REPRESENTATION OF COMPETITIVE SEROTYPES IN DYNAMIC MODELS

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Abstract

Health economic questions demand accurate models for the spread of diseases. There already exist various approaches. Health economists mostly use Markovian models which are not suitable when analyzing dynamic effects like herd-immunity or serotype shifting. Wanting to understand these effects dynamic models like differential equations or agent-based models have to be used. Correctly modeling the transmittance of pathogens automatically considers herd-immunity. Serotype shifting on the other hand is a far more complex effect.

Usually a disease is not caused by a certain bacteria where vaccination prevents from getting infected with it. A more realistic view considers many different serotypes which all interact with each other. Vaccination only prevents from carrying certain serotypes but does not immunize against all of them. Wanting to establish a model representing different serotypes and especially simulating occurring serotype shifting, we show several ways how to extend an ordinary differential equation model. First we analyze the trivial case where they are not interacting with each other. Afterwards we run a scenario where people can carry strains of both serotype groups and then the most sophisticated way where serotypes affect each other in non-trivial ways.

Most of the time it is unknown how serotypes interact with each other therefore data of studies and expertise must be used to identify the model parameters. Model structure has to be chosen problem-dependent therefore there is not one correct method.

Keywords: Epidemiology, Serotype shifting, Vaccination, Health technology assessment

Presenting Author's biography

Christoph Urach studied *Technical Mathematics* at *Vienna University of Technology*, specializing on modeling and simulation, where he earned his master degree in 2010. He now works at *dwh simulation services* in the section for health technology assessment (HTA) and health economics. Currently he is also pursuing a PhD degree under Prof. Felix Breitenecker at *Vienna University of Technology*.

1 Motivation

Epidemiological models are used to evaluate the spread of diseases and are recently also used for health technology assessment and health economics. Most researchers in this area use Markovian models. They concentrate on economic costs and social impacts of illnesses whereas the epidemiologic model in the background is not regarded in detail. Most of the time people get infected with certain probabilities in one time-step. The impact of the already infected population or dynamic effects like herd-immunity, serotype shifting and changing population structure are not considered.

Dynamic models using transmission probabilities between people describe the spread of bacteria much better. A good description of the epidemiological background is essential to improve the models results. Most illnesses are not caused by a specific bacterium strain but by many different serotypes. In Austria the effectiveness of PCV 7 is evaluated. In this case over 90 serotypes exist. Studies about carrier rates suggest that they influence each other in a way that a person usually only carries one serotype [1]. We want to create an accurate model of the spread of these bacteria, despite not knowing exactly how pneumococci strains influence each other. Therefore it is necessary to establish ways to represent different bacteria strains in our model and find the best fitting solution for our actual problem.

2 Objective

In the beginning we take a look at the usual model assumptions in epidemiology. Each individual of the population is in one state. Their original states can be susceptible, where they can get contaminated by the considered illness, infected, whereas these persons can immediately infect others, or ill. Infected individuals do not need to get ill. When ill people get healthy they immediately get susceptible again. For some illnesses these requirements can change, especially regarding possible resistances after an infection. As there are over 90 serotypes in the case of pneumococci and there is no knowledge about cross-immunity this does not apply for them.

A SEI-model based on differential equations is implemented in Matlab®. Basic epidemiologic models like these are thoroughly analyzed and used for various problems [2]. Afterwards the possibility of vaccination is added. These basic models usually address the effect of herd-immunity, which means that even non-vaccinated people profit from vaccination programs [3], but lack the ability to simulate different serotypes.
We assume that both, susceptible and infected people can be immunized. Ill people can get vaccinated after their recovery. The model structure can be seen in Fig. 1. We have to note that in this model vaccination is equal to a total immunization against the illness. One of the consequences of this structure is the simple possibility to eradicate the pathogen when the amount of vaccinated people is above a certain threshold.

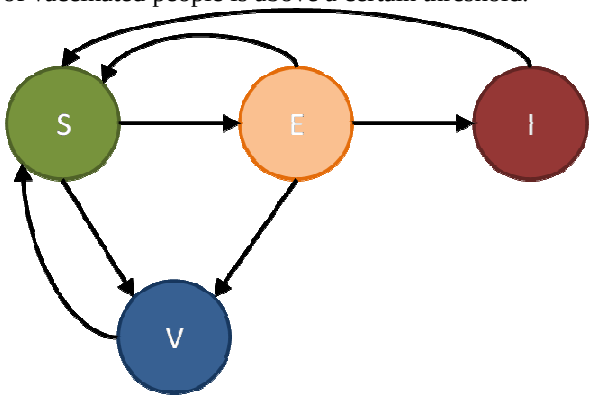

Fig. 1: Structure of the base SEIV-model

This basic model is well-known and can be used to model the spread of one specific pathogen. Though, it does not describe infections of bacteria which can be split into several competitive serotypes. In the next section we will extend this basic structure to enable exactly this ability.

3 Representation of serotypes

When modeling two or more serotypes the ratio between them can remain constant. Otherwise, when certain strains get stronger and some others get weaker, we talk about serotype shifting. Whenever the model has the ability that a carrier of one serotype can get infected with another strain and afterwards loses his or her previous strain we talk about the possibility of serotype replacement.

3.1 No serotype-change

Using the basic model as described above we now investigate the behavior of the model when people can get either infected with a serotype of bacteria group 1 or by a serotype of bacteria group 2 whereas all parameters for getting exposed, ill and healthy remain the same, only the starting ratio between the two groups is different. People carrying bacteria of serotype group 1 cannot get exposed to pathogens of the other group and vice versa. With exactly the same parameters as in the previous model and an overall amount of exposed and ill people as above the model reaches the same steady state. The ratio between the two serotype groups remains the same over the whole simulation period.

Vaccination is supposed to immunize against one of the two serotype groups. People carrying bacteria of the other one can still get infected. Running the model under these assumptions leads to the behavior seen in Fig. 2. No matter how the carrier rates were chosen in the beginning, apart from the trivial case of setting the

amount of people in one group to zero, the serotype against which the vaccine works becomes extinct. The other group takes its place, gets stronger and finally replaces the previously bigger one completely. Compared to the model without the possibility of serotype shifting (cyan in Fig. 2) the effectiveness of vaccination is evaporating. In fact this is the only possible behavior of the model. Analyzing the equations analytically, setting the equations to zero to calculate possible equilibriums, the only solutions are where either serotype group 1 or serotype group 2 vanishes. Such behavior is not observed in real world scenarios. The error lies within the assumption that infected people cannot get a pathogen from the other group. In the next task we will address exactly this problem.

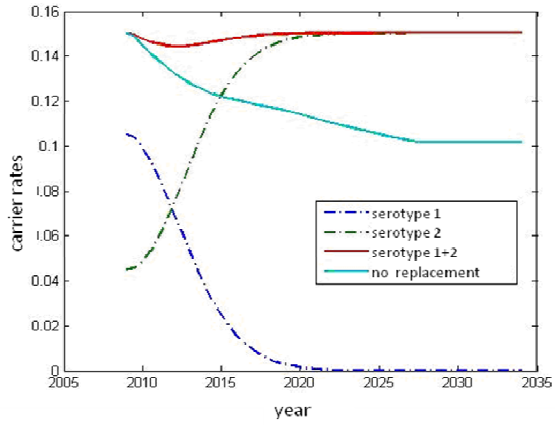

Fig. 2 Serotype-shifting without the possibility to change group

3.2 Spontaneous serotype-change

After discussing the flaws of the last model we now assume that serotypes interact in a way that carriers from serotype group 1 can be infected with serotypes from serotype group 2 but still, as one person can only carry one serotype at the same time, if a person changes its serotype, this happens immediately without delay. The vaccine immunizes against serotypes of group 1.

If a carrier of serotype group 1 has contact with another person an event of the following list occurs:

- The other person is susceptible and can get infected with the usual probability.
- The other person already carries bacteria from serotype group 1. Nothing happens. Swapping serotypes within one group has no influence on the spread of the illness at all because all serotypes in one group are treated as equals.
- The other person is vaccinated. Nothing happens.
- The other person carries a strain from serotype group 2 and is not vaccinated. There is a possibility one or even both persons get infected with the strain of the other. In this case the concerned person changes its serotype immediately.
- The other person carries a strain from serotype group 2 and is vaccinated. Only the first person can get infected with a strain from serotype group 2 in which case he or she changes the strain immediately.

If a carrier of serotype group 2 has contact with another person the same rules apply except one:

- If the other person is vaccinated it can get infected.

We now test the model behavior when parameters for infection and recovery or starting parameters change. At first infection probabilities for the two serotype groups remain identical. The ratio between the two serotype groups is only dependent of the starting values and remains the same for the whole simulation. The steady state of the model is only dependent on the infection probability in proportion to the recovery probability whereas the overall number of infected people remains the same.

Changing the ratio of infection probabilities leads to the results seen in Fig. 3. As soon as they are not identical the weaker serotype group gets extinct and completely replaced by the other group.

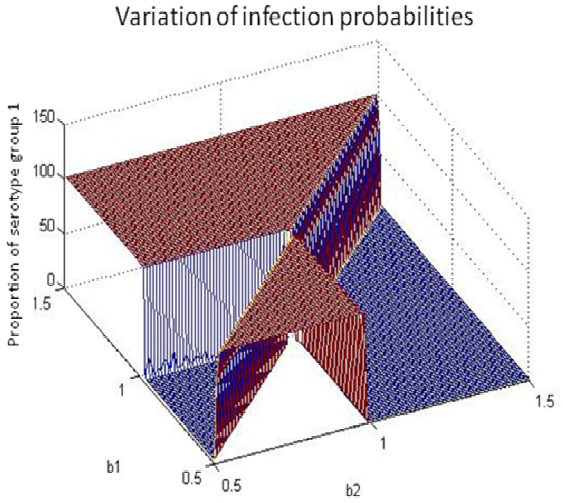

Fig. 3: Dependence of the steady state when varying infection probabilities.

These results fit reality in very few situations. When different strains co-exist but influence each other the model structure therefore has to be improved.

3.3 Carriers of strains from both groups

After analyzing the model for cases where a person can carry only one strain at the same time we abandon

this assumption. For now people without vaccination can get infected anytime, even with strains of both groups. The different serotype groups exist completely independent next to each other.

Analyzing the models dependence on different starting values we find out that after a certain amount of time a state of equilibrium is reached. This timeframe depends on the starting values though the steady state itself is not correlated to them. Without vaccination no serotype gets extinct, if the basic reproduction number for a single serotype is greater than one. After the transient oscillation phase group sizes remain at a constant ratio (Fig. 4).Vaccination changes this ratio and when enough people get immunized, the threshold number is defined by the basic reproduction number, one serotype group can vanish.

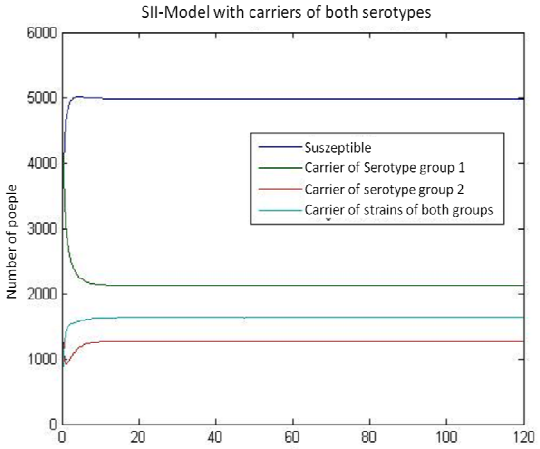

Fig. 4: Behavior of the model if carriers of both strains are possible

Remembering previously used model assumptions we realize that the following points could distort the results when simulating the spread of certain bacteria, for example pneumococci:

- One serotype cannot replace other serotypes.
- Serotype replacement happens immediately.
- Carriers can carry both serotypes but they do not influence each other.
- People carry two serotypes for a long time.

The next model extension will address this problem. We propose a structure to describe two serotype groups which are able to interact and replace each other.

3.4 Carriers with serotypes of both groups and delayed serotype replacement

This approach is most useful when many different serotypes cause a disease, they interact with each other in a way where a person usually carries only one serotype and the efficacy of a vaccination program shall be evaluated. In this case the bacteria can be split up into two groups, one containing the strains against which the vaccine works and the second one containing all other strains.

When the replacing time is not very long compared to the average infectious time the model equations, when using ODEs in the simple case of a static homogeneous population, can look like in equation 1.

$$\begin{aligned}
\dot{S} &= -S \cdot \frac{b_1 \cdot (I_1 + I_{1,2} + I_{2,1}) + b_2 \cdot (I_2 + I_{1,2} + I_{2,1})}{N} + a_1 \cdot I_1 + a_2 \cdot I_2 \\
\dot{I_1} &= b_1 \cdot S \cdot \frac{I_1 + I_{1,2} + I_{2,1}}{N} + d_1 \cdot I_{2,1} - \frac{b_{1,2} \cdot I_1 \cdot I_2}{N} - a_1 \cdot I_1 \\
\dot{I_2} &= b_2 \cdot S \cdot \frac{I_2 + I_{2,1} + I_{1,2}}{N} + d_2 \cdot I_{1,2} - \frac{b_{2,1} \cdot I_2 \cdot I_1}{N} - a_2 \cdot I_2 \\
\dot{I_{1,2}} &= \frac{b_{1,2} \cdot I_1 \cdot I_2}{N} - d_2 \cdot I_{1,2} \\
\dot{I_{2,1}} &= \frac{b_{2,1} \cdot I_2 \cdot I_1}{N} - d_1 \cdot I_{2,1} \\
N &= S + I_1 + I_2 + I_{1,2} + I_{2,1}
\end{aligned} \tag{1}$$

If a person who carries a strain of serotype group 1 meets a person carrying a serotype from group 2 the following events can occur:

- Nobody gets infected with the others strain.
- The carrier of serotype one infects the carrier of serotype two and within *d* days serotype one replaces serotype two. In the meantime the person is infectious with both serotypes.
- The carrier of serotype two infects the carrier of serotype one and within *d* days serotype two replaces serotype one. In the meantime the person is infectious with both serotypes.
- Both persons get infected with the strain of the other person and within *d* days the new strain replaces the previous one.

Depending on the problem it can be necessary to extend this structure to represent different interacting groups or population dynamics like changing age-structure and of course vaccination.

The impact of this structure on the model behavior, especially compared to previous approaches, will now be discussed.

Without vaccination both strains can co-exist even if their infection probabilities differ (Fig. 5). How the model responds to changing infection parameters is discussed later. Varying the starting values shows that the equilibrium is independent on them as long as both serotype groups are not zero at start in which case the model can be reduced to an ordinary SIS-model. Only the parameters for infection, recovery and replacement delay determine the steady state. For many illnesses this behavior fits very well. Especially for

pneumococci this is the best basic structure to describe their epidemiology.

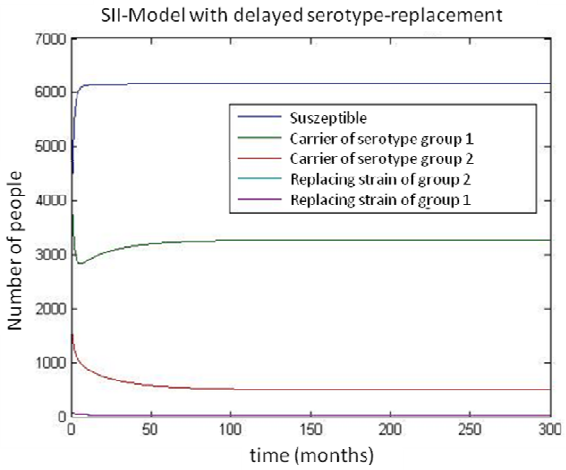

Fig. 5: Behavior of the model approach with delayed serotype replacement

An interesting thing to analyze is how much stronger one serotype group can be before it completely dominates the other one. It is obvious that a serotype group will get extinct with a basic reproduction number lower than 1. To investigate other non-trivial scenarios several different simulations are run. One of them is shown in Fig. 6 using the parameters of tabular 1. The strength of a serotype is represented by its infection probability, though the parameters for replacement have an influence too.

Tab. 1: Parameter values for the simulation shown in Fig. 6

Parameter	Value
Population N	10 000
Recovery probability	1
Infection probability b1	0.71 – 1.7
Infection probability b2	0.71 – 1.7
Overall carrier rate	30%
Proportion of serotype 1	70%
Simulated timeperiod	10 years

As expected both serotype groups are equal when their infection probabilities b1 and b2 are equal. Investigating the other cases shows that raising one probability strengthens the concerned group in a non-linear way. However, the possibility of one serotype group being stronger is not equal to exterminating the other group.

The overall carrier rate is also only dependent on the infection and recovery probabilities. Also the amount of people carrying both strains is only dependent on the replacement and recovery probabilities.

When modeling competitive serotypes this behavior is essential because in nature the spread of an established strain is usually only dependent on its infection probability especially if there was already enough time for the ecosystem to build up accordingly.

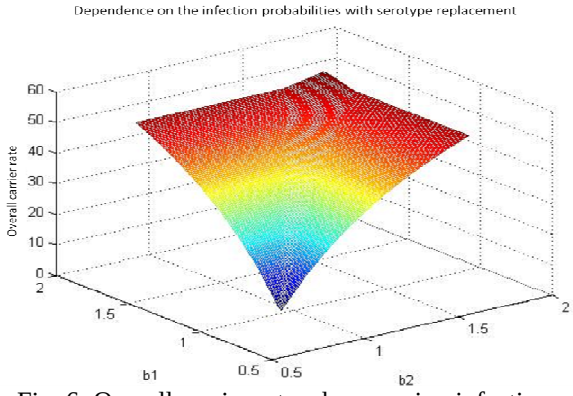

Fig. 6: Overall carrier rate when varying infection probabilities

4 Vaccination and serotype shifting

After having developed systems for representing various serotypes we have to discuss the impact of vaccination programs on the model structure.

4.1 Adding vaccination to the SII-structure

We now assume that we could divide all concerned bacteria strains into two groups whereas vaccination immunizes against the first one. When adding vaccination to the model we realize that people who get infected with a strain of serotype group 2 and are vaccinated need to be treated special because their serotypes cannot be replaced by strains from serotype group 1.

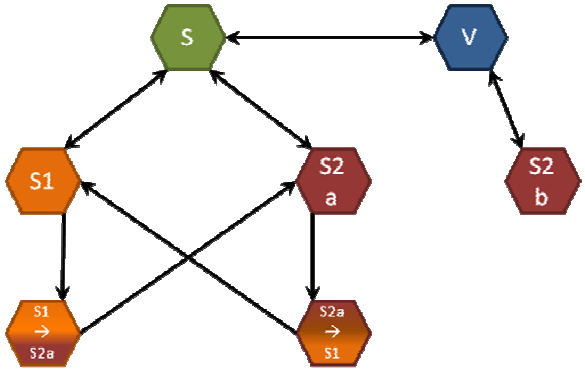

Fig. 7: Meta-structure of the SII-model with vaccination and delayed serotype-replacement

The meta-structure of the model regarding this problem is visualized in Fig. 7. Serotype group 2 (S2) is split up (S2a and S2b). People who are not vaccinated (S) are put into the first group where serotype replacement is possible (S2a). The others are

put into the second category of serotype group 2 where no replacement can occur (S2b).

4.2 Influence of vaccination on serotype distribution

Without modeling several serotypes the decision whether vaccination prevents from infection is given in a probabilistic way. When an infectious contact happens there is a certain chance that the vaccine immunizes against exactly this serotype. Often that is the only possible way adding vaccination to a model, but as soon as more information on pathogens and the vaccine is available, models that are only simulating one bacteria group become very limited. They often cannot represent the impact of vaccination on the spread of the bacteria accurately enough. Regarding scenarios where one person can only carry one strain, like in the case of pneumococci, it is therefore absolutely necessary to consider serotype replacement. When people are immunized against one or a group of serotypes the environment of the pathogens changes. Strains that previously restricted others from infecting certain people are now not as present in the population anymore. The number of possible hosts for other strains therefore increases, so they can spread better. This effect is nonlinear. More hosts and more space for these serotypes could theoretically lead to exponential growth. In real environments resources are limited and therefore this will not happen, but it certainly has an impact on effectiveness evaluations of vaccines and are not observed immediately after its introduction. This effect is known as serotype-shifting and is often not addressed when using too simple models.

5 Results

We examined how different model structures represent serotypes in dynamic models. For each epidemiologic problem considering various serotypes one must consider the epidemiological situation and then decide which approach is appropriate. In this paper we presented methods to model two competitive serotypes …

- without serotype replacement.
- where serotypes can replace each other immediately.
- which can be both carried at the same time from the same person.
- which can replace each other whereas a person can carry both during the replacement time.

Afterwards the model structure is again expanded to additionally provide the possibility to vaccinate people. In this case the impact of modeling two serotype groups is essential. Not regarding serotype shifting leads to overestimating the epidemiological impact of vaccination. Cost-effectiveness analyses showed that models with too simple structures, which do not regard dynamical effects well enough, overestimate the cost-effectiveness of vaccination programs.

6 Conclusion

Epidemiological models can be used for various purposes. Traditionally the spread of an illness is simulated regarding several known influential factors like population structure or herd-immunity.

Recently similar models are also used for cost-effectiveness analyses especially regarding vaccination programs. Lacking information on the interference of different bacteria strains it is only possible to model the pathogen as one homogeneous group. However, as soon as more information on serotypes and the effect of the vaccine on certain strains becomes available, additional dynamic effects can be considered. Therefore first it has to be decided which model structure describes the competition between the serotypes best. Second if there is enough data and/or expertise to identify the model parameters and finally which impact this new model structure has on vaccination.

The proposed structures show how different serotypes can be represented for certain epidemiological assumptions. However, there are still many possibilities for the behavior of competitive serotypes where new model structures have to be developed.

7 References

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