cases of two infections with this upper boarder we see that there is still no significant difference. Therefore it is allowed to assume that a person can only suffer from one illness each time point.

3 Results

Current results from the Markovian model with data from the UK adapted to Austrian population where herd immunity and the cost of long-term sequelae are considered based on predefined values from UK and USA show positive effects if children get vaccinated. However, all of these calculations are quite sensitive regarding the percentage of cases of illnesses caused by strains included in the serum as well as the influence of herd immunity and serotype replacement. In the moment herd immunity is implemented in the Markovian model as a fixed value and replacenment of vaccinated strains is not included. The ODE model does not support vaccination right now, at the moment it is only a base model that does not consider some effects that could lead to better results if children are vaccinated. The only shown result in this paper is that the model can be reduced by getting the same quality of results by using less parameter.

4 Conclusion

The Markovian model can accurately describe the infection with pneumococcal bacteria if proper data exists and there is no need to use dynamic effects or feedback-loops. If we want to estimate the dynamics of how the introduction of vaccination for children affects the illness-distribution in all age classes and want to consider additional dynamic effects (like herd immunity, demographic structure, ...) we have to use another model, in this case we chose an ODE-model. The results for cost effectiveness of vaccination are very sensitive to cost rates and other effects like herd immunity and serotype shifting. Answering the question of cost effectiveness of the vaccination of children under the age of two years in Austria can not be answered with the current status of the model. Further work on the dynamical model and data structure analysis

5 Current work

To get a more accurate model the population model is reworked to be closer to the estimations to Statistik Austria [7]. The datasets for infection probabilities [6] are investigated to ensure good parameters for the age classes. The ODE model will be expanded with the possibility of herd immunity and literature research for methods for serotype replacement has to be done. Afterwards the most promising methods will be implemented in the ODE model. After these steps the Markovian and ODE model will be compared again to see if the two different approaches to examine this problem deliver similar results or why the results differ from each other. In the end sensitivity analysis and best and worst case scenarios will be calculated to get estimation for the cost effectiveness.

6 References

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