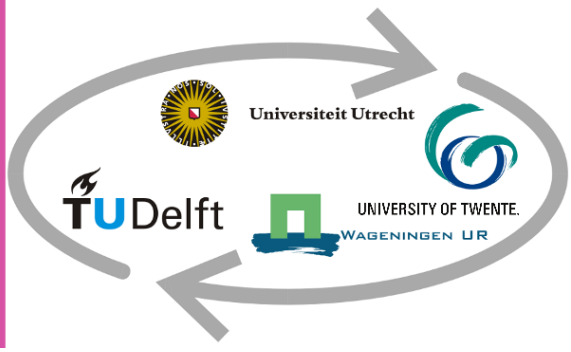
GIMA
Geographical Information Management and Applications

AN AGENT-BASED MODEL TO COMPARE VACCINATION STRATEGIES FOR PERTUSSIS IN THE NETHERLANDS

Sietske Tjalma



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MSc. Thesis
May 2016

Colophon

May 2016

GIMA MSc. Thesis

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ACKNOWLEDGEMENTS / PREFACE

First of all, I would like to extend my sincere gratitude to Ellen-Wien Augustijn for the guidance, support, and motivation provided throughout the research project. Your ability to help me find back a clear and structured overview, when lost in details, has been of great support. Your criticisms enhanced my writing and line of thought, for that I am grateful.

Furthermore, I would like to thank Jasper for motivating me through his never ending, heartfelt support and interest.

Finally, I thank my family and friends for their encouragements and the needed distraction during this period of writing my thesis.

Sietske Tjalma
Utrecht, May 26th 2016

SUMMARY

Since 1996 a resurgence of pertussis has occurred in the Netherlands. Although mostly adolescents and adults are infected, vaccination strategies have focussed on protecting infants. Whereas pertussis is generally harmless for adults, it may be deadly for infected infants. Recently, the strategy of maternal vaccination has been introduced to protect this vulnerable group. There is great charm to the maternal strategy, as vaccinated mothers can transfer antibodies to their children; when unvaccinated, they are often infector of their own children. In this thesis the maternal vaccination strategy is compared with network vaccination, interventions in locations that form important nodes in a network of population movement. Rising immunity to pertussis in these nodes could hypothetically limit the overall diffusion of pertussis, and thus decrease the risk of a population-wide epidemic.

The current pertussis diffusion of the Netherlands is simulated on municipality level by mathematical modelling. The population per municipality is divided in 9 age categories. Disease diffusion is simulated via an extended SEIR model, by turning it into a commuter group model, taking job- and school commuting into account. Contact is defined via a Who Acquires Infection From Whom matrix. Furthermore, a framework is provided for agent-based modelling of the health units who provide vaccinations in the Netherlands. Due to time limitations, vaccination is simulated in a static manner. This is done by increasing the number of immune people with a pre-defined percentage of vaccination, at pre-defined times.

Eight vaccination strategies have been tested in this research. Four one-time intervention strategies for network vaccination: vaccinating in (1) Amsterdam and (2) Rotterdam to see the effect of vaccinating in large cities; vaccinating in (3) Zoetermeer and (4) Haarlemmermeer to see the effect of vaccinating in smaller network cities. Also four strategies are tested for maternal vaccination: (5) routine vaccination of pregnant women in all municipalities; (6) a one-time vaccination intervention of pregnant women in all municipalities; (7) routine vaccination in all municipalities with the same number of vaccinated pregnant women as total vaccinated population in the Zoetermeer network strategy; (8) and routine vaccination in all municipalities with the same number of vaccinated pregnant women as total vaccinated population in the Haarlemmermeer network strategy.

The base model of pertussis diffusion could not be fully validated. The main concern in this validation is the movement of job commuters, which seem to be the cause of unexpected model behavior. Large parts of the model could, however, be validated. The three maternal strategies with the highest vaccination rate resulted in less infections in infants. According to this model, the best way to reduce the total number of infections in the population is by vaccinating a large population in Amsterdam, or Rotterdam, two of the biggest cities of the Netherlands. Vaccinating in smaller amounts, but all over the Netherlands slows pertussis diffusion down, which can buy time to start targeted interventions at non-infected places. With these model outcomes it is not possible to identify one of the vaccination strategies as best. But the model proved the possibility of modelling spatial diffusion of a disease, which shows potential to look further into modelling spatial diffusion of pertussis.

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INTRODUCTION

Pertussis (or whooping cough) is a bacterial infection causing persistent coughing that can last for three to four months. As an infectious disease, it spreads easily by coughs or sneezes of an infected person (RIVM, 2015). Originally pertussis was seen as a childhood disease, nowadays the largest increase in pertussis is seen in adolescents and adults. Although relatively harmless for adults, pertussis can cause brain damage or even death when infants are infected (Van der Maas et al., 2013).

Since 1996, notifications of pertussis have increased in the Netherlands. In several countries, among which the UK, New Zealand, Canada the US, Portugal, and Belgium, a similar resurgence in pertussis is seen (Amirthalingam et al., 2014; Dabrera et al., 2015; Mooi & De Greeff, 2007). Despite high vaccination rates, the infection level of 1996 did not recede, it even reached additional peaks every three to four years (Figure 1.1). Although the resurgence might be partly due to improved methods to confirm diagnosis and increased awareness among health professionals, reasons of the resurgence are not fully understood (Amirthalingam et al., 2014).

In the Netherlands strategies to reduce pertussis prevalence focus mostly on vulnerable infants (Van der Maas et al., 2013). Currently Dutch infants receive their first vaccinations after two, three, and four months, only becoming immune a few weeks after the third injection (Mooi & De Greeff, 2007). Infants younger than 5 to 7 months are susceptible to pertussis, this is in line with the observed morbidity and mortality rates, that are highest among infants in this age category (Mooi & De Greeff, 2007).

Various epidemiologic studies have researched ways to reduce pertussis, and to protect the vulnerable infants. One of the most investigated strategies to combat the disease has been maternal vaccination, immunizing pregnant women. The charm of this vaccination strategy is that it limits the risk of infants being infected in two ways: the mother is no longer able to infect her child, and additionally the mother's antibodies are passed on to the infant through the placenta and breastfeeding (Mooi & De Greeff, 2007; Dabrera et al., 2015).

But what if an epidemic can be prevented altogether? Mooi & De Greeff (2007) claim that this might be acchieved by decreasing the circulation of the bacteria that cause pertussis. The movement of humans (daily commuting, incidental movement) is the ultimate cause of the difussion of pertussis to new (previously uninfected) locations. By looking at network structures, tactical hubs, crucial to the difussion of pertussis, could theoretically be identified. Exstensive vaccination in such tactical hotspots could stop the difussion of a disease (Colizza & Vespignani, 2008).

In this thesis the two vaccination strategies are studied by mathematical and agent-based modelling. As will be argued in section 2.3 and 2.4, both strategies have their pro's and con's. Although vaccinating in network hubs is most effective in reducing the total number of pertussis cases, the strategy of vaccinating mothers protects the most vulberable and relevant group.

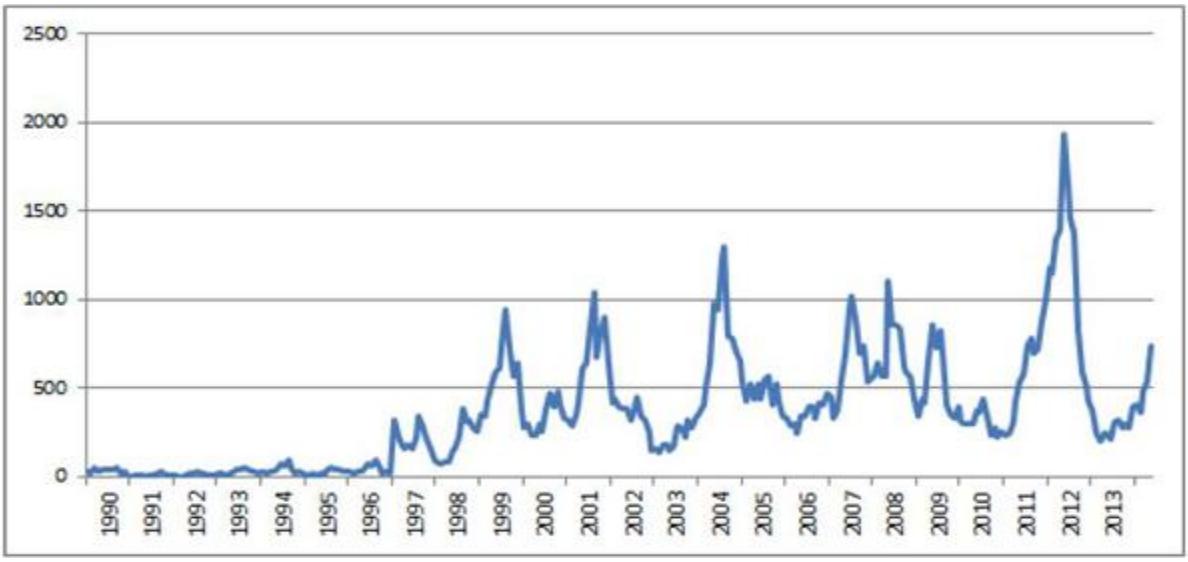


Figure 1.1: *Number of pertussis notifications in the Netherlands per month. (Medischcontact, 2014)*

1.1 Objectives and research questions

The main goal of this research is to investigate alternative interventions to decrease the spread of pertussis in the Netherlands via agent-based modelling. A comparison will be made between vaccination of pregnant women to vaccinating in certain municipalities that form important nodes in a network, and the effects on the spread of the disease will be analyzed. The main question of this research is:

What are the effects of maternal vaccination and network vaccination on the number of pertussis cases, and on the spatial diffusion of pertussis, in the Netherlands? And to what extent can one of these vaccination strategies can be identified as best?

To be able to reach this goal several objectives with sub questions are identified:

1. Develop a model simulating the spread of pertussis in the Netherlands.
    - Which pertussis diffusion models exist already?
    - How can disease diffusion be modelled taking advantage of existing model components?
    - How can commuting be modelled taking advantage of existing model components?
    - How can the behavior of health units be modelled?
    - Which input parameters are best suited for the pertussis model in the Netherlands? (Scale, time-span, time steps, disease spreading factors, behavior of population)?

2. Verify the pattern of the model with known pertussis patterns in the Netherlands from previous years.
    - What data about pertussis in the Netherlands are available?
    - Is the model able to represent the epidemic curve of pertussis?

3. Evaluate the impact of the maternal vaccination strategy on the spread of pertussis using the developed simulation model.

- How can immunization of pregnant women be modelled?
- What are the effects on the spread of pertussis when pregnant women are vaccinated?

4. Evaluate the impact of vaccination in commuter cities using the developed simulation model

- What is the commuting behavior of Dutch citizens?
- What are the effects on the spread of pertussis when the population of certain 'commuter municipalities' are vaccinated?

5. Evaluate and compare results of the two different vaccination methods using long term predictions of 20 to 40 years.

- When comparing these two methods, to what extent can one of the two methods be identified as best in reducing the spread of the disease?

1.2 Scope

This research will only look at the effects of the vaccination strategies on the spread of pertussis in the Netherlands. The fact whether the vaccination strategies are achievable in terms of practical aspects or in terms of costs will not be considered.

The model will be designed to run for many years. To be able to verify the model, the starting year will be 1996, the moment when pertussis notifications started to rise, and the end year will be 2014, the year until which data about pertussis notifications is available. After these calibration years the model will be run for another 20 to 40 years. The goal of the model is to see what the long term effects of the vaccination strategies are. A model will never be an exact representation of the reality, hence there will be a difference between the number of infected people in the model and in reality. The focus will be on general trends in the number of pertussis cases and spatial variation of disease occurrence. The spatial scale of the model will be municipality level.

1.3 Innovation aimed at

Modelling the diffusion of a disease, or more specific of pertussis, is not something that has not been done before. Several international examples can be found in Black & McKane (2010), Hethcote (1999) and Van Rie & Hethcote (2004). Also models simulating pertussis in the Netherlands have been created (De Vries et al., 2010; Girmay, 2012; Rozenbaum et al., 2012; Van Boven et al., 2000). However, the focus in these researches is almost never on the geographic spread of the disease. What is new in this research is that the impact of interventions is tested. This is done by simulating the heterogeneous behavior of health units in an agent-based model.

In the Netherlands each municipality should in theory have a municipal health unit (in Dutch: Gemeentelijke Gezondheidsdienst; GGD). To make the services more efficient many health units have merged, resulting in 25 health regions in 2014, for 403 municipalities (Figure 1.2). The health units are responsible for general preventive care, public safety and crisis management, advice, indexing and information services, and the medical reception of asylum seekers (RIVM, 2014a). Among these responsibilities is also vaccination to reduce the number of infective disease cases.

A national program exists for pertussis vaccination. The health units are instructed from a higher level to ensure a coherent approach in all regions of the Netherlands. There is a difference in how active the health units are. By active is meant for example the amount of effort they put in promoting pertussis vaccination, or spreading information about the symptoms of a disease. Some health units spend time on finding epi-links: If someone is diagnosed with pertussis whom else might this person have infected? While other health units do not do this (RIVM, 2016). Therefore, it can be said that the Dutch health units have heterogeneous behavior. Since the health units are the institutions that provide vaccinations, also for pertussis, it is of interest to model the heterogeneous behavior of these health units to create a more realistic model of pertussis diffusion in the Netherlands.

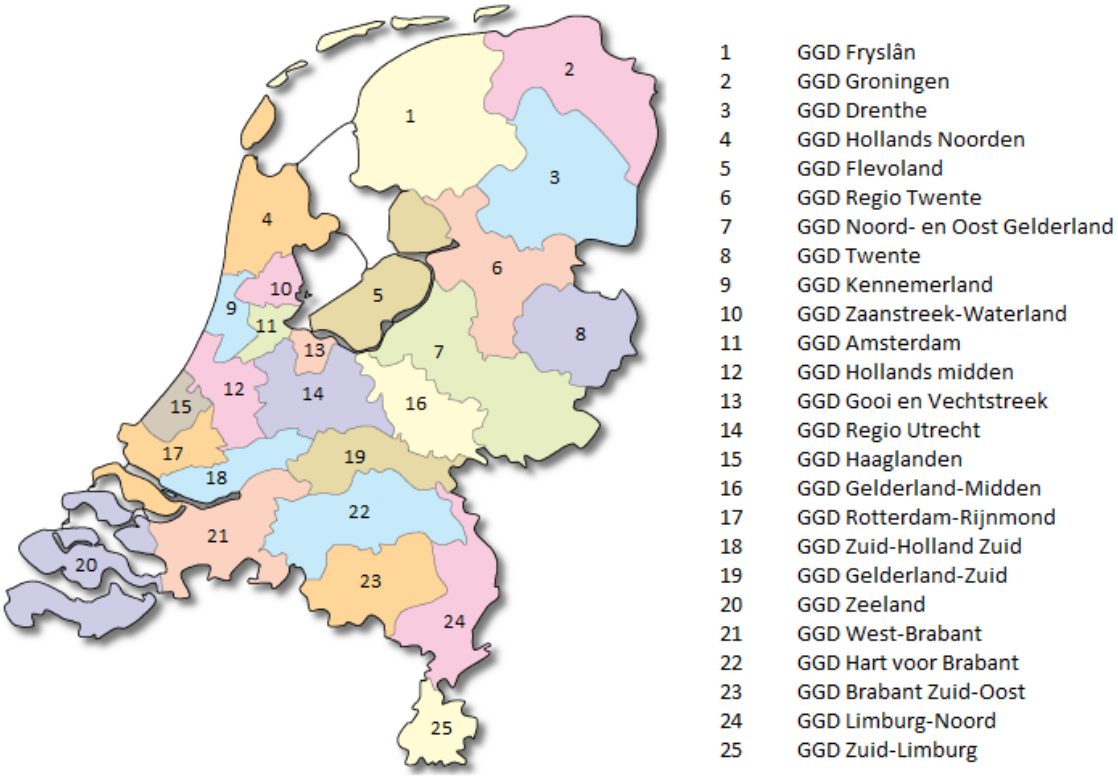


Figure 1.2: *The service regions of the 25 health units (GGDs) in the Netherlands. (RIVM, 2014a)*

2 THEORETICAL BACKGROUND

In this chapter some general theories and ideas that are of interest for the research are elaborated upon. The chapter is structured as follows: In section 2.1 the characteristics of pertussis will be described. Subsequently there will be looked into how a disease diffuses through a population in section 2.2. Furthermore, there will be touched upon different vaccination strategies. Maternal vaccination in section 2.3 and network based vaccination in section 2.4.

2.1 Pertussis

Pertussis is caused by the bacteria Bortadella pertussis (RIVM, 2011). Initially pertussis symptoms are comparable to those of a common cold. Sometimes a fever is a symptom as well. After one - or two weeks typical pertussis symptoms arise; severe coughing fits followed by a high pitched whoop or gasp. Patients can get stuffy or have to vomit. These coughing fits can last for weeks, after which they change to a less intense coughing that can last for another few weeks. The coughing can make pertussis patients exhausted (RIVM, 2014c).

Pertussis can lead to complications such as ear infections and nosebleeds. In more than 20 percent of pertussis cases the patient gets pneumonia, in 3 percent of the cases febrile seizures and in 1 percent of pertussis cases a patient gets brain tissue inflammation. Pertussis can also cause permanent damage to the lung tissue. Pertussis is especially severe for young children, and can be deadly for infants (RIVM, 2014c).

Pertussis is treatable with antibiotics, if the treatment is started in an early stage. The antibiotics do not make the disease less severe nor shorten the duration of the disease. Treatment can only decrease the infectiousness of a patient (RIVM, 2014c). The most infectious period is normally in the first four weeks after symptoms have started. After antibiotics, the infectious period is reduced to 5 to 7 days. At the moment of pertussis diagnosis the most infectious period has often passed already, and infection of somebody else might have happened before this time (RIVM, 2011).

Vaccination is the best method, since it prevents people from getting infected with pertussis. In the Netherlands pertussis vaccination has been part of the standard childhood vaccinations since 1953. Before the introduction of this vaccination 200 children died yearly because of pertussis, after introduction of vaccination this number decreased to approximately one each year (RIVM, 2014c). Vaccination protects for 4 to 12 years (RIVM, 2011).

Pertussis is known to have an incubation time of 7 to 10 days, with a maximum of 21 days. An infectious period of around 14 days, with a maximum of 21 days. Once recovered from pertussis, a person gets immune to the disease for about 4 to 20 years (RIVM, 2011).

2.2 Disease diffusion

Diffusion is the process in which a phenomenon spreads from one place to another; this phenomenon can be, among others, information, a material or a disease. Different processes of diffusion are identified by Cliff (1981). He distinguishes between expansion diffusion and relocation diffusion. Expansion diffusion is the process in which the item being diffused remains, and often intensifies in the region of origin, but new, often neighbouring, areas are also being occupied by the phenomenon in subsequent time periods. Relocation diffusion is the process in which the phenomenon leaves the area of origin and moves to new areas (Figure 2.1) (Cliff, 1981).

Expansion diffusion can occur in two ways; hierarchical diffusion and contagious diffusion (Figure 2.1). Hierarchical diffusion describes transmission through an ordered sequence of classes or places, for example innovations that start in big cities that are adopted later in remote villages. Contagious diffusion depends on direct contacts. This diffusion process is typical for the spread of infectious diseases, like pertussis, from person to person. Hierarchical diffusion in diseases is driven by long distance commuting between cities, and shorter distance commuting between cities and surrounding villages. Contagious diffusion is influenced by distance. Nearby individuals or regions have higher probability of contact than remote individuals or regions, hence contagious spread tends to occur from the source region outwards (Cliff, 1981).

Even though contagious spread is categorised as expansion diffusion, the spread of pertussis can better be seen as a combination of expansion and relocation diffusion (Figure 2.1). A disease is introduced in a population at a certain location; from there it expands to different regions. At a certain point, however, the disease dies out in the origin location due to a lack of susceptible people in the population, because people get immune after recovering from pertussis. This contradicts with the intensification of the phenomenon in the origin location for expansion diffusion as Cliff (1981) states.

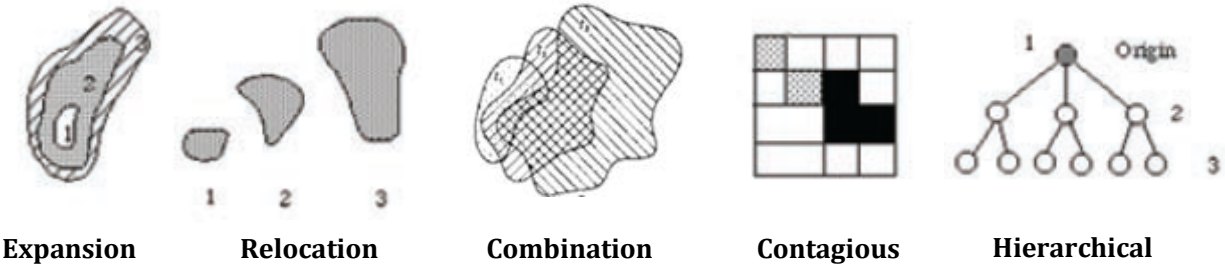


Figure 2.1: *Different processes of diffusion. (Adapted from Cliff, 1981)*

2.3 Maternal vaccination

The philosophy behind maternal vaccination is that infants are protected against pertussis in the first few months of their life, when they are too young to be vaccinated. This can be achieved in different ways. First by making the mother immune to pertussis. Mothers are frequently identified as the source of infection for infants. By immunizing pregnant women, the risk of infants being infected by their own mother is eliminated (Dabrera et al., 2015). Besides limiting the risk of an infant being infected with pertussis by their own mother, it is also believed that vaccinating pregnant women can lead to (partial) immunization of new-born babies. Infants that are breastfed by a vaccinated woman passively acquire antibodies from breastmilk (Mooi & De Greeff, 2007). Furthermore, Dabrera et al. (2015) state that there is evidence that antibodies are passed on from mother to unborn child via the placenta. Vaccinating during pregnancy boosts antibody levels in the mother, which are transferred to the baby via the placenta.

Partly based on this evidence, a programme has started in the UK that offers pertussis vaccination to pregnant women (Dabrera et al., 2015). Also in the USA, New Zealand and Belgium vaccination is offered to pregnant women. From these last three countries findings about vaccination effectiveness are not available yet (Amirthalingam et al., 2014). Findings of the UK programme are available. In September 2012, the UK Department of Health recommended a temporary programme

to offer a combination vaccine of different diseases, including pertussis, to all women between 28 and 38 weeks of pregnancy. The programme reached a coverage of almost 60 percent. Furthermore, a vaccination effectiveness of 91 percent is seen in infants younger than three months when vaccination of the mother happens at least 7 days before birth. When comparing infant deaths, a fall of 79 percent was observed when comparing numbers from 2012 and 2013 (Amirthalingam et al., 2014). The high percentage of vaccination effectiveness is probably due to a combination of trans-placental antibody transfer, and the mother not infecting her baby. The results are also in line with a clinical trial that showed that vaccination during pregnancy leads to significantly higher levels of antibodies at birth in both mothers and infants (Dabrera et al., 2015). The first results for maternal vaccination are thus promising.

Not all countries recommend maternal pertussis vaccination. Limited evidence is available about the method, and concerns about interference with childhood vaccination exists. Pre-existing antibodies, gained in the embryotic phase, might affect the infant's immune response to vaccination at a later stage. Furthermore, little is known about side-effects in mother and child. On the other hand, maternal vaccination has shown to be effective and safe for tetanus toxoids over longer periods of time (Mooi & De Greeff, 2007). Besides this, a major advantage of maternal vaccination is the accessibility of the target group. Pregnant women and mothers with infants regularly visit health-care centres (Mooi & De Greeff, 2007).

In January 2014 a study has started in the Netherlands that is being performed by the Centre Infectious Disease Control of the National Institute for Public Health and Environment (Rijksinstituut voor Volksgezondheid en Milieu; RIVM). In this study 116 pregnant women participate, the effects of maternal pertussis vaccination on mother and child are being investigated (RIVM, 2014b). As of December 2015 the Dutch Health Council made public in newspapers and journals that they advise pregnant women to get vaccinated against pertussis (Effting, de Volkskrant, 2015).

Whether maternal vaccination is a successful method in reducing pertussis cases is largely dependent on the number of pregnant women that want to participate. It is unclear who will be paying for the vaccination if maternal vaccination is going to be the new strategy in the Netherlands. If the women have to pay for the vaccination themselves, they might see an extra reason not to get the vaccination. If the government pays, they might be more willing. Furthermore, there might be women with a religious background that do not want to get vaccinated. In the Netherlands vaccination rates in religious towns are lower than in non-religious towns (RIVM, 2013). The infants of those mothers that do get vaccinated will, however, be protected.

2.4 Network based vaccination

By decreasing the circulation of the bacteria that causes pertussis, an epidemic outbreak of a disease might be prevented (Mooi & De Greeff, 2007). Miller & Hyman (2007) consider information about contact network structures highly relevant for improving vaccination strategies. Network based vaccination might lead to so-called herd immunity. Only when the vaccination rate is high, herd immunity can be reached. Herd immunity is the effect that when many people are vaccinated, people without vaccination will not get infected, since everybody around them is immune to the disease.

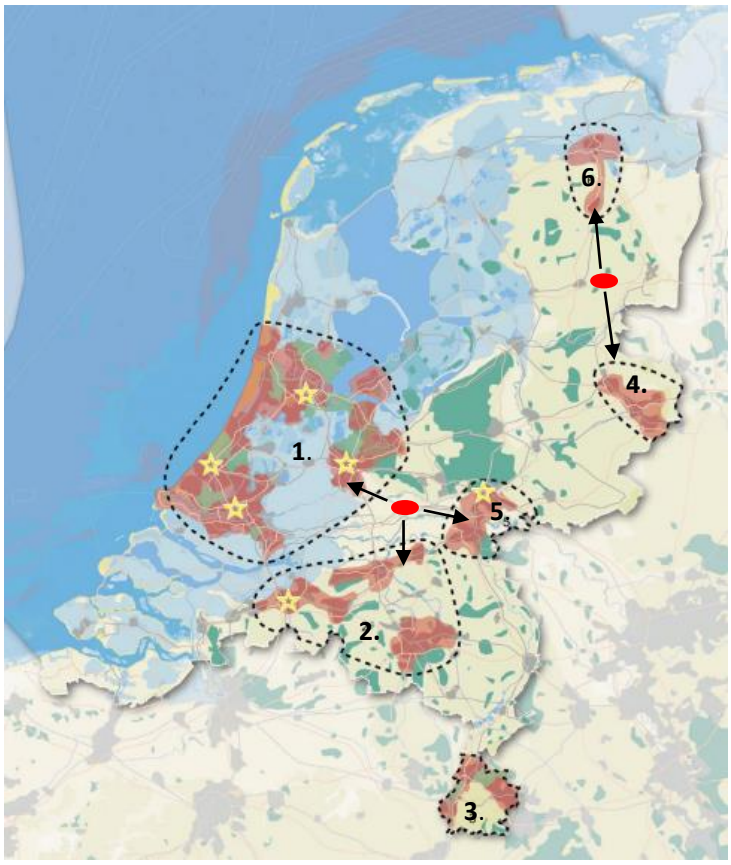
Most logical would be to vaccinate those people that have the most contacts, such as bus drivers or school teachers. However, if these persons' contacts also have many contacts the impact of vaccinating someone with many contacts is reduced. An easier method would be to vaccinate

those people that visit the most locations. This might be less effective, but is easier to measure and still shown to be more effective than random vaccination (Miller & Hyman, 2007).

Touching upon localizing people that visit most locations, is looking at commuting; daily movements of people going to work or school. Data about commuting has been widely used in spatial mobility models, however, according to Charaudeau et al. (2014), little research has been done about whether commuting explains the spatial spread of epidemics. In their research Charaudeau et al. (2014) show that commuting data does explain the spread of influenza in populations. This result can be generalized to other diseases that diffuse in similar ways as influenza, namely by drops of coughing or sneezing by an infected person.

Even though network based models are increasingly used to forecast the spread of infectious diseases (Colizza & Vespignani, 2008), it is doubted if travel based vaccination strategies are better than general other strategies, such as vaccinating risk groups (Miller & Hyman, 2007). Furthermore, it is often difficult to determine the exact network structure, since not all data about commuting or human interaction are available (Lee et al., 2012). Since computational power is increasing, however, it becomes easier to acquire more data about network structures, and use these data in a model. This can result in more realistic data driven models (Colizza & Vespignani, 2008). Dalziel et al. (2013) see the importance of network based models as input for vaccination strategies. Since the urbanization rate of the world continues to rise past 50 percent.

In this research the contact among different cities is seen as most important, especially cities that link different urban networks. In the Netherlands six national urban networks were identified in 2005 in a governmental spatial planning report (Ministerie van VROM et al., 2005) (Figure 2.2). These urban zones consist of separate cities that are strongly connected to each other, however still distinguishable from each other. By forming an urban network of these cities it was hoped that a strong economic, infrastructural and knowledge partnership between these connected cities is formed (Ministerie van VROM et al., 2005). It can be assumed that there is a lot of commuting within and between these urban systems. The commuting within these urban networks is, however not of great importance. It is more interesting to look at commuting between two or more urban networks (Figure 2.2). Commuter flows between different urban networks can make a disease spread easily to a whole new region in the Netherlands. If cities can be identified that form a link between two or more urban networks, vaccination strategies targeting those cities can potentially limit the diffusion of a disease in the Netherlands.



National Urban Networks

1. Randstad Holland
2. Brabantstad
3. Zuid-Limburg
4. Twente
5. Arnhem – Nijmegen
6. Groningen - Assen

Hypothetical city
Hypothetical commuter flows

Figure 2.2: *National Urban Networks of the Netherlands. (Adapted from: Ministerie van VROM et al., 2005)*

3 METHODOLOGY

In this chapter the methodology of the research will be elaborated upon. First some general theories and literature about disease- and commuting modelling will be set out to provide a base for the methodology in section 3.1. Subsequently these theories will be used to explain the methodology for creating the model of this research in section 3.2 Conceptual model.

3.1 Theories of modelling

In this research a model over time will be created to predict the diffusion of pertussis, and different vaccination strategies will be compared to find a possible idealisation of reality for reducing pertussis cases in the Netherlands. The model will consist of a combination of mathematical modelling and agent-based modelling, which will be explained in the following sections.

3.1.1 MATHEMATICAL MODELLING

Mathematical models are built using formulas, symbols and integrals to communicate concepts, ideas and arguments. Traditionally mathematical models have been the golden standard in scientific modelling, and they still are being used in most professional fields. One of the core characteristics of mathematical models is determinism. Mathematical models are formulated in equations, and once the initial conditions are fixed, equations can be calculated for different moments in time, resulting in quantities that tell us something about the probability of an event taking place, or the deviation of actual behavior from mean behavior. Mathematics allows extracting deterministic features from random events in nature. Even though randomness and chance can be implemented in a mathematical model, true randomness is rare in these models (Barnes & Chu, 2010).

Besides the lack of stochastics in mathematical modelling, there are some other aspects that motivated researchers to start searching to find different ways of modelling. One of these aspects is heterogeneity. A system is heterogeneous when it consists of different parts that do not necessarily behave according to the same rules. Social behavior is difficult to capture in a strictly mathematical model. Contacts between humans or animals are not easy to define in equations. As soon as more complex features need to be modelled, problems arise when using mere mathematical models. This is, however, exactly the beauty of these models at the same time. Mathematical models can be used to derive very general relationships between variables, and are often a good starting point when wanting to model something. However, the simplicity of mathematical models can be too high to be able to represent a real life situation in a model. Therefore, other computer models have been created for more complex situations, one of which is agent-based modelling (Barnes & Chu, 2010).

3.1.2 AGENT BASED MODELLING

Opposed to mathematical models, agent-based models (ABMs) are extremely useful when modelling heterogeneous, random and social interactive phenomena. The principle of an ABM is exactly to represent the heterogeneous parts of a system, instead of grasping the general behavior of a system. The basic principle of an ABM is that the behavior of an agent is traced over time and observed (Barnes & Chu, 2010). An ABM typically consists of three elements (Barnes & Chu, 2010; Macal & North, 2010):

1. A set of agents
2. A set of agent relationships and methods of interaction
3. The agents' environments

Agents are self-contained, modular and uniquely identifiable, autonomous and self-directed, social beings that have a state that varies over time. The behavior of agents depends on the rules that are defined in the model, often formulated as if-then statements (Barnes & Chu, 2010). Agents are goal directed, and agents can learn and adapt their behavior, when they are intelligent agents. Agents are able to interact with other agents, but they can also interact with the environment (Macal & North, 2010). An agent must be embedded in some type of environment. In the simplest case, this environment is just an empty space without inherent geometry. The environment can also be a detailed representation of the real-world, including for example networks or height maps (Barnes & Chu, 2010). An ABM thus consists of agents that behave according to a defined set of rules and characteristics, these agents can have certain relationships to each other or to the environments and interact accordingly (Figure 3.1) (Macal & North, 2010).

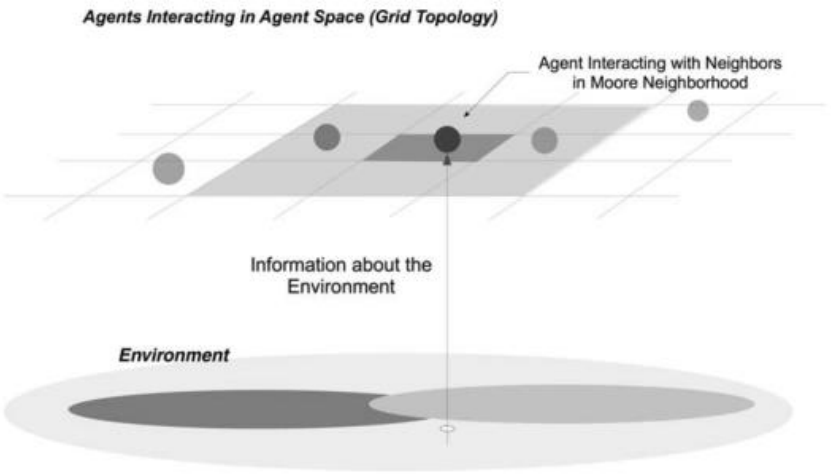


Figure 3.1: *The structure of an agent-based model. (Macal & North, 2010)*

The connection of the agents to each other is termed ABM topology or connectedness. The connectedness can be defined by a grid (Figure 3.1), this is also called cellular automata, by Euclidean 2D- or 3D space, or by a social network topology. How the agents are connected to each other defines a great deal of the model. Since agents are often restricted to interacting only within a certain distance, or network topology (Macal & North, 2010).

An agent-based model is better able to represent heterogeneity and stochastic events than mathematical models. ABMs make use of rule-based approaches; they can also contain mathematical equations. These will never be used to define the behavior of the system as a whole; they can, however, be used to determine individual parts and their interactions (Barnes & Chu, 2010).

3.1.3 HYBRID MODELLING

Whereas there are agent-based models and mathematical models, there are also models that combine these two, or more, methods. Such models are called hybrid models. Agent-based models are good in simulating real-world phenomena in a very detailed way. They are explicitly suitable to

represent processes at the local level. Mathematical models on the other hand are best in simulating the more generic, large scale, level. When combining these two methods the best of both can be used (Bobashev et al., 2007).

Since agent-based models are most suited for bottom up simulations and mathematical models for top down simulations it is often seen that these two strategies are combined in a model that simulates different hierarchical systems. The agent-based model part can be used to simulate locally heterogeneous interacting components, the mathematical part to simulate the higher levels. The different parts interact with each other via feedback loops. The results of a certain level are input for another level (Figure 3.2) (Parrott, 2011). The agent-based approach does not necessarily have to be used to simulate the lowest level in hierarchy. Agent-based modelling should be used to represent the heterogeneous behavior in a model, no matter on which level.

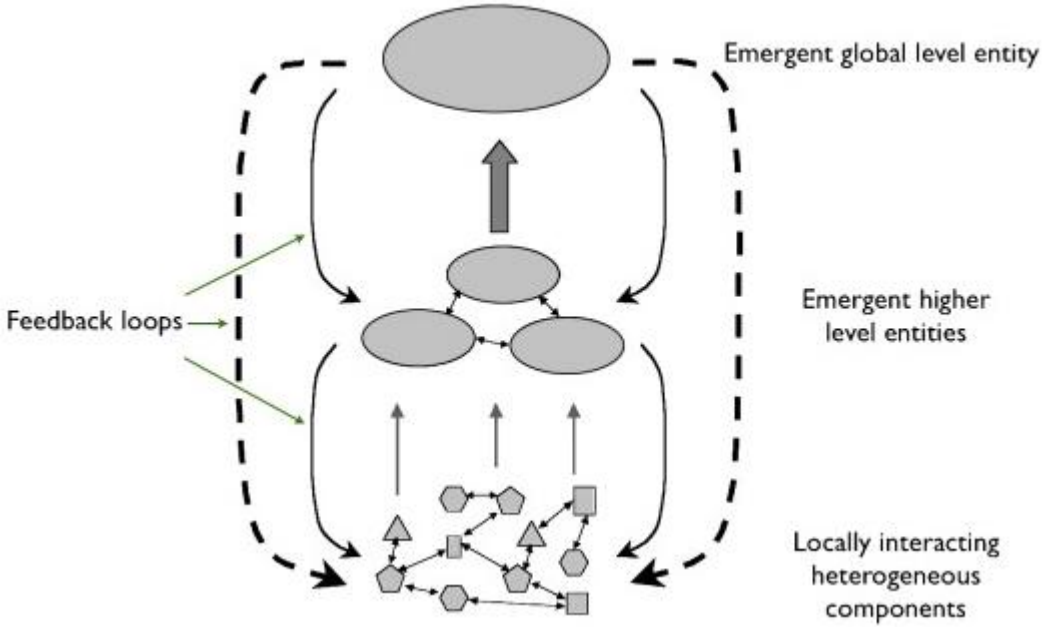


Figure 3.2: *Different hierarchical levels with feedback loops. (Parrott, 2011)*

3.1.4 MODELLING DISEASE DIFFUSION

There are many ways in which a disease can be simulated. However, the SIR model is prominent among mathematical models of epidemics. The SIR model was originally created in 1927 by Kermack and McKendrick. The model assumes that a population consists of three subgroups: Healthy individuals who are susceptible (S) to a disease, the already infected (I) individuals who can transmit the disease to healthy individuals, and the individuals who are removed (R) from the cycle, they can either be recovered from the disease and have gained immunity, be immune due to vaccination, not being susceptible to a certain disease, or through their demise (Satsuma et al., 2004). The SIR model can be formulated in the following equations (Hethcote, 2000):

$$\begin{aligned} dS/dt &= -\beta SI/N \\ dI/dt &= -\beta SI/N - \gamma I \\ dR/dt &= \gamma I \end{aligned} \tag{3.1}$$

Where N is the total population and $S(t) + I(t) + R(t) = N$. βSI is the number of adequate contacts of a susceptible person with an infected person per unit time, adequate for the disease to transmit (or the contact rate). Infected individuals recover with the constant recovery rate γ.

The SIR model can be extended by adding more disease specific classes, such as a latent period, or by making it more realistic by adding contact networks. The following section will explain the extended SIR models that are of relevance for this research.

3.1.4.1 MSEIR model

The SIR model has been used by many researchers, for modelling different kind of diseases. A researcher that has done extensive research about modelling pertussis according to the SIR model is Herbert W. Hethcote. Hethcote (2000) describes an extended version of the SIR model; the MSEIR model (Figure 3.3). The class M contains infants that have passive immunity due to maternal vaccination, when this immunity wanes the infant moves to the susceptible class S. In this class are also the infants of whom the mothers were not vaccinated, and individuals who are not immune (anymore) to pertussis. When a susceptible individual gets in contact with an infectious person, and the disease is transmitted, the individual enters class E. The individual is infected, however not yet infectious (the latent or exposed period). After the latent period, the individual moves to the infectious class I. When this infectious period ends, the individual moves to class R, recovered from pertussis, and immune for a certain amount of time, before the individual moves back to the susceptible class.

Different variations on the MSEIR model can be used, depending on the disease one wants to model. The classes M and E are often omitted since they are not crucial for the susceptible-infective interaction. For different epidemiological models MSEIRS, SEIR, SEIRS, SIR, SIRS, SEI, SEIS, SI and SIS models have been used (Hethcote, 2000). In this research the SEIR model will be used to model the spread of pertussis. Pertussis is known to have a latent period of 7 to 10 days (RIVM, 2015). In these days a person may already be infected with pertussis, but is not able to infect other persons with the disease yet. This exposed period is thus important to take into account in the model.

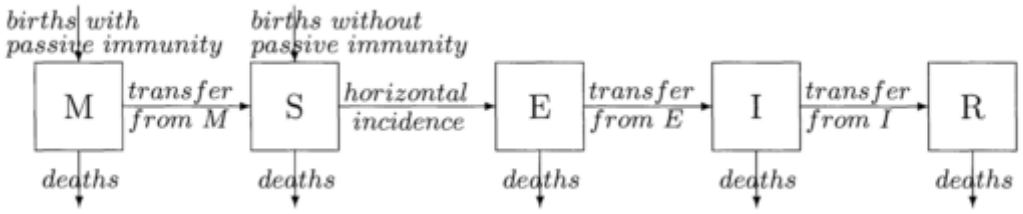


Figure 3.3: *The general transfer diagram for the MSEIR model. (Hethcote, 2000)*

The SEIR model in its most basic form can be described according to the following system of differential equations (Van den Driessche, 2008).

$$\begin{aligned} dS/dt &= b - \beta SI - pbE - qbI - dS \\ dE/dt &= \beta SI + pbE + qbI - (\epsilon + d)E \\ dI/dt &= \epsilon E - (\gamma + d)I \\ dR/dt &= \gamma I - dR \end{aligned} \tag{3.2}$$

Where S, E, I, and R denote the fractions of the population that are susceptible, exposed, infected and recovered. In this model the birth rate is denoted by b and death rate by d. They are often assumed to be constant so that $b = d$. Horizontal incidence is assumed to be of the bilinear mass action form βSI (the contact rate). A fraction p of the offspring from exposed individuals and a fraction q of the offspring from infective individuals are born into the exposed compartment. Thus the term $pbE + qbI$ is subtracted from the susceptible department, and added to the exposed compartment. Exposed individuals become infective with rate constant ϵ, and infected individuals recover with constant γ (Van den Driessche, 2008).

An important aspect in many epidemiological models is the basic reproduction number (R_0). This basic reproduction number can be defined as the average number of secondary infections produced, when one infected individual is introduced in a fully susceptible population. For many epidemiological models an infection can only get started in a fully susceptible population when $R_0 > 1$, this is also the case for pertussis models. The basic reproduction number is thus often seen as the threshold quantity, it defines when an infection can invade a new population (Hethcote, 2000). The basic reproduction number of this SEIR model with the same birth and death rate can be defined as (Van den Driessche, 2008):

$$R_0 = \frac{\beta\epsilon + pb(\gamma + b) + qb\epsilon}{(\epsilon + b)(\gamma + b)} \tag{3.3}$$

3.1.4.2 Heterogeneous population groups

The above explained equations form the mathematical basis for the spread of a disease. To make the model more realistic it can be extended by looking at population groups and contact networks. What is often seen in disease modelling is a heterogeneous population divided in two or more groups. Often these groups are based on different species (in animals or plants) or age groups (in humans) (e.g. Del Valle et al., 2007; Hethcote, 1997, 2000; Rock et al., 2014). Instead of having just the disease states SIR, now each population group has the three disease states. SIR diagrams, and its equations, are logically different in this case. In Figure 3.4 the disease diagram of a SIR model with two age groups (children C and adults A) is shown. Susceptible individuals can be infected (β) by an infectious person in their own age group, but also by an infectious person in the other age group. Furthermore, over time people change from the younger to the older age group (L), while keeping their disease status S, I or R. Births (b) are happening only in the youngest age group. Death (d) is mostly assumed to happen in all age groups (Rock et al., 2014).

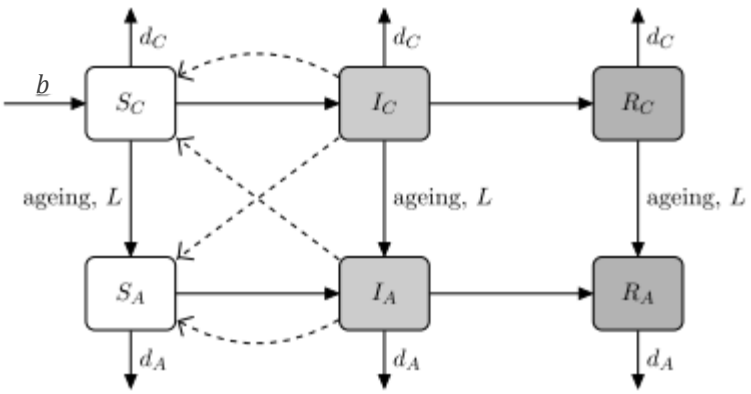


Figure 3.4: *SIR diagram with two age groups. (Rock et al., 2014)*

Following the SIR diagram for a population divided in two age groups the following equations can be defined for the spread of the disease (Rock et al., 2014):

$$\begin{aligned}
\frac{dS_C}{dt} &= b - \beta_{CC} S_C I_C - \beta_{CA} S_C I_A - L S_C - d_C S_C \\
\frac{dI_C}{dt} &= \beta_{CC} S_C I_C + \beta_{CA} S_C I_A - \gamma I_C - L I_C - d_C I_C \\
\frac{dR_C}{dt} &= \gamma I_C - L R_C - d_C R_C \\
\frac{dS_A}{dt} &= -\beta_{AC} S_A I_C - \beta_{AA} S_A I_A + L S_C - d_A S_A \\
\frac{dI_A}{dt} &= \beta_{AC} S_A I_C + \beta_{AA} S_A I_A - \gamma I_A + L I_C - d_A I_A \\
\frac{dR_A}{dt} &= \gamma I_A + L R_C - d_A R_A
\end{aligned} \tag{3.4}$$

3.1.4.3 Meta-population modelling

Meta-population models assume that a population is structured and localized in relatively isolated and discrete patches that are connected by some degree of migration. These isolated patches are defined as subpopulations. The model can thus be used to understand the spread of a disease in a country, where different cities or states function as subpopulations. The arrival of an infection in a subpopulation is determined by mobility processes, such as commuting, between the different subpopulations (Colizza & Vespignani, 2008).

A disease is transmitted within each subpopulation and between different subpopulations. Within cities the regular SIR model (or a variance on this model) can be used. For modelling the spread of a disease between different subpopulations some extra input is needed, such as temporary demographic movements. Assuming that each person has a permanent home population, one can write the number of people whose home location is the 1st area but are temporarily located in the 2nd area as $N_{21}(t)$, with $S_{21}(t)$ and $I_{21}(t)$ for the number of susceptible - and infectious individuals. Movement can be modelled by using matrices with rates of individuals leaving the home location 1, commuting to location 2 (l_{21}), and the rate of return (r_{21}) (Figure 3.5, Equation 3.5) (Rock et al., 2014).

$$\begin{aligned}
\frac{dN_{22}}{dt} &= -\sum_{1} l_{12} N_{22}(t) + \sum_{1} r_{12} N_{12}\,(t) \\
\frac{dN_{21}}{dt} &= l_{21} N_{11}(t) - r_{21} N_{21}\,(t)
\end{aligned} \tag{3.5}$$

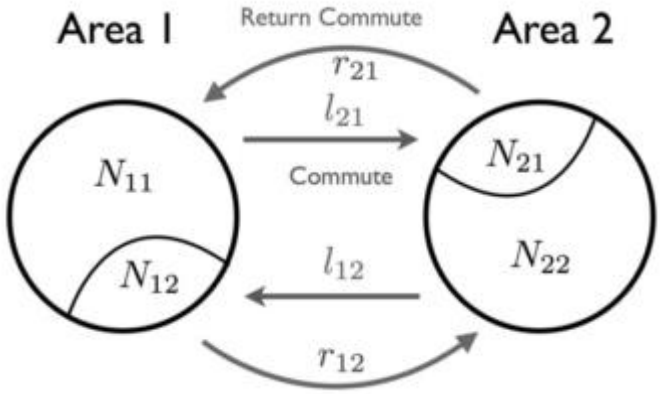


Figure 3.5: *Schematic representation of a two commuter group model. (Rock et al., 2014)*

Generation of new infected people from the S_{21} group can be modelled as frequency-dependent transmission between all people currently in the 1st location. Hence, the force of infection, for a basic SIR model, is (Rock et al., 2014):

$$\lambda_{21}(t) = \beta \frac{\sum_1 I_{21}(t)}{\sum_1 N_{21}(t)} \tag{3.6}$$

3.1.5 NETWORK MODELLING

The diffusion of a disease is caused by interaction of people. To make a disease model more realistic it is helpful to take contact networks into account. Daily commuting is found to be of importance in the spread of an infectious disease (Charaudeau et al., 2014).

Explaining network modelling can best be started at explaining the graph theory of Euler, first touched upon in 1736. This theory gained new popularity in the 1960s, when it was further developed by Erdős and Rényi (Montis et al., 2010). In the graph theory a network consists of nodes (or vertices) and edges (or links). The links form the connections between the nodes. These connections can be directed or undirected. A graph can be depicted as follows (Gross & Yellen, 2004, p.2):

A graph $G = (V, E)$ consists of two sets of V and E.

1. The elements of V are called vertices/nodes.
2. The elements of E are called edges/links.
3. Each edge has a set of one or two vertices associated to it, which are called the endpoints. An edge is said to join its endpoints.

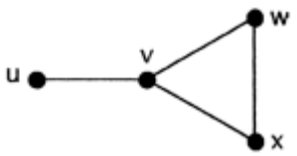


Figure 3.6: *A simple undirected graph. The graph (G) has vertice-set V= {u, v, w, x} and edge-set E= {uv, vw, vx, wx}.* (Gross & Yellen, 2004)

Based on the graph theory is the complex network theory, which is, among other things, being used to study commuting networks (Montis et al., 2010). There are three concepts that play a key-role in complex network theories; the average path length, the clustering coefficient, and the degree distribution. Whereas the path length is the distance between different nodes, and the clustering coefficient identifies whether there are certain nodes that have many more connections than others. In a pure random graph there is a small average shortest path length (varying as the logarithm of the number of nodes) and a small clustering coefficient. In real-world networks (e.g. commuting networks, social networks), it was found that the average shortest path length is small, but the clustering coefficient significantly higher than in random networks (Wang & Chen, 2003). Where the clustering coefficient is high, so-called hubs are generated (Figure 3.7) (Wang & Chen, 2003).

The degree (k_i) of a node (i) is usually defined as the total number of connections of that node. The nodes with a high degree are the hubs of a network. The average degree of a network is the average k_i over all i. The spread of node degrees over a network is depicted by a distribution function $P(k)$. This represents the probability that a randomly selected node has exactly k edges. The degree distribution of a regular lattice, where all nodes have the same number of connections, takes the shape of a sharp spike (a delta distribution). Randomness broadens the spike, since there are some nodes with more connections than others. Clustering causes an even more gradual decline of the peak, this allows some nodes to have many more connections than others (Wang & Chen, 2003).

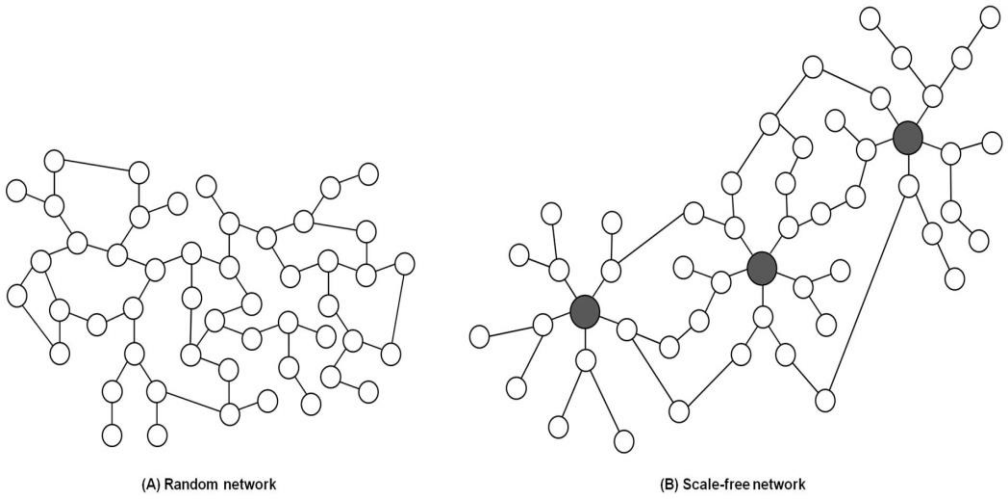


Figure 3.7: *A random network, and a scale-free network, where the hubs are represented as the bigger and grey nodes. (Seo, et al., 2013)*

3.1.6 CONTACT MATRICES

Networks with nodes and edges are useful in agent-based models. There is however also a method to mathematically simulate contact networks. In epidemiology studies this is often done using transmission- or WAIFW (Who Acquires Infection From Whom) matrices. These matrices are used to make an estimation of social networks, of who gets in contact with whom, and can thus infect each other with a disease. These matrices are often based on several age groups, since a difference in degree of mixing and contact within and between different age groups is seen (Del Valle et al., 2007).

To estimate who can infect whom it should first be determined which people have adequate contacts with whom, within and among different age groups. Mossong et al. (2008) have done a survey to estimate contact patterns in different age groups in eight European countries, among them the Netherlands. Figure 3.8 shows among which age groups the most contact exists. It can be seen that people tend to have the most contact with people of roughly the same age. Other high contact rates are seen between people of 0 to 20 years old and 30 to 50 years old. This can be explained as contact between parents and their children.

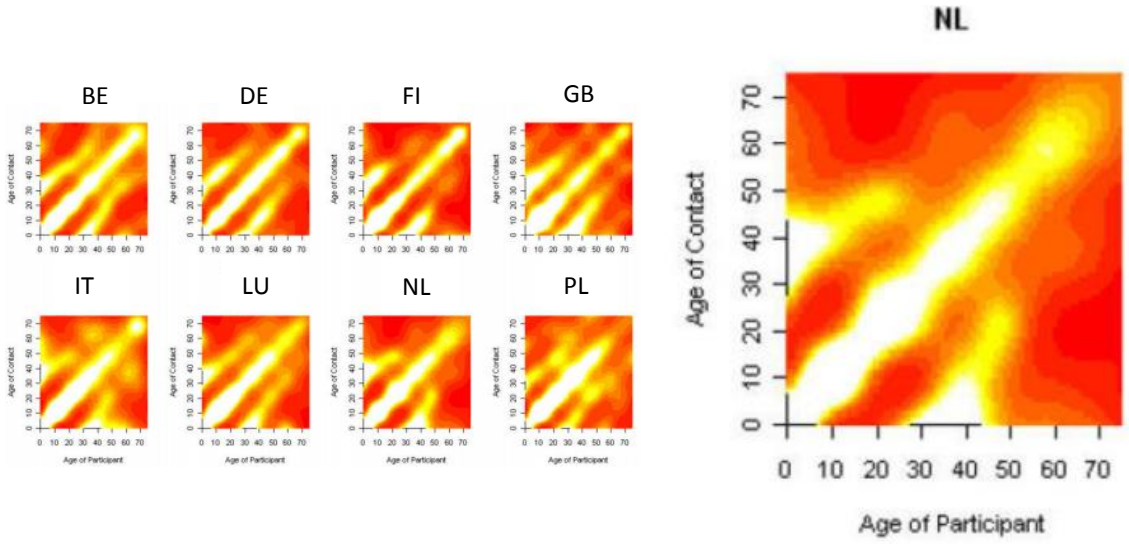


Figure 3.8: *Smoothed contact matrices showing among which age groups is the most contact. White indicates high contact rates, yellow intermediate contact rates and red low contact rates. Zoomed in to the Netherlands. Similar patterns can be seen in Belgium, Denmark, Finland, Great-Britain, Italy, Luxembourg and Poland. (Hens et al. (2009) based on the study of Mossong et al. (2008))*

Information about contact rates can be useful for determining how a disease diffuses in a population. The infection rate (λ) can be estimated by a linear combination of the number of adequate contacts (β) and the number of infectious people (I) (Del Valle et al., 2007). In Equation 3.7 an example of a WAIFW matrix can be seen based on four age groups.

$$\begin{bmatrix}\lambda_1\\ \lambda_2\\ \lambda_3\\ \lambda_4\end{bmatrix} = \begin{bmatrix}\beta_{11} & \beta_{12} & \beta_{13} & \beta_{14}\\ \beta_{21} & \beta_{22} & \beta_{23} & \beta_{24}\\ \beta_{31} & \beta_{32} & \beta_{33} & \beta_{34}\\ \beta_{41} & \beta_{42} & \beta_{43} & \beta_{44}\end{bmatrix} \cdot \begin{bmatrix}I_1\\ I_2\\ I_3\\ I_4\end{bmatrix} \tag{3.7}$$

Some equations are defined to calculate a transmission matrix for specific diseases and populations. The force of infection (λ_{ijk}) can be defined as (Del Valle et al., 2007):

$$\lambda_{ijk} = \begin{pmatrix} \text{Number of} \\ \text{contacts} \\ \text{per unit time} \end{pmatrix} \begin{pmatrix} \text{Probability of} \\ \text{disease transmission} \\ \text{per unit time} \end{pmatrix} \begin{pmatrix} \text{Fraction of} \\ \text{contacts that} \\ \text{are infected} \end{pmatrix}$$

$$\lambda_{ijk} = \left(\varphi_{ij}(t)\right) \left(\alpha_i \xi_j P_{ij}\right) \left(\frac{I_{jk}(t)}{N_j(t)}\right) \quad (3.8)$$

Where:
φ_{ij} = the probability of the disease transmission.
α_i = the susceptibility of a susceptible in age group i
ξ_j = the infectivity of an infective in (infectiveness) stage k of age group j
P_{ij} = the probability of transmission, based on the average contacts between age groups i and j
I_{jk} = the number of people in infection stage k of age group j
N_j = the size of age group j

The probability of infection is defined by the mean duration of contacts (T_{ij}) and the mean number of transmission events per hour of contact between fully infectious and fully susceptible people (σ) (Del Valle et al., 2007).

$$P_{ij} = 1 - e^{-\sigma T_{ij}} \quad (3.9)$$

As a last step the rate of disease transmission (β_{ij}) between a susceptible in age group i with people in age group j can be defined as the product of the average number of contacts, the susceptibility, the infectivity, and the probability of disease transmission (Del Valle et al., 2007).

$$\beta_{ij} = \varphi_{ij} \times \alpha_i \times \xi_{jk} \times P_{ij} \quad (3.10)$$

Logically the results of Equation 3.10, when performed for all different age groups, will result in a similar figure as in Figure 3.8. Where contacts rates are high, the transmission of a disease will be high as well. In order to estimate the force of infection for a specific disease in a specific population information is needed about the contact network, the susceptibilities (α_i) for each age group, the infectivity (ξ_{jk}) and the transmissibility parameter (σ) for the disease (which is based on the basic reproduction number of a disease). The susceptibility and infectivity can be set to 1, if it is assumed that all people in a population are equally susceptible, and all infected people equally infectious (Del Valle et al., 2007).

3.2 Conceptual model

In this section the conceptual model of the research will be explained. A broad distinction can be made between four sub models in the model; a commuting sub model, a disease sub model, a population sub model and an intervention sub model (intervention by health units). The disease- and network model will depict the current spread of pertussis in the Netherlands and have a population model as input. The agent-based model part will represent the two vaccination strategies (Figure 3.9). In this chapter the different aspects of the model will be explained.

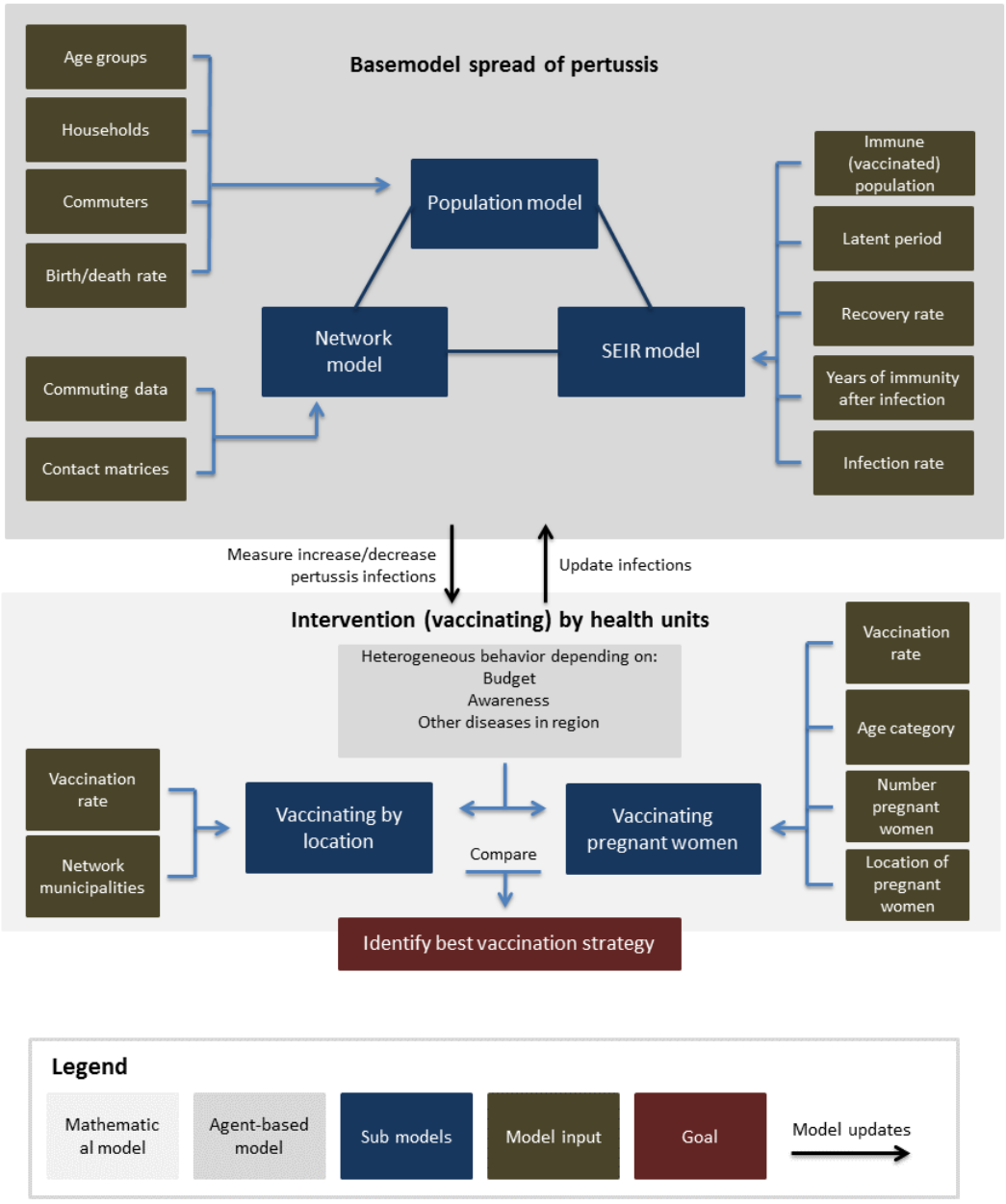


Figure 3.9: *Conceptual model.*

3.2.1 POPULATION MODEL

To model the network - and disease sub model a certain population is needed. As will be explained in section 3.2.3, each node in the network represents the population of the municipality that the node depicts. The population model will control the population dynamics (birth, death) over the simulation period, and the number of people per age group (ageing process). The start population per node is based on actual population data per municipality, acquired via the Dutch Central Bureau of Statistics (CBS, 2014). The population is divided in age groups and these are again categorized by groups such as commuting-state and households (Figure 3.10).

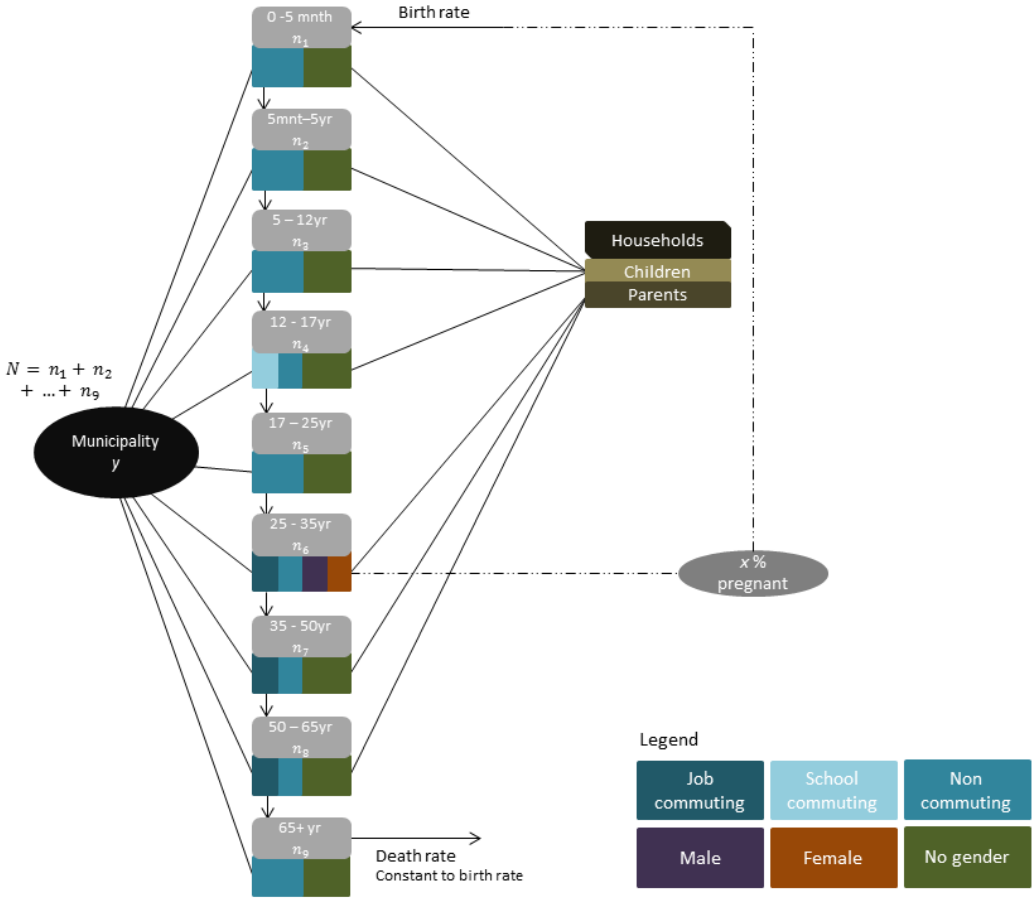


Figure 3.10: *Population model. The age groups are defined as 0-5 & 5-12 etc. by which is meant 0 up to and including 4, 5 up to and including 11 etc.*

3.2.1.1 Categorizing population

The population is divided in 9 age groups. From 0 to 5 months old (up to and including 4 months), 5 months to 5 years old, 5 to 12 year, 12 to 17 year, 17 to 25 year, 25 to 35 year, 35 to 50 year, 50 to 65 year and older than 65 years. These classes are chosen based on pertussis and vaccination factors (e.g. likelihood of spreading a disease is higher among kids than among adults since children tend to be close to each other while playing) and logical ages for commuting groups.

Vaccination of infants starts at the age of 2 months, it is thought that immunity is being reached after 5 to 7 months (Mooi & De Greeff, 2007). Therefore, the first age group is defined as 0 to 5 months. The next group is 5 months to 5 years old. This is an age group that has a large share of immune people because a large share of this age group is vaccinated as an infant. Immunity from this

vaccination lasts between 4 and 12 years. The ages 5 months to 5 years are grouped together, since it is assumed they are immune to pertussis. From 5 to 12 years old is the regular age to go to primary school, a share of this group is still immune to pertussis due to childhood vaccination. Teenagers who attend secondary school are on average between 12 and 17 years old. The age group of 17 to 25 year is assumed to be studying. The group of 25 to 35 years is the group that is working, and of whom the women are most likely to get pregnant. Furthermore, the groups 35 to 50 and 50 to 65 are defined as regular working age. At last, the 65 years and older group, whom are mostly retired.

Gender is only taken into account in the age group 25 to 35 year. There are thus three gender groups, no gender for all groups, except the 25 to 35 years' group. This group is divided in male and female because it is of interest for the intervention method that deals with vaccinating pregnant women.

Besides age and gender, sub groups will be created based on commuting state. There are three different commuting states; non-commuting, school-commuting and job-commuting. The age groups 0-5 months, 5 months to 5 years, 5 to 12 years, 17 to 25 years and 65 and older are assumed to be non-commuters. They either stay at home, or live in the same municipality as where they study or go to school. Not in all municipalities is a secondary school, therefore the age group of 12 to 17 years are either school-commuting to another municipality, or going to school in the same municipality as where they live. The age groups 25 to 35 years old, 35 to 50 years old and 50 to 65 years old are either non-commuters (working in the same municipality as where they live, or non-working) or job-commuters (Figure 3.10).

It is also defined whether the population of certain age groups is being part of a household, since a disease is likely to be transmitted quickly within a household (e.g. from parent to child, or between siblings). Children being part of the age groups 0 to 5 months, 5 months to 5 years, 5 to 12 years and 12 to 17 years have to be part of a household. Students of the age group 17 to 25 years old are assumed to live on their own. Of the age groups 25 to 35 year, 35 to 50 year and 50 to 65 year a certain percentage is part of a household, and a certain percentage is not. Pregnant women have to be part of a household. People of the age group 65 year and older are not part of a household.

Based on age, commuting-state and household groups unique combinations can be made. There are in total 25 unique combinations, each representing a certain percentage of the total population of a municipality. The proportions of each unique group will be the same for each municipality. Only the total number of people will be changed for each municipality. The ratios will be based on national demographic data derived from the Central Bureau of Statistics (see section 4.1).

3.2.1.2 Ageing

Since the model is run for several years, people are changing from younger to older age groups. The model does not take a growing or ageing population in account, but the total population, and the population in the subgroups is kept constant. This is done to avoid empty groups which might lead to errors in the disease model.

In the Netherlands there are on average 470 births each day (CBS, 2014). It is assumed that the birth rate is the same in each municipality. There are 396 municipalities (see section 3.2.1.3), hence the birth rate per municipality is 1.19 per day. To keep the population constant, the death rate is set to the same number. To keep all the subgroups constant as well, the in- and outflow per day is 1.19 in each age category.

3.2.1.3 Merging municipalities

The population per municipality is divided in 5 categories. For small municipalities this can lead to population groups with very few people. This is the reason that it was chosen to merge the smallest municipalities of the Netherlands with their neighbouring municipalities to avoid problems in the model. Municipalities with less than 7500 inhabitants are merged. Which municipalities these are can be seen in Table 3.1. In the column *Merged Municipalities* the name that will be used in the rest of the research for these merged municipalities is stated. After merging there are 396 municipalities left, of the original 409.

Table 3.1: *Merged municipalities for better performance of the model.*

Municipalities with <7500 inhabitants	**Merged with**	**Merged municipalities**
Baarle Nassau	Gilzen en Rijen	Gilze en Rijen – Baarle Nassau
Graft de Rijp	Schermer	Graft de Rijp - Schermer
Schermer	Graft de Rijp	
Muiden	Weesp	Weesp – Muiden
Rozendaal	Rheden	Rheden – Rozendaal
Vlieland	Texel, Ameland, Terschelling, Schiermonnikoog	Waddeneilanden
Ameland	Texel, Vlieland, Terschelling, Schiermonnikoog	
Terschelling	Texel, Ameland, Vlieland, Schiermonnikoog	
Schiermonnikoog	Texel, Ameland, Terschelling, Vlieland	
Renswoude	Scherpenzeel	Scherpenzeel – Renswoude
Haarlemmermeer	Haarlemmerliede & Spaarnwoude	Haarlemmermeer - Spaarnwoude & Haarlemmerliede
Millingen aan de Rijn	Ubbergen	Ubbergen – Millingen aan de Rijn
Zeevang	Edam & Volendam	Edam & Volendam – Zeevang

3.2.2 DISEASE MODEL

The spread of the disease will be modelled according to the SEIR model (see section 3.1.4 Modelling disease diffusion). Several parameters should be provided to be able to calculate the spread of the disease (Figure 3.9). The SEIR model in its basis is a non-spatial model. In this research it will however be combined with the commuting network to make it spatial. The SEIR model identifies which percentage of the population in each municipality is in the susceptible, exposed, infected or recovered group. Since the commuting is done over a network, the disease will only spread over this network.

Each unique group, described in the Population model (3.2.1), can be in all of the four stages of the SEIR model. Resulting in a total of 100 unique combinations in which each population in a municipality is divided. How much of each group is susceptible, exposed, infected or recovered/immune to the disease depends on the different ages and commuting states. Since the starting year of the model will be 1996 (see section 1.2 Scope of the project) the amount of susceptibility will be relatively high, and the number of infected- and immune people will be relatively low at the starting point of the model, because 1996 is the moment when pertussis notifications started to rise. In the age group 5 months to 5 years the number of people in the R

section (recovered/immune) will be high, since pertussis vaccination is part of the standard childhood vaccinations since 1957 (RIVM, 2014c). These childhood vaccinations are not obliged, however, and a vaccination rate of 100% is not being reached. Children in this age group can, thus, also be susceptible, exposed or infected to/with pertussis. The number of children that are immune to pertussis is derived from the childhood-vaccination rate per municipality, which is available data from the RIVM (see section 4.1).

During the runtime of the model the proportions in each S, E, I and R compartment changes, since each compartment has its own typical duration. Per unique population group, a flow can be identified from S to E to I to R, and from R back to S. The susceptible state can in theory last forever. The exposed state normally lasts between 7 to 10 days. The infected period lasts approximately 3 months, of which the first 21 days are the most infectious. The recovered state, and immune state can last somewhere between 4 to 20 years (RIVM, 2015). Movements of individuals from one state to the other are modelled by daily transfers of the fraction that are equal to the time this state lasts. For example, if the exposed period is 8 days, 1/8th of the individuals of the exposed class are transferred to the infectious class each day.

3.2.2.1 Seasonal transmission rates

To be able to generate an epidemic pattern with disease modelling, another aspect is needed; seasonal transmission rates. When running a model with a constant transmission rate it is impossible to generate a recurrent epidemic cycle (Earn, 2008). When a model is also run without a birth rate, so without a new input of susceptible people, all that can be generated is one peak. After this initial peak people gain immunity and the disease dies out (Figure 3.11). Another possible outcome would be that the transmission rate is too low to generate any infections at all. By using a birth- and death rate, and the correct transmission rate for a population, oscillations can be formed. These oscillations fade out after a certain amount of time, however (Figure 3.11). To keep the oscillations from fading out seasonal forcing should be taken into account in the model (Earn, 2008).

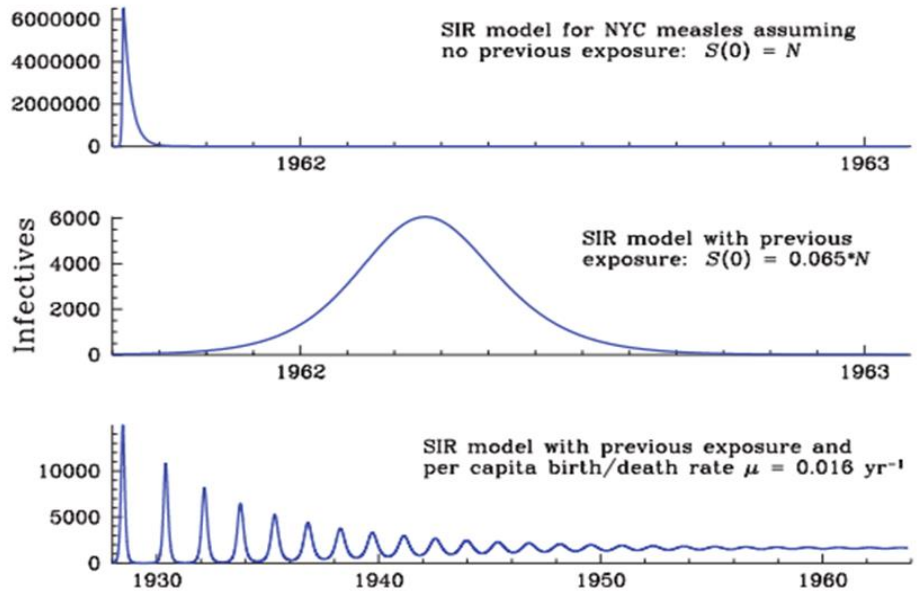


Figure 3.11: *Different model outputs by changing previous exposure and birth/death rate. (Earn, 2008)*

As Earn (2008, p. 13) states: “The transmission rate is really the product of the rate of contact among individuals and the probability that a susceptible individual who is contacted by an infectious individual will become infected. But the contact rate is not constant throughout the year”. The transmission rate should thus be varied seasonally. Even though this might seem a small change in the model, the variation has a big impact on the behavior of the model. This can be compared with a pendulum. When you tap a pendulum only once it will exhibit fading oscillations and settle to an equilibrium. If you keep tapping the pendulum periodically it will never settle down, and it can lead to chaotic dynamics. The same happens in a SEIR model, by changing the transmission rate seasonally complex dynamics can occur, that seem like random occurring epidemics (Earn, 2008) (Figure 3.12).

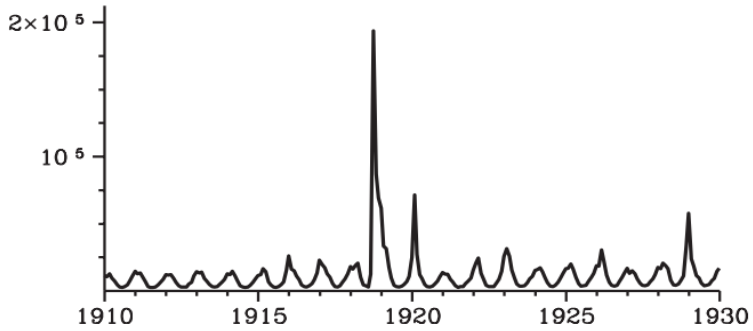


Figure 3.12: *A SIR model with previous exposure, per capita birth/death rate, and seasonal forcing can simulate epidemic curves. (Earn, 2008)*

3.2.2.2 Integrating disease- and population model

In Figure 3.13 a schematic representation of how the population model and the disease model are integrated is shown. In this figure ageing from younger to older age groups is represented by the vertical flow L. Depending on how many subgroups an age group has there are one or more ageing flows. In Figure 3.13 an example can be seen of two ageing flows (L_1 and L_2) from the age group 5 to 12 years to the age group 12 to 17 year. This is needed because the 5-12 year group only has one group in total, since all 5-12 year olds are non-commuters and live in a household. In the 12-17 year group a distinction is being made between people who travel to another municipality for secondary school, and those who attend school in their home municipality (non- or school-commuters). The ageing in two flows happens according to the ratio of people who are non- or school-commuters.

The disease model is represented by the horizontal flow in Figure 3.13. The infection rate β flows between the S and E compartment. This infection rate is based on the contact matrices between susceptible and infectious people. The flow between the people in the latent period (E) and the infectious period (I) is represented by ϵ, and is based on the duration of the latent period. The recovery rate γ flows between the infectious people and the recovered group. People stay in the recovered group for as long as their immunity lasts, then they go back to the susceptible class S, represented by ν. The different variables can be calculated as defined in Equation 3.11.

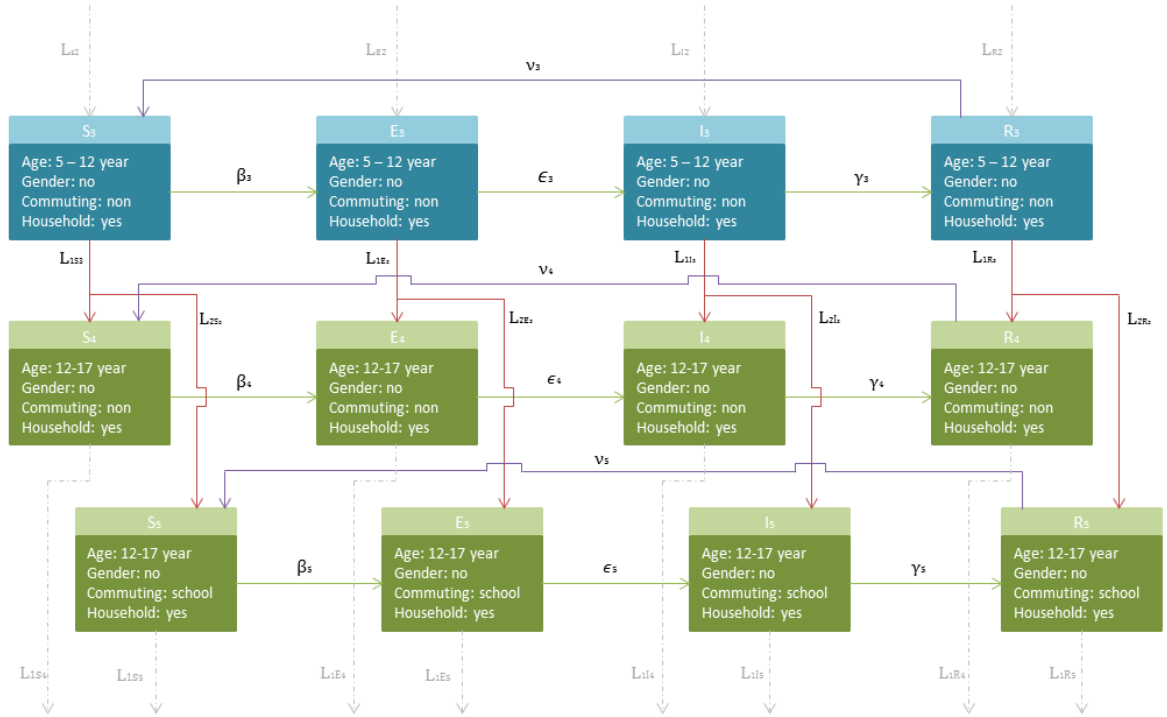


Figure 3.13: *Schematic representation of the disease and ageing flows of a part of the integrated model.*

$$\beta_3 = \beta S_3 I_1 + \beta S_3 I_2 + \beta S_3 I_3 + .. + \beta S_3 I_{25}$$

$$\epsilon_3 = \frac{E_3}{e}$$
$$\gamma_3 = \frac{I_3}{i} \qquad (3.11)$$
$$\nu_3 = \frac{R_3}{r}$$

$$L_{1S_3} = S_3 * l_{1non}$$

$$L_{2S_3} = S_3 * l_{1school}$$

Where:

e = the time the exposed period lasts, translated in time steps
i = the time the infectious period lasts, translated in time steps
r = the time the recovered (immune) period lasts, translated in time steps
l_{1non} = the fraction of people that ages each time step into the non-commuter group
$l_{1school}$ = the fraction of people that ages each time step into the school-commuter group

Subsequently the number of people in each compartment of the SEIR model can be calculated as:

$$\frac{dS_3}{dt} = S_3 - \beta_3 + \nu_3 + L_{S_2} - L_{1S_3} - L_{2S_3}$$
$$\frac{dE_3}{dt} = E_3 + \beta_3 - \epsilon_3 + L_{E_2} - L_{1E_3} - L_{2E_3} \quad (3.12)$$
$$\frac{dI_3}{dt} = I_3 + \epsilon_3 - \gamma_3 + L_{I_2} - L_{1I_3} - L_{2I_3}$$
$$\frac{dR_3}{dt} = R_3 + \gamma_3 - \nu_3 + L_{R_2} - L_{1R_3} - L_{2R_3}$$

3.2.3 COMMUTING MODEL

Another core aspect of the model is the commuting model. This sub model can broadly de divided in two parts. The first being a network consisting of the municipalities of the Netherlands and their interconnections, created by commuter flows. The network will consist of nodes and edges. The nodes of the network represent a population. Each population is split in several groups as explained in section 3.2.1. The interconnections, or edges, are based on daily commuting patterns. The second part is based on contact matrices. There is being looked at the chance that people get in sufficient contact with each other to transmit the disease. The route of pertussis diffusion is defined by a network, the number of infections is defined by a contact matrix model.

3.2.3.1 Commuting

The daily commuting patterns are derived from existing commuting data at municipality level (see Figure 3.14). The model will have one time step per day. It is assumed that all people who commute for their work return to their home municipality that same day. Commuting will be done five days a week, the other two days commuters will stay in their hometown. The majority of the working population in the Netherlands works fulltime (CBS, 2013a), which is seen as five days a week. It is assumed that people stay in their hometown during the weekends. This is partly seen as an acceptable assumption, it is, however, also chosen because it is hard to make realistic estimates about leisurely day- and weekend trips.

School commuting is also taken into account. Not everybody goes to school in their home municipality, and not every municipality has a secondary school. There is however no data available about origin and destination municipalities for school children. An assumption is being made that there is random commuting between each municipality and all its' neighbouring municipalities. Of the school-going children of a "home" municipality 5% travels to each neighbouring municipality for 5 days a week.

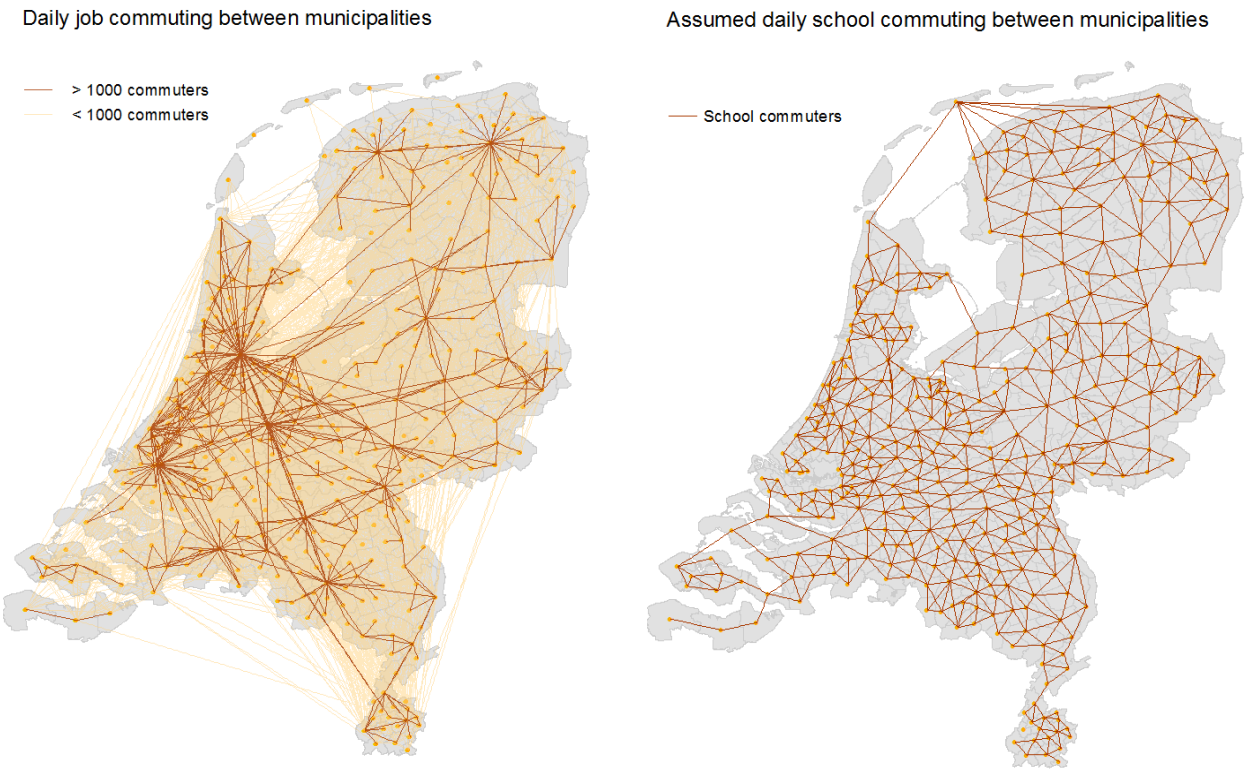


Figure 3.14: *Daily job commuting (left). Distinguished between more- or less than 1000 commuters a day. Based on actual commuting data acquired at the CBS (2013). And assumed daily school commuting. Based on randomized commuting to neighbouring (merged) municipalities.*

3.2.3.2 Contact

Since the disease model is a mathematical model, there are not actually individuals/agents traveling over the network. The commuting will be simulated via a mathematical WAIFW matrix (see section 3.1.6). This matrix will first be used to identify contacts within the different municipalities. Subsequently the model will be extended in a way that contact matrices are also established for the population that commutes to another municipality (Rock et al., 2014).

A contact matrix is established in which all possible contacts are defined. Including the different disease statuses there are 100 unique population groups, since each group from the population model can further be divided in the S, E, I or R compartment (see 3.2.3. Disease model). A matrix of 100 by 100 can thus be established. Since only the contacts between an infectious person and a susceptible person are of interest, the matrix can be reduced to 25 by 25. In total four matrices are created (see Appendix B). The first defines the number of contacts between a susceptible from a certain population group and infectious persons from all the other population groups, per day. This matrix is based on data acquired by the RIVM (RIVM, 2016). The matrix is based on contact of persons on a distance of 1 meter, which is the distance from which one can breathe in drops of coughs or sneezes.

The second matrix defines the mean duration of these contacts in hours. This information is derived from Del Valle et al. (2007), Mossong et al. (2008) and Wallinga et al. (2006). Since the model only simulates one time step each day, the contact rates do not take commuting status into account for the contact matrices within municipalities. People who commute and have a household have the same probability of infecting their children as people who go to work in their own municipality (and

are thus non-commuters). The commuting state is taken into account when looking at infection rates among municipalities.

Subsequently the probability (P) of infection can be calculated in the next matrix, by making use of the mean duration of contacts (T) and the mean number of transmission events per hour of contact (σ) (Equation 3.13). The value for the number of transmission events per hour will be derived via calibration, since it is not known. Knowing the probability of infection, the rate of disease transmission (β) can be calculated, which will be used as input for the disease model (see Appendix B for the matrices). It is assumed that everybody in the population has the same susceptibility and infectivity. In reality there are differences in susceptibility and infectivity. There is however little consensus in literature in which age groups the susceptibility and infectivity is higher or lower. Instead of generating random values for susceptibility and infectivity this value is set the same for the whole population. Thus every susceptible person is equally susceptible to pertussis and every infected person is equally infectious. Therefore, the parameters susceptibility (α) and infectivity (ξ) are set to 1, and can be left out of the equation for the rate of disease transmission. The resulting equations for defining the contact matrices are:

$$P_{ij} = 1 - e^{-\sigma T_{ij}}$$

$$\beta_{ij} = \varphi_{ij} \times P_{ij} \qquad (3.13)$$

3.2.3.3 Integrating the commuting model

A simplified commuter model will be used in which it is assumed that everybody returns back to their home municipality each day. The only addition that has to be made to the equations in which he disease- and population model are integrated (3.2.2.2) is an extra chance of getting infected. This is done via a separate contact matrix.

A distinction is being made between infected commuters, susceptible commuters, and the type commuter. Infected job-commuters are able to infect all non-commuting susceptible people in the age groups 25-35 year, 35-50 year and 50-65 year. Infected school-commuters are only able to infect non-commuting school children in the destination municipality. In the destination municipality the chance of infection is thus increased; by how much depends on the amount of infectious commuters arriving in the destination municipality, and from how many different municipalities they are. Susceptible commuters can be infected by an infectious person in the destination municipality, and can subsequently take the disease home. Susceptible job-commuters can be infected in the destination municipality by non-commuting people from the age groups 25-35 year, 35-50 year and 50-65 year. Susceptible school-commuters can be infected by infectious non-commuters of the same age-group.

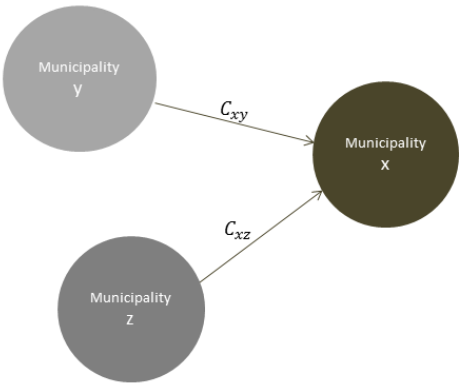


Figure 3.15: *Schematic representation of commuters between municipalities.*

Integrating the commuters in the model results in a change in the equations for the S and E classes in the SEIR model as explained in Equation 3.12. The force of infection from the incoming commuters is added to the equation. For the example in section 3.2.2.2 (Integrating disease- and population model) and Figure 3.15, for the destination municipality x, in case the commuters are infectious, this results in:

$$CI_{xy} = \beta S_x I_y$$
$$CI_{xz} = \beta S_x I_z$$

$$\frac{dS_{3x}}{dt} = S_{3x} - \beta_{3x} + \nu_{3x} + L_{S_{2x}} - L_{1S_{3x}} - L_{2S_{3x}} - C_{xy} - C_{xz} \quad (3.14)$$

$$\frac{dE_{3x}}{dt} = E_{3x} + \beta_{3x} - \epsilon_{3x} + L_{E_{2x}} - L_{1E_{3x}} - L_{2E_{3x}} + C_{xy} + C_{xz}$$

For home municipality y, in case the commuters are susceptible, this results in:

$$CS_{xy} = \beta S_y I_x$$

$$\frac{dS_y}{dt} = S_{3y} - \beta_{3y} + \nu_{3y} + L_{S_{2y}} - L_{1S_{3y}} - L_{2S_{3y}} - C_{xy} \quad (3.15)$$

$$\frac{dE_y}{dt} = E_{3y} + \beta_{3y} - \epsilon_{3y} + L_{E_{2y}} - L_{1E_{3y}} - L_{2E_{3y}} + C_{xy}$$

3.2.4 INTERVENTION MODEL

The base model of pertussis diffusion is fully mathematical. The rest of the model will be agent-based. The only entities in the model that have a certain behavior are the municipal health units of the Netherlands. The health units are the institutions that provide vaccinations to the population. They are seen as the decision makers in the model; hence they are programmed as agents. Each health unit behaves differently in terms of when they conduct an intervention (change their behavior) and which intervention they will perform (e.g. promoting pertussis vaccination, and tracking down the disease path).

Each health unit, and thus agent, is assigned its own spatial service region. The agents are static in location, their interventions only apply to the service region they are responsible for. The agents do not interact with each other. Health units have the following attributes and behavior:

Behavior	Attributes	Comments
- Sense the number of disease cases in their health unit and will update this.	- Total current infected	
- Can compare the sensed number of disease cases to a basic level of disease cases.	- Total current infected - Basic infection level - Difference between current infected and basic infection level	If number of currently infected is high: Change behavior (first randomly to either increase vaccination or tracking – later based on previous impact)
- Measure impact of previous changes in behavior.	- Intervention 1: Difference between high sensed number and number infected after intervention - Intervention 2: Difference between high sensed number and number infected after intervention - Intervention 3: Difference between high sensed number and number infected after intervention - Behavior with the best score	Behavior that leads to biggest decrease in infections is assigned the highest score.
- Adjust behavior to behavior that leads to best results.	- Behavior with the best score	
- Identify population groups.	- Pregnant women - Infants	
- Identify network locations.	- Number of links	The municipalities with the most links are identified as network locations.

The mathematical part of the model interacts with the agent-based part of the model. The number of immune people changes due to the behavior of the agents, which is fed back as input for the SEIR model. The two vaccination strategies will be compared with each other by looking at the number of infected people. Especially if there is an increase or decrease over time, and how big this increase or decrease of infected people in the population is.

Each health unit measures the number of infected people in its own service region (Figure 3.16). If the number of infections in the service region is higher than a certain percentage of the total population in that region intervention starts. Intervention is simulated by an increase in the percentage that is in the recovered, and thus immune, group. How big this increase is will be based on vaccination rates known for childhood vaccinations per municipality. Even though it is known that health units do have heterogeneous behavior, there is no data available on this topic.

In which subgroups of the recovered group (e.g. age, commuting state, pregnant) the increase is pushed depends on the scenario that is tested. In the maternal vaccination scenario only an increase in immune people in pregnant women, and their infants, is simulated. For the network vaccination scenario an increase in immune people is modelled in all subgroups, however only in a few municipalities. The total number of infections in the whole of the Netherlands is measured, and based on this number it is analyzed which vaccination strategy is best in reducing pertussis in the country.

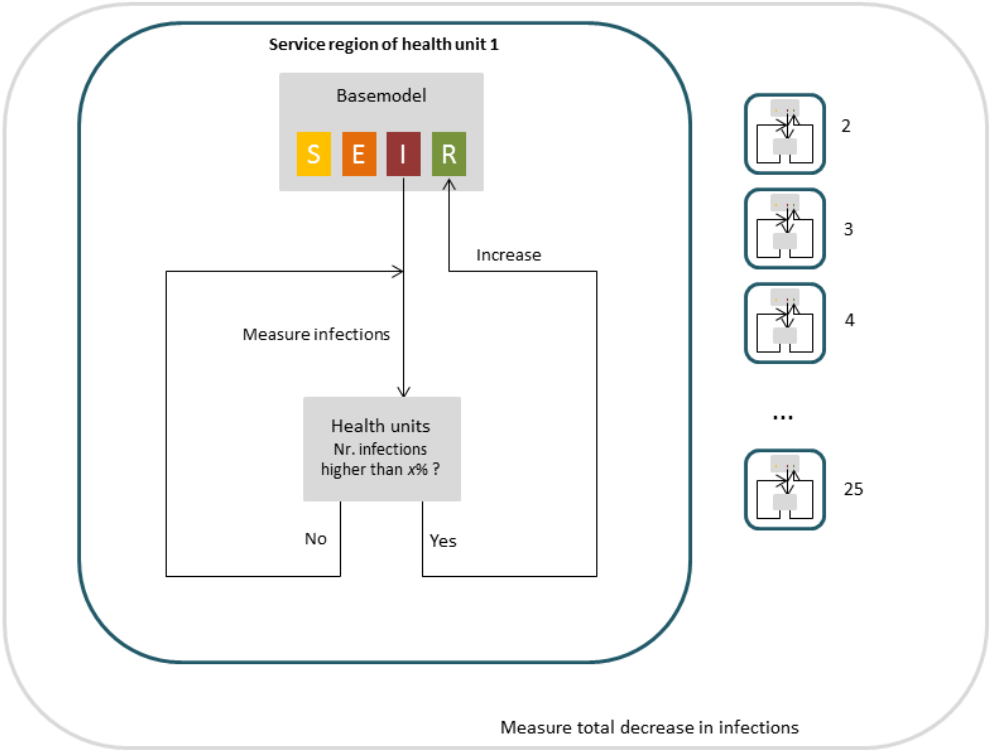


Figure 3.16: *Schematic representation of the behavior of the health units.*

4 IMPLEMENTATION, VALIDATION & CALIBRATION

In this chapter the used data and software will be explained to create the model. Before the model is used to generate any results a process of validation and calibration has been conducted. Validation has been performed to make sure the model behaves as expected, represents reality to a certain extent, and can be called good for fit. A sensitivity analysis has been performed to see how sensitive the model is to certain parameters. As a last step, calibration is needed to acquire the still unknown input values. The sensitive parameters are most useful in the calibration process. Furthermore, it functions as a measure for how reliable the results will be.

4.1 Data and software

The pertussis diffusion model in this research will be created in NetLogo. NetLogo is a multi-agent programmable modelling environment (NetLogo, 2015).

As input for the model some data is needed. First of all, information of the municipalities of the Netherlands and their population is needed. This data is easily accessible online, via the central bureau of statistics of the Netherlands (CBS), and the Dutch governmental geo-information service: PDOK (see Table 4.1) To establish the commuter network there will be made use of existing commuter data, which is available on municipality scale at the central bureau of statistics (CBS, 2013b).

For the SEIR model information about input parameters such as latent period, recovery period, years of immunity are easily accessible in literature (e.g. Hethcote, 2000) or via the RIVM. Also information about the number of vaccinated people in the population can be acquired via the RIVM. Data about the percentage of vaccinated children are available at municipality level. However, also data is needed about the infection rate of pertussis, or more specific the number of transmission events per hour. This data is unknown and will be acquired via calibration (see section 4.4).

To create the contact matrices data about number of adequate contacts to transmit pertussis is used from the RIVM. In this matrix contact within a distance of 1 meter is taken into account. Which is the distance over which pertussis can be transmitted. The research of (Del Valle et al. (2007), Mossong et al. (2008), and Wallinga et al. (2006) has been used to make estimations of the average duration of contacts between different age categories.

Data needed for the two vaccination strategies are somewhat more difficult to acquire. The vaccination rate of pregnant women will be an estimate, based on data about childhood vaccination rates per municipality. Researches in other countries can provide background information about realistic vaccination rates (see Amirthalingam et al., 2014; Van der Maas et al., 2013).

Data about the numbers of new-borns per year in the Netherlands are available at the CBS. This data can be used to make an approximation of pregnant women per year. It will be an approximation, since no information about whether these new-borns are twins is given. The location of the new-borns, or pregnant women is difficult to obtain. If this proves to be impossible, the best alternative is to distribute the pregnant women over the municipalities, relatively to the size of the age category that is most likely to become pregnant.

Last of all information is needed to model the heterogeneous behavior of the health units. This information can be acquired by looking at the different year reports of the health units or by personal contact with these units. If this proves to be difficult, random behavior can be assigned.

Table 4.1: *Data sources, for links to the sources see References - Data sources.*

Data	Source	Year
Municipality data (geographic)	PDOK	2013
Number of people per municipality	CBS[1]	2013
Percentage gender in population	CBS[1]	2013
Percentage age in population	CBS[2]	2013
Percentage households in population	CBS[3]	2013
Job commuter data	CBS[4]	2013
Birth- and death rate	CBS[5]	2013
Vaccination rate	Zorgatlas[1]	2013
Contact rates	RIVM	Unknown
Contact duration	Literature (Del Valle et al., 2007)	2007
GGD locations/regions	Zorgatlas[2]	2014

4.2 Conceptual validation

To conceptually validate the model, certain aspects of the output are compared with real world data. Since a model is an abstraction of reality it cannot be expected that the output is exactly the same as reality, however to be able to call the model good for fit some similarities must be seen. First of all, some experiments will be conducted to test whether the model reacts as expected by making changes in certain parameters. After this, the models' behavior in one municipality will be evaluated. Subsequently the models' behavior for the whole of the Netherlands will be compared with data of pertussis infections in the Netherlands.

4.2.1 VERIFICATION

To test the general behavior of the model six experiments have been formulated and tested. These are just simple experiments that will show whether the model behaves as expected to certain changes in the parameters in the model.

- If everybody in the population is immune, there will be no infections
- If commuting is turned off, the disease will not spread to other municipalities
- If the infectious period is shorter, less people will get infected
- If the recovered period is shorter, in total more people will get infected
- If the infection rate is lower/higher less/more people will get infected
- If the recovered period is shorter, a repeating pattern with a higher frequency will occur

The models' behavior on all of the experiments is as expected. This means that the core functionalities of the model are working.

4.2.2 MUNICIPAL DISEASE CYCLE

Before the full functioning of the model for the whole of the Netherlands will be validated, the behavior of the model for only one municipality will be evaluated. In this situation there will be no interaction between the different municipalities. The commuter flows are thus not taken into account. This will be done to be able to validate the working of the SEIR model in its most basic form; in a constant population in a closed system without input from other places.

As municipality Utrecht is chosen. It is known that most epidemics are noticed first in the bigger cities of a country. This can be explained by two factors, bigger cities often have many links to smaller cities (Lund et al., 2013), and a disease does not die out in a bigger city due to the higher amount of susceptibility (Monteiro et al., 2006). Utrecht is one of the largest cities in the Netherlands, it has an important central function in the Netherlands, due to its location, where there is a lot of interaction between people from different regions. It is therefore seen as a representative municipality where a pertussis epidemic could be started.

To test the behavior of the SEIR model in Utrecht the different possible cycles of infections that can be generated will be generated with a SEIR model, as described in section 3.2.2.1. The model should not be able to create a repeating pattern when using a constant transmission rate for the full runtime. Seasonal forcing should be able to push the model to create epidemic curves.

The top two graphs of Figure 4.1 show what happens when running the model with a constant transmission rate. Either the transmission rate is too low, and no pertussis outbreak occurs (not shown in Figure 4.1), or only one peak is created, or in the best case; some oscillations can be formed. A truly repeating pattern that does not die out cannot be reached however. When varying the transmission rate seasonally, different patterns arise. The output of the model can be described as an endemic, or even epidemic curve (Figure 4.1, bottom). The total number of infections vary quite a lot between these different outputs. When varying the transmission rate seasonally the model tends to create more infections. The number of infections generated in Utrecht are higher than feasible, therefore the model should be calibrated, which will be described in section 4.4.

These figures show that the model is able to generate endemic and epidemic disease cycles in one municipality. The SEIR model without commuter flows behaves as expected and wanted.

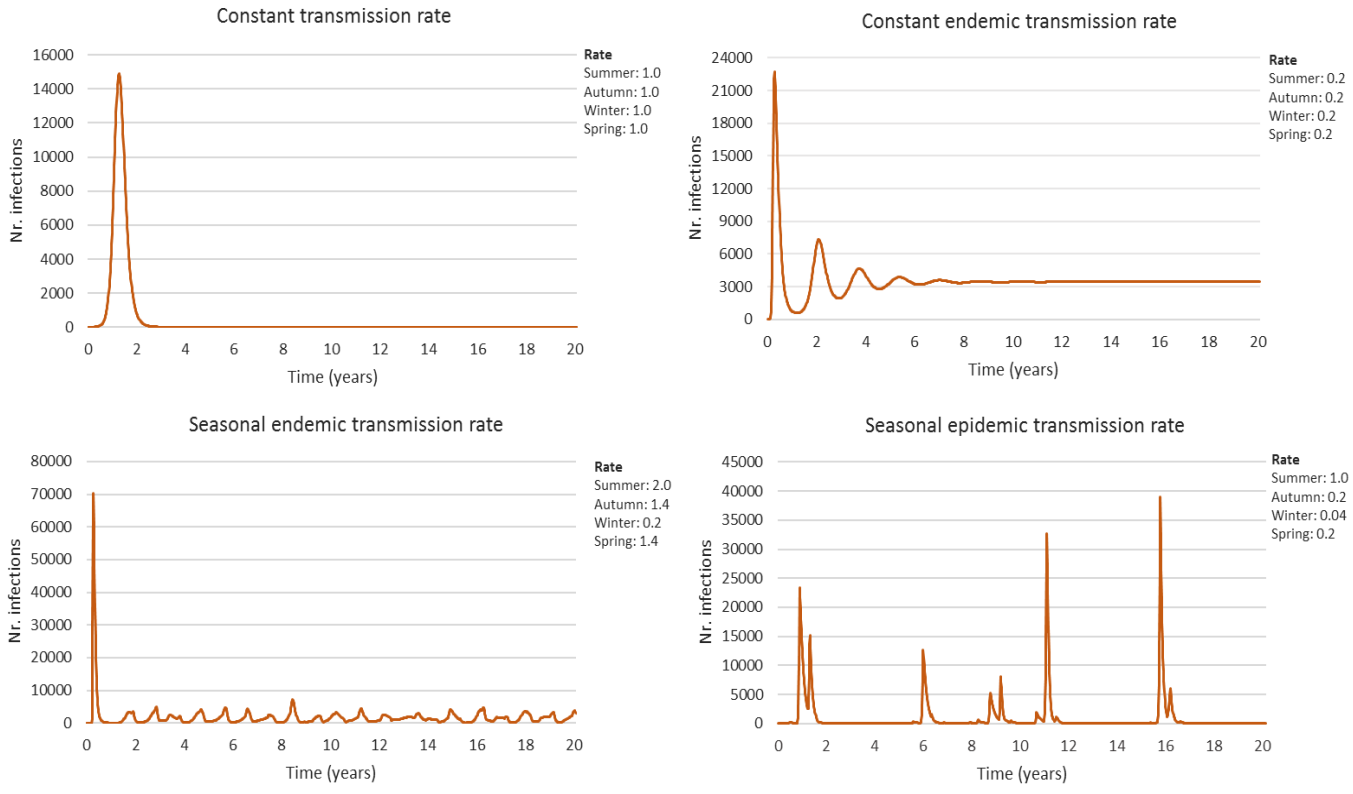


Figure 4.1: *Infection curves after running the model for Utrecht with different transmission rates.*

4.2.3 DISEASE CYCLE OF THE NETHERLANDS

The basics of the SEIR model are working, and for one municipality the model behaves as expected, and is therefore seen as correct. The next step is to validate the model for the whole of the Netherlands. Basically this says something about whether the model, including commuter flows, works as it should. The model will be validated by looking at the cycle of pertussis infections. In the Netherlands a typical cycle can be seen in which there is a peak in pertussis notifications every two to four years apart. If the base model results in a similar cycle the model is seen as realistic. To validate the model with more detailed notifications of pertussis would be difficult due to the lack of such data. Besides, it would not make the validation more trustworthy if more detailed data would be used. Not all people with pertussis are diagnosed with the disease, so differences in the model and the real world are insuperable. There will be looked at a general similarity between the model outputs and the real world.

There are two sorts of commuting taken into account in the model; school commuting and job commuting. The first group of commuters travels only to neighbouring municipalities, the second group of commuters travels both short and long distances and has therefore a bigger impact on the geographic diffusion of pertussis. This geographic diffusion will not be validated. There is too little data available about the spatial diffusion of pertussis in the Netherlands to be able to do this. There will be looked at the speed at which the disease diffuses. This can be derived from looking at the time it takes for a pertussis outbreak to reach the top of its epidemic peak.

4.2.3.1 School- and job commuting

To validate the model several runs have been performed with different values for the input parameters. The first method for validation is visual interpretation of the curve of the number of infected people in the population. The curve should have a similar shape as in Figure 1.1, which is the curve of reported pertussis cases in the Netherlands from 1996 till 2013. This curve is characterised by an epidemic peak every three to four years.

The model has been run with a variety of input parameters (see Appendix D for all tried combinations), however the model failed to generate an epidemic curve. In Figure 4.2 two graphs are shown of outputs that have been generated, and that are similar to the outputs of most runs performed. First an epidemic outbreak is seen, after this the line can be described as endemic. The disease lingers around, and some oscillations are seen, but no new outbreak occurs.

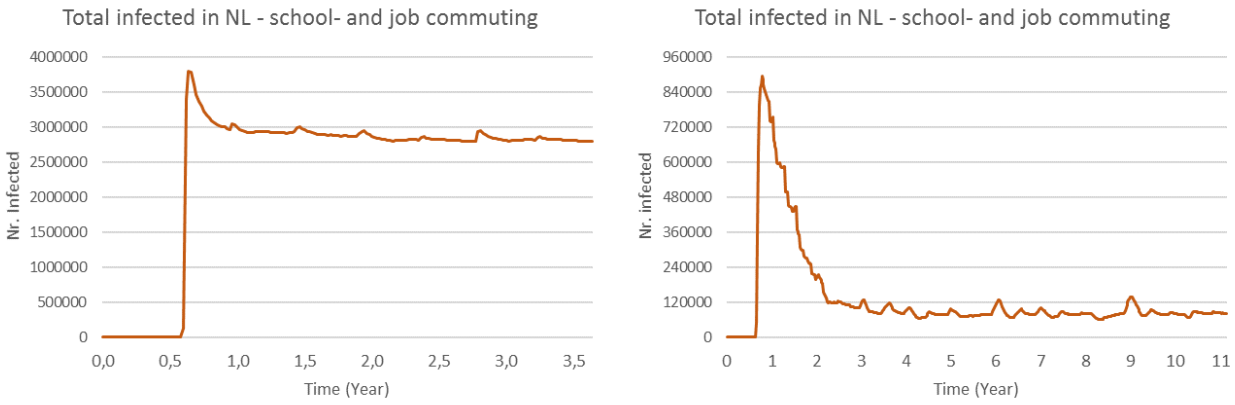


Figure 4.2: *Infection curves for infection in the Netherlands, generated by taking school- and job commuting into account.*

A possible explanation for the disease staying in an endemic cycle might have to do with the way the interaction between different municipalities by commuters is programmed. Once there is an infection in a municipality, the number of infections in all municipalities that are linked with that municipality via a commuter flow will increase with a fraction each weekday. This might be a very small fraction. However, there is an endless input of infections as long as there is one municipality with an infected individual, all municipalities are linked with each other in the end.

To try and overcome this problem, commuter thresholds have been introduced in the model. These thresholds make sure that an infection can only spread to a new municipality once the fraction of infected people in the commuter population groups is higher than a certain percentage. The working of the threshold is depicted in Figure 4.3. When the threshold is set to zero, the disease diffuses very quickly throughout the country. When the threshold is set to a higher percentage the disease diffuses in a slower rate, or will not spread to other municipalities at all, because the percentage of infected commuters will not be higher than the threshold value.

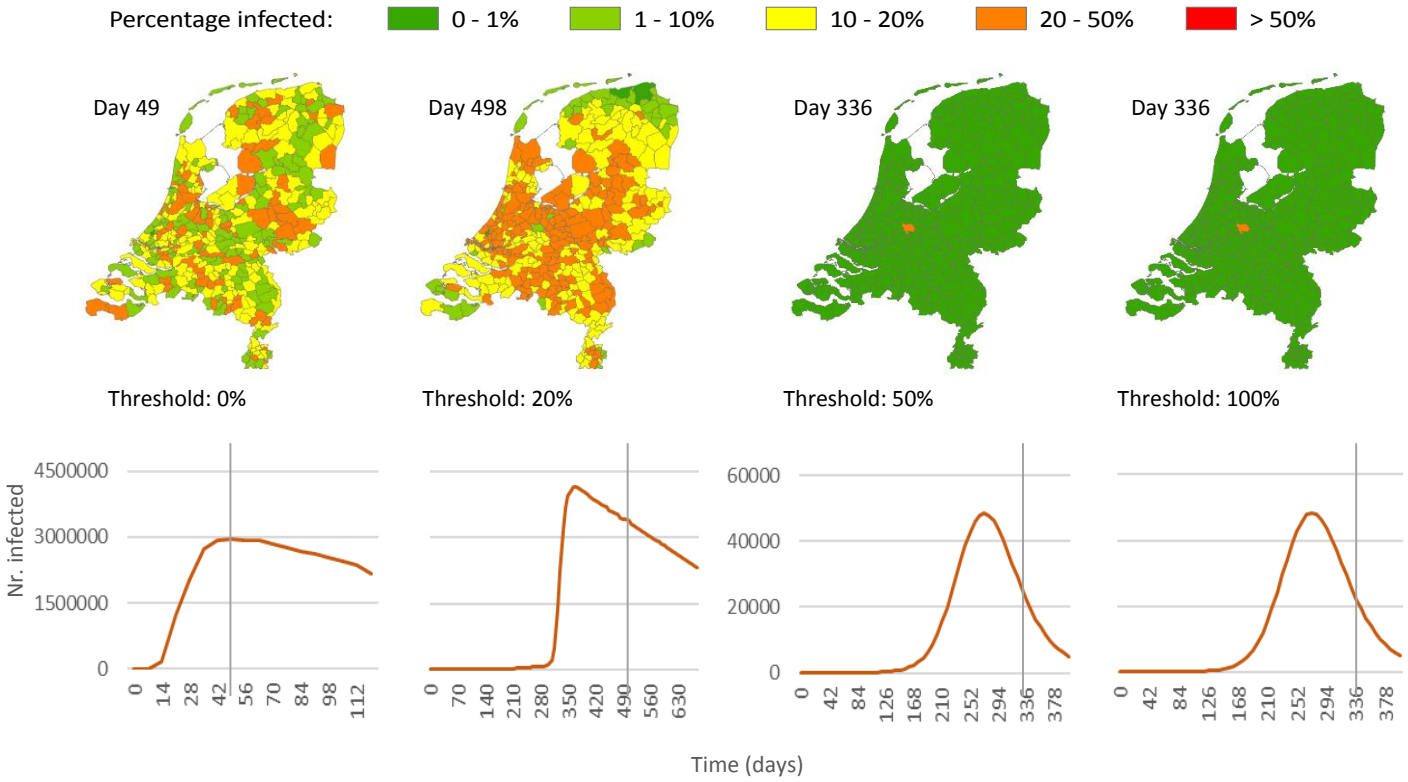


Figure 4.3: *The impact of commuter threshold values on the spatial spread of pertussis, the time it takes for pertussis to spread through the Netherland, and the number of infections.*

To test the impact of the thresholds on the models' behavior, again several runs have been performed, with different threshold values. The thresholds have an influence on the models' behavior in terms of the speed with which the disease diffuses from one municipality to another, and on the total number of infections. It does, however, not have the wanted impact on the endemic curve. Running the model with thresholds still results in an endemic disease cycle (see Figure 4.4 for two outputs, see Appendix D for the tried combinations of parameter values).

It can thus be concluded that the model, including school- and job commuter flows cannot be validated. To reflect on why the disease stays in an endemic state instead of regenerating a new

epidemic outbreak, model outputs will be analyzed by running the model separately with only school commuters or only job commuters in the following sections.

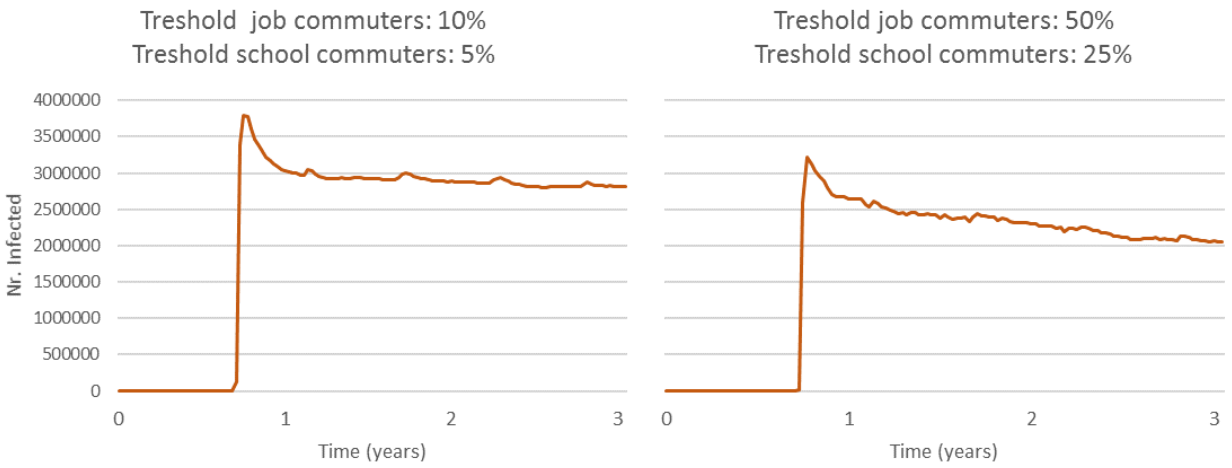


Figure 4.4: *The number of infections when running the model with different commuter thresholds.*

4.2.3.2 School commuting

When running the model where the only interaction between municipalities comes from school commuters an epidemic disease cycle can be generated (Figure 4.5). The infection curves are quite similar to the infection curve of notified pertussis cases in the Netherlands (Figure 1.1). Every three to four years an epidemic peak can be identified. In between, the disease does not drop to zero, but lingers around. Furthermore, the general shape of the curves is similar to the observed pertussis notifications. The peaks are characterised by two or more smaller peaks that together form the epidemic peak.

By only taking school commuting into account the general shape of the disease curve can be called good for fit. The downside of only taking school commuting into account is that it is not very realistic, both in terms of amount of school commuters as in spatial diffusion. The school commuter flows are created purely based on assumptions. Besides, school commuters only travel short distances, while in reality there is more long distance commuting in the Netherlands.

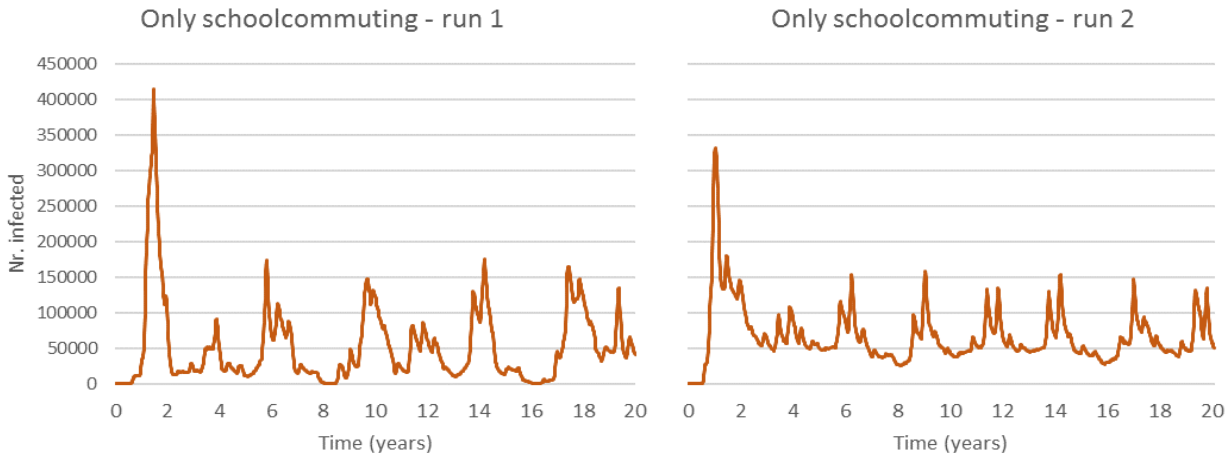


Figure 4.5: *Epidemic curves generated by running the model with only school commuting. Run 1: transmission rate: summer 0,6; spring/autumn 0,2; winter 0,067. Run 2: transmission rate: summer 0,6; spring/autumn 0,4; winter 0,2.*

4.2.3.3 *Job commuting*

When the model is run with only job commuter flows that cause interaction between municipalities, an endemic curve is generated. The problem of not being able to validate the model by taking all commuter flows into account lies in the job commuting part. Figure 4.6 shows that not only for the whole of the Netherlands an endemic curve is generated, the infection curves of separate municipalities are all more or less endemic, moreover not epidemic.

The problem might be caused by the very high amount of commuters that travels daily between municipalities in the Netherlands. In reality this amount of commuting still leads to epidemic pertussis cycles, however, the mathematical base of the model might not be able to grasp this. This might also explain the difference between school commuting and job commuting outputs. School commuting is done in much lower numbers, besides it is based on an assumption in which equal percentages in all municipalities travel in and out, which allows for more predictable modelling.

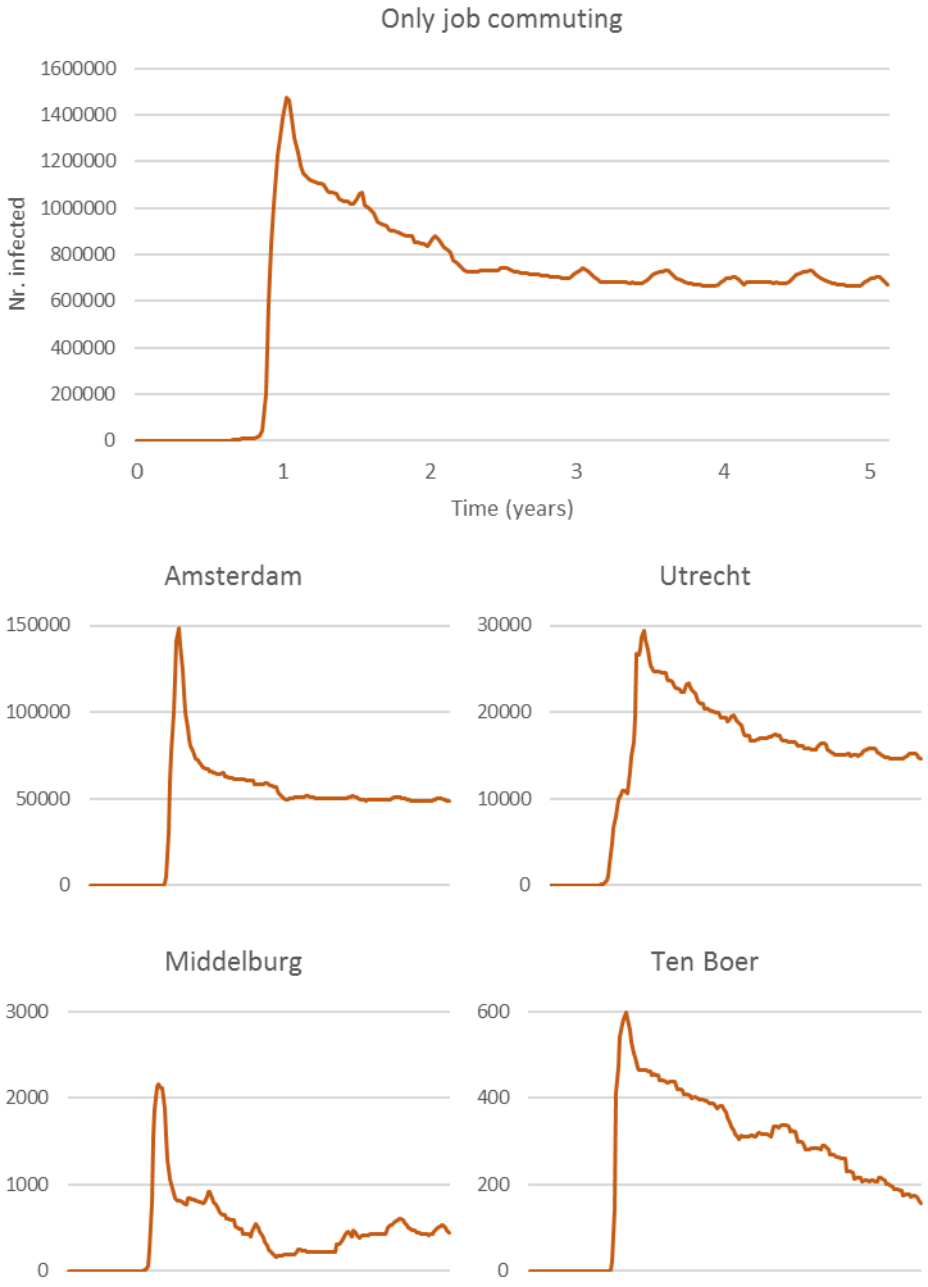


Figure 4.6: *Endemic curves generated by running the model with only school commuting. Split out to separate municipalities over the same time span. Used transmission rate: summer 0,6; spring/autumn 0,2; winter 0,067.*

4.2.4 CONCLUSION OF CONCEPTUAL VALIDATION

The very basic behavior of the model has been tested by doing simple experiments and the behavior of the model on these experiments is fully as expected, and wanted. When running the model for only one municipality, the model behaves as expected, and predictable disease cycles are generated. When introducing commuter flows, and thus interaction between different municipalities, the model does not behave according to expectations anymore.

When only school commuters are taken into account the generated disease curve is exactly as expected, and wanted. This proves that the way commuters are programmed is not wrong. When looking at job commuters, only an endemic pertussis cycle can be generated. In some sense pertussis has reached an endemic state in the Netherlands, therefore the model is not seen as entirely wrong. The model can, however, not be fully validated due to the lack of recurring outbreaks.

4.3 Sensitivity analysis

A sensitivity analysis is performed to test how the model reacts to changes in certain parameters. The parameters that are tested for sensitivity are: The length of the infected period, the length of the recovered period, the impact of the number of immune people in the start population, the transmission rate (the mean number of transmission events per hour), and the impact of the location where infections are introduced. These parameters are chosen because there is either randomness in the parameters, or the values cannot be acquired via a reliable source. The duration of the exposed period also knows some randomness, however, the possible values are so close to each other that it is decided not to test this parameter for sensitivity (Table 4.2).

To test the model on sensitive parameters, runs are being performed with a standard set of parameters. The parameter that is tested for sensitivity is changed within a certain range to see the impact on the model results (Table 4.2). The models have been run with a transmission rate of 0.2, which is the adequate transmission rate for influenza (Del Valle et al., 2007), which is transmitted similarly as pertussis. An exposed period of 8.5 days, an infective period of 21 days, and an average recovered period of 12 years (these values will be reflected upon in the following sections of this chapter). One infected person has been introduced in Utrecht municipality. The percentage immunity in the start population has been set to 0%. In most cases the sensitivity of the model parameters has been tested without commuting, only for sensitivity of the location where the disease is introduced it is seen as necessary to take commuting, and thus disease diffusion, into account.

Table 4.2: *Standard parameter values for the sensitivity analyses.*

Parameter	Range for sensitivity	Standard value	Reference
Transmission rate (mean number of transmission events per hour)	0.02 – 2.00	0.20	Del Valle et al., 2007
Exposed period (days)	7 – 10	8.5	RIVM, 2011
Infected period (days)	14 – 122	21	RIVM, 2011
Recovered period (years)	4 – 20	12	RIVM, 2011
Percentage immunity start population	0 – 90	0	-
Number infective people introduced	-	1	-
Start location (municipality)	Amsterdam, Utrecht, Ten Boer, Middelburg	Utrecht	Lund et al., 2013

4.3.1 EXPOSED PERIOD

The length of the exposed period is said to be between 7 and 10 days (RIVM, 2011). The influence of this small variation will not be big on the outputs of the model. Since the scope of the research is to run the model for 40 years, it can be wondered however, whether it is necessary to simulate the relatively short exposed period. Not simulating the exposed period could increase the speed of the model, and make it less complex, hence the behavior of the model might be easier to understand.

To test the influence of the exposed period, the model has been run with and without the exposed period, so a SEIR and a SIR model. The results are shown in Figure 4.7. The SIR model produces more infections than the SEIR model. In the SEIR model the highest degree of infections is reached at a later state than in the SIR model. As a logic result the disease dies out in a later stage in the SEIR model as well, however, the time between the highest level of infection and the disease dying out again is longer in the SEIR model as well. This can be seen in the peak of the SIR model being steeper.

It can be said that the exposed period has an influence on the number of infections in a population in the model. Therefore, the most logical choice is to keep taking the exposed period into account, since it is known that pertussis is a disease with an exposed period.

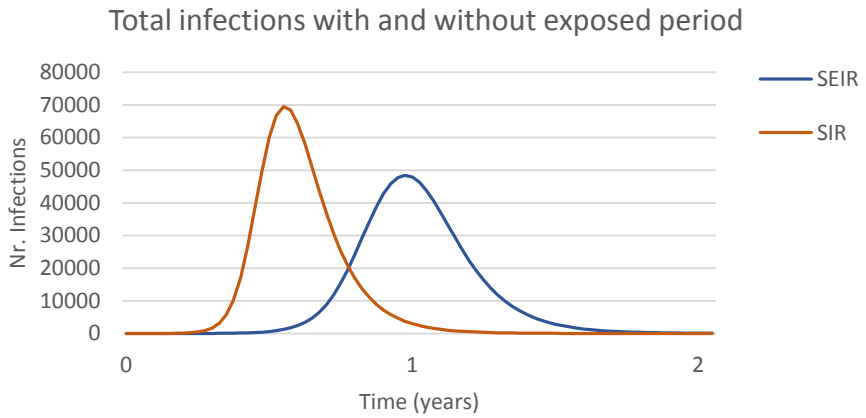


Figure 4.7: *Difference between SEIR and SIR models in total number of infections.*

4.3.2 INFECTED PERIOD

The length of the infected period varies between 21 days and 4 months. Around 21 days is said to be the duration of the most infectious period, 4 months is the duration that a person can suffer from the symptoms of pertussis (RIVM, 2011). The sensitivity of this parameter is tested by running the model on the standard set of parameters (Table 4.2), and only changing the duration of the infected period. The values for the infected period that the model has been run on are the two extremes, and the most realistic value; 14 days, the minimum duration of the infectious period, 21 days, the most realistic, and 4 months, the total duration that one can have symptoms.

As can be seen in Figure 4.8 there is quite a difference in number of infections when changing the duration of the infectious period. This is logical, since the longer the infectious period is, the more people one infectious person can infect. The timing for pertussis outbreak does not differ a lot. In all cases the peak of the outbreak is reached about one year after an infection is introduced in the population. When running the model for a longer time span it can be expected that new outbreaks will be generated quicker when the infectious period is set as shorter period. This is due to the

fraction of recovered people being lower, and fraction susceptible people higher in this case. The case of 122 days is, however, not fully realistic. Infected people can suffer from the symptoms of pertussis for 122 days, they will not be infectious for this full period of time. But it can be said that the model is sensitive for this parameter, in terms of number of infections and frequency of outbreaks.

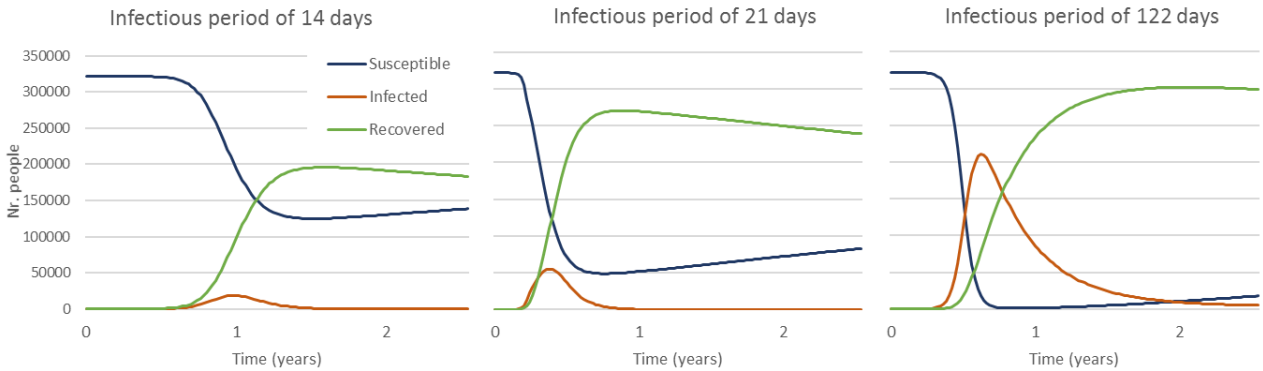


Figure 4.8: *Difference between duration of infected period in total number of infections*[1].

4.3.3 RECOVERED PERIOD

The length of the recovered period, or the duration of immunity after infection, has the most variance in duration. This is said to be between 4 and 20 years. The sensitivity of this parameter is tested by running the model on the standard set of parameters (Table 4.2), and only changing the duration of the recovered period. The values for the recovered period that the model has been run on are; 4 year, 12 year, and 20 year.

Changes in the duration of the recovered period barely have an impact on the number of people that get infected with pertussis (Figure 4.9). It does have an impact on the time between a first and second pertussis outbreak. In Figure 4.9 for a recovered period of 4 years a new (smaller) peak is visible at 4.3 years, and no second peak occurs for the longer recovered period. With a recovered period of 20 years it takes longer for someone who has been infected with pertussis to become susceptible again. Logically, it takes longer in this case for a new pertussis outbreak to occur. The model is sensitive to the duration of the recovered period on the frequency of pertussis outbreaks.

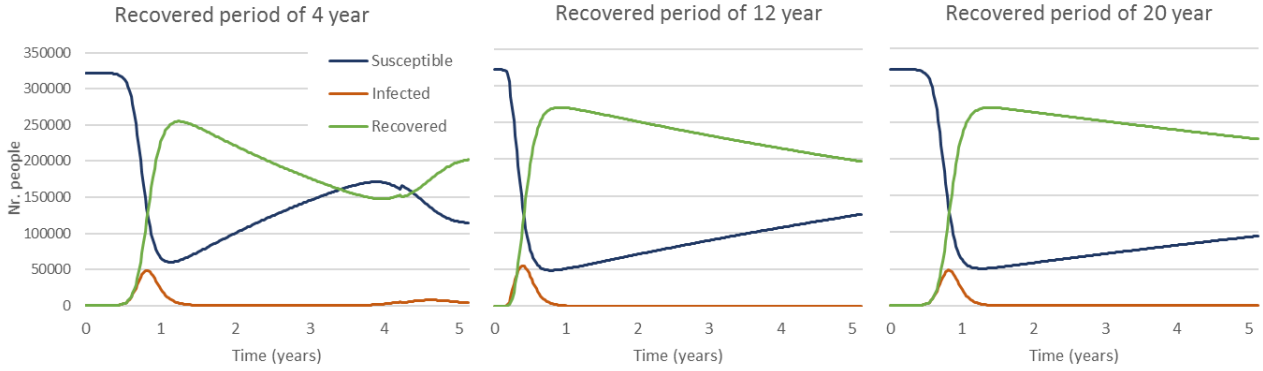


Figure 4.9: *Difference between duration of recovered period in total number of susceptible, infected, and recovered people.*

[1] For clarity reasons the fraction of the population that is exposed is not shown in this figure, and the figures following in this chapter. The results are, however, generated by taking the exposed period into account.

4.3.4 PERCENTAGE IMMUNITY IN START POPULATION

The impact of the number of immune people in the start population is expected to have an impact on the severity of the first outbreak. The sensitivity of this parameter is tested by running the model on the standard set of parameters (Table 4.2), and only changing the percentage of the population that is immune to pertussis in the start population, that is used as input for the model.

As can be seen in Figure 4.10, changing the percentage of immunity in the population that is being used as model input does have an impact on the number of infections of the initial pertussis outbreak. After some time (4 to 5 years), however, the number of susceptible, recovered and infected people in the population is almost on the same level for the model that has been run with a start population in which 0% of the population is immune, and the models that have been run with a start population in which 70% or 90% of the population is immune. This can be explained, because after an initial outbreak the level immunity of a fully susceptible population will rise enormously. Therefore, the amount of immune people in the start population does not have a big impact on the further proceedings of the model, and the model is thus not very sensitive to this parameter.

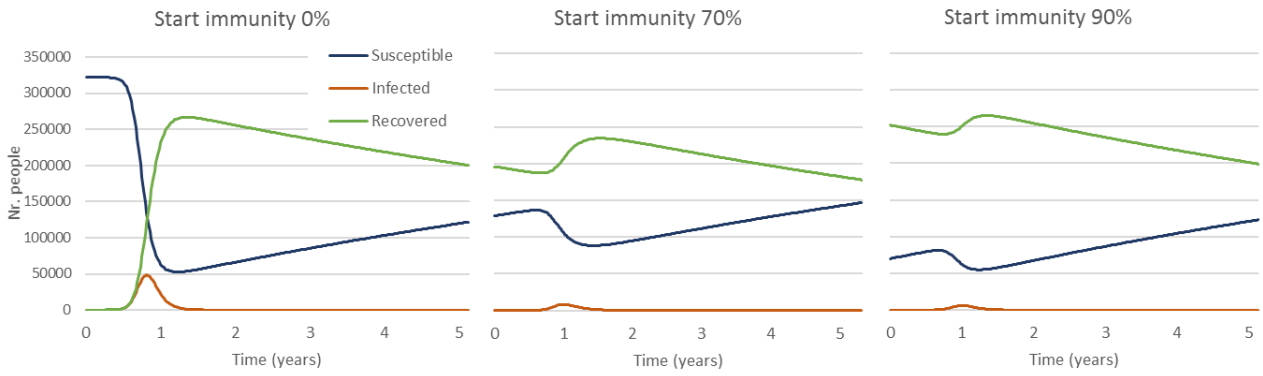


Figure 4.10: *Difference between percentage immunity in start population on number of susceptible, infected and recovered people in the population.*

4.3.5 TRANSMISSION RATE

The transmission rate is expected to be a parameter that has a high impact on the outcomes of the model. The parameter defines the infection rate, together with contact rates between people from different age groups. The contact rates are acquired via the RIVM, and are assumed to be correct. The transmission rate is however an unknown value that might have a big influence on the outcomes of the model.

To test the sensitivity of the model for the transmission rate, the transmission rate for influenza (which is transmitted similarly as pertussis) is taken as a starting point; 0.2 (Del Valle et al., 2007). This rate is changed with a factor ten to see what happens with the number of susceptible, infected and recovered people in the population. When running the model with the smallest rate; 0.02, no infections are generated at all, the transmission rate is too low for a pertussis outbreak to occur (Figure 4.11). In Figure 4.11 the outcomes for the rates 0.2 and 2.0 can also be seen. Not only is there a difference in the number of infections generated, there is also a big difference in the fraction of the population that is in the recovered phase. The line of recovered people in the middle figure is declining, while the line for recovered people in the right figure has some minor oscillations and stays high, even though the duration of the recovered period is set to the same length.

It can be said that the transmission rate has a big impact on the behavior of the model, because it influences not only the number of infections generated, but also has an influence on the frequency of pertussis outbreaks.

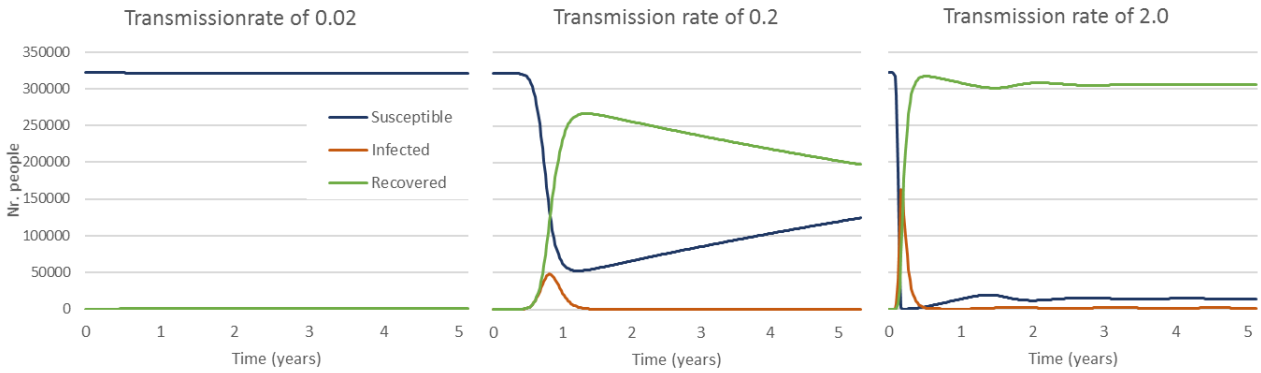


Figure 4.11: *Difference between transmission rate on number of susceptible, infected and recovered people in the population.*

4.3.6 LOCATION OF DISEASE INTRODUCTION

At the start of the model an infection is introduced in a chosen municipality. Which municipality this is might have an impact on the spatial temporal pattern of diffusion. To test this, the model has been run with the standard set of parameters (Table 4.2), but each time the municipality where the infection was introduced was changed. Four municipalities have been chosen to test the model for sensitivity on this parameter. They have been chosen based on their population size. The municipalities are: Amsterdam; the biggest municipality, in terms of population, of the Netherlands, Utrecht; another large municipality, but a lot smaller than Amsterdam, Middelburg; a medium sized municipality, and Ten Boer; the smallest municipality of the Netherlands (after merging the even smaller municipalities, see section 3.2.1.3).

When looking at the susceptible population, infected population and recovered population a difference can be seen in the different municipalities (Figure 4.12). This is of course logical, since the different municipalities have a different population size. However, it is even the case that a pertussis outbreak will not occur in Middelburg and Ten Boer when the model is run with a transmission rate of 0.2. For Middelburg the transmission rate had to be increased to 0.6 for an outbreak to occur. For Ten Boer the transmission rate had to be increased to 2.0 for an outbreak to occur. So in smaller municipalities the transmission rate should be higher for an outbreak to occur. It can also be seen that it takes more days in smaller municipalities for an outbreak to reach its peak.

When looking at the geographic diffusion, one should take into account where in the Netherlands an infection is introduced. After a longer runtime most municipalities have been infected with pertussis, however the route the disease has travelled throughout the country is defined by the location where an infection is introduced (Figure 4.13, p.47).

It can be said that the model is sensitive for this parameter. Both in terms of spatial diffusion and the time it takes for an outbreak to occur, and thus starts to spread to other regions. The bigger the difference in population size the bigger the difference in the time it takes for an outbreak to occur. For differences in spatial diffusion the size of the population does not have an influence, purely the geographic location of the city.

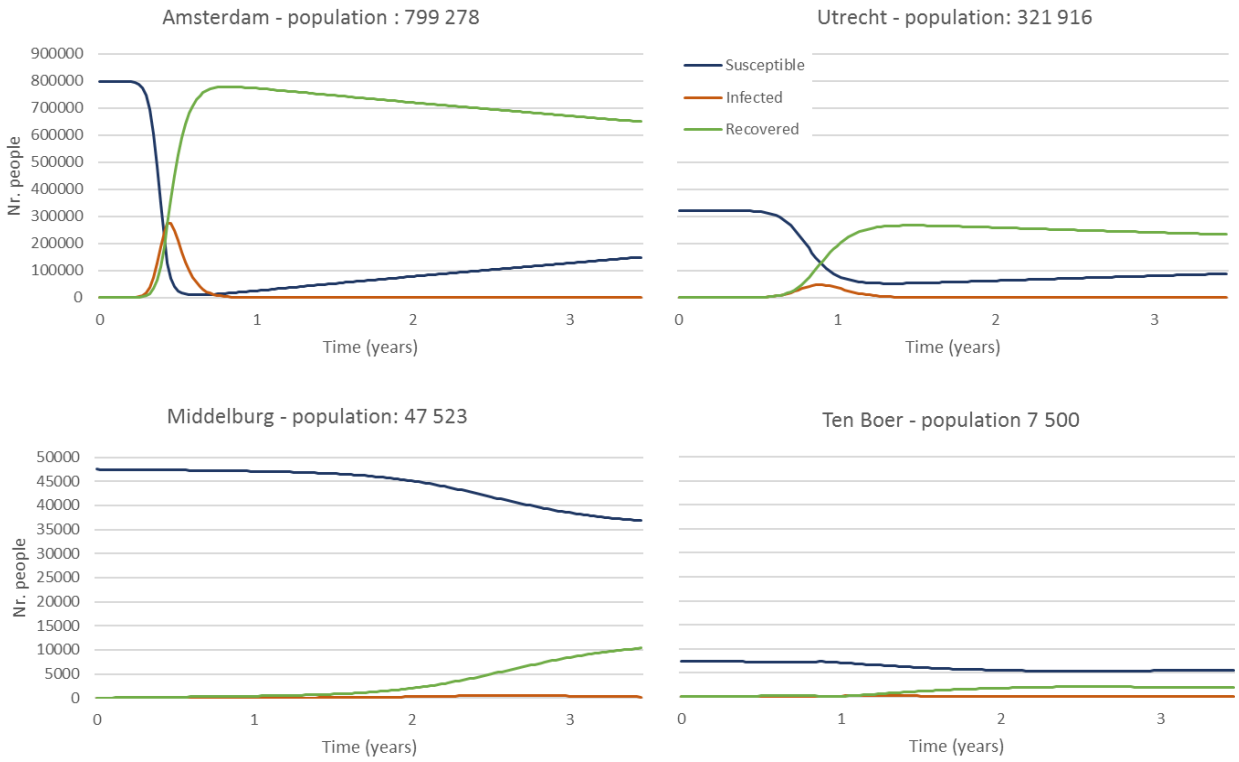


Figure 4.12: *Differences between locations where an infection is introduced on number of susceptible, infected and recovered people in the population.*

4.3.7 CONCLUSION OF SENSITIVITY ANALYSIS

The model has been tested for sensitivity on different parameters. The parameters that have been tested are the influence of the duration of the infectious period, the duration of the recovered period, the percentage immunity in the start population, the transmission rate, and the location where the disease is introduced at the start of the model.

Making changes in the parameters had an influence on the output of the model for all parameters. The model is least sensitive to changes in the percentage of immunity in the start population. The model is most sensitive to the transmission rate, the duration of the infectious period, and the location where the disease is introduced. The transmission rate and duration of the infectious period have an impact on both the fraction infected persons in the population as well as on the fraction recovered people in the population. The location where the disease is introduced has a big impact because it largely defines the spatial diffusion of the disease.

Figure 4.13: *Spatial diffusion of pertussis from different start locations. The first maps are from different time steps (days) (Amsterdam: 84, Utrecht: 182, Middelburg: 658, Ten Boer: 56). The next maps are all a week apart. This is not a realistic time span, but allows for comparison.*

4.4 Calibration

The sensitivity analysis showed which parameters have a high impact on the outcomes of the model, the model validation showed that parts of the model are able to generate a similar disease curve as observed in real life. In this part, the sensitive parameters will be used in the process of calibration, on the parts of the model that are validated. Since information is known about pertussis epidemics in the past the parameters will be adjusted in a way that the output of the model is most comparable with real pertussis epidemics in the past.

4.4.1 CALIBRATION PARAMETERS

The exposed period will not be varied in the process of calibration. It is chosen to set the value of the exposed period to 8.5 days; the average expected duration of this period. A random duration could have been implemented, each time step the value for the exposed period would have been set to either 7, 8, 9, or 10. It is chosen to set it to one number to make the base model deterministic, which allows for better interpretation of the behavior of the agents of the model in a later stage. The duration of the infectious period will also be set to a chosen value. For this the most realistic duration of this infectious period is chosen; 21 days. For the duration of the recovered period the average duration is chosen; 12 years. These durations are assumed to be correct, since they are named in different researches and sources (Hethcote, 1997; RIVM, 2011).

The model showed to be less sensitive to the percentage immunity in the start population, changing this parameter only has an effect on the first modelled pertussis outbreak. For this parameter also a set value is chosen. The immunity of the start population will be set to 70%. The first year of the model simulates 1996, before this year few pertussis cases were reported. Therefore, the percentage immunity is relatively low, children were already being vaccinated (between 90 and 95% of the infants of around 2 months old; Zorgatlas, 2014), however there was less immunity due to previous infections by people. This number cannot be validated entirely, but is based on logic, besides it does not have a big impact on the model (see section 4.3.4).

Utrecht is chosen as the municipality where an infection will be introduced at the start of the model, for the same reasons as explained in section 4.2.2. The transmission rate will be used as calibration parameter. The least is known about this parameter, furthermore, it was one of the parameters for which the model is most sensitive.

4.4.2 CALIBRATION PROCESS AND RESULTS

Because of the long runtime of the model when taking all municipalities and the commuting between these municipalities into account, the calibration had to be performed on a single municipality (see Appendix C for runtimes). The true behavior of the model can only be evaluated after the implementation of the agent-based part, this partial calibration should, therefore, not be a problem.

Data about pertussis notifications in Utrecht, per age category, have been acquired for the year 1996 (Table 4.3, personal contact: P.W.M. Augustijn, 2016). A note should be taken when looking at the number of reported pertussis notifications. This amount is lower than the actual number of pertussis infections. There is notification obligation in the Netherlands, however, not all people who are infected with pertussis are diagnosed.

To get some idea about the number of pertussis cases it is taken into account that according to Van der Maas (2013) only around 0.3% of all pertussis cases in the Netherlands are reported. A study of Mcdonald et al. (2014) found that around 1 to 2% of all pertussis cases in the Netherlands

are reported. The number of infected people generated by the model is thus allowed to be a lot higher than the number of reported cases by the RIVM.

Table 4.3: *Number of reported pertussis cases in Utrecht in 1996. The expected number of cases are based on the number of reported cases being just 0.3 to 2% of the total pertussis cases.*

Age group	**Number reported cases in 1996**	**Expected total cases**	**Percentage**
0 – 4 year	16	800 – 5333	32%
4 – 12 year	21	1050 - 7000	42%
12 – 18 year	3	150 – 1000	6%
18 – 24 year	1	50 - 333	2%
24 – 45 year	8	400 - 2666	16%
45 +	1	50 - 333	2%
Total	**50**	**2500 - 14265**	**100%**

Since the data is about 1996, and the model simulates the time period from 1996 onwards, the first generated peak of the model will be used for calibration purposes. This first peak represents the outbreak of 1996. The model has been run with several input transmission rates (see Appendix D). The model best represented the expected real pertussis infection in the Netherlands when it was run with the input transmission rates of 0.4 for summer, 0.2 for spring and autumn, and 0.1 for winter.

The total number of infections rose to 8057 people, when using these transmission rates (Table 4.4). This lies between the range of expected total cases (Table 4.3). More runs generated a total number of infections between that range. However, this run was chosen as most suitable, because it is almost exactly the average number of cases of the expected range. Furthermore, there has been looked at whether the distribution of infections over the different age categories of the model is similar to the observed distribution. For most age categories, the number of infections lies between the expected range. The order of age categories from most expected infections to least expected infections is the same as the order that is generated by the model, except for the youngest and oldest group. The percentage infections in the youngest age group is lower than in reality, and higher than in reality for the oldest age group. The number of infections generated by these transmission rates are seen as a good representation of reality.

Table 4.4: *Number of generated pertussis infection by the model in 1996. The model does not calculate the same age groups as depicted in Table 4.3, therefore the results are summed to reach age groups that are comparable. Coloured by whether the summed totals are within the expected range or not. Transmission rates: Summer 0.4; Spring/Autumn 0.2; Winter 0.1.*

Age group	Number infections	Summed for comparable age groups	Percentage
0 – 5 months	22		
5 months – 5 year	1488	1510	18.8%
5 – 12 year	3362	3362	41.7%
12 – 17 year	761	761	9.4%
17 – 25 year	327	327	4.1%
25 – 35 year	507		
35 – 50 year	959	1466	18.2%
50 – 65 year	441		
65 +	190	631	7.8%
Total	**8057**	**8057**	**100%**

Furthermore, it is evaluated whether the model generates an epidemic pattern using these input transmission rates. It has been shown that changes in transmission rates can be the cause of the pattern staying endemic or epidemic (see section 4.2.2). As Figure 4.14 shows, the transmission rates are adequate to generate an epidemic disease cycle. When evaluating the temporal evolution of the epidemic per age group, we see that there are clearly different patterns between these groups. The first observation is the fact that the first peak is mainly generated by a single age group (5-12 years old). The second observation is that this peak does not repeat itself in years afterwards. Although a second peak occurs between 8-9 years this peak is much smaller. The age group 12-17 years has a repetition in peaks but not in synchrony with the other age groups. Because of this a-synchronicity the total variation in infection is not large yet, a cyclic pattern seems to occur with a peak for adults in the years 2, 10, 16 and for teenagers at 1, 8, 14 and 19 years.

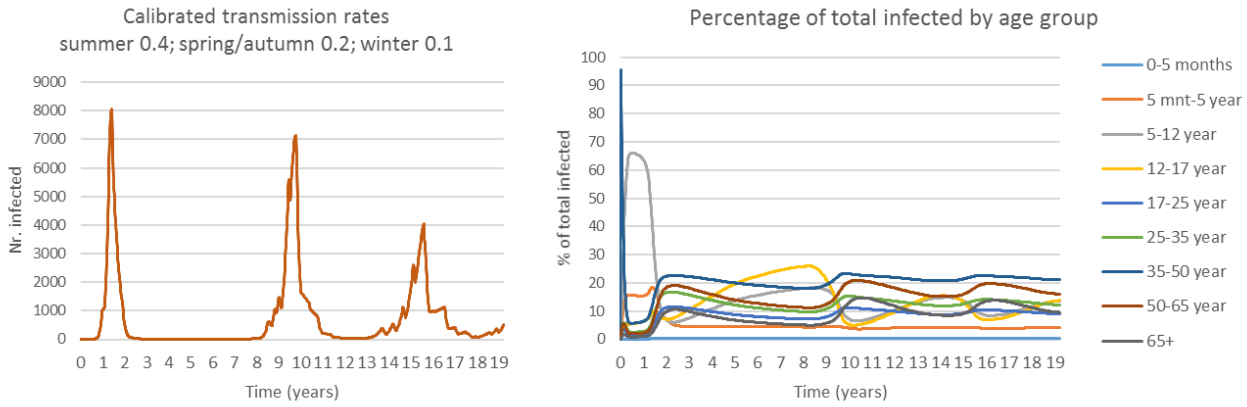


Figure 4.14: *Epidemic disease curve generated with the calibrated transmission rates, disaggregated by relative infections per age group.*

4.4.3 CONCLUSION OF CALIBRATION

The model has been calibrated solely on the transmission rate. The transmission rates that generated a model output that represent reality the most were 0.4 for summer, 0.2 for spring and autumn, and 0.1 for winter. With these transmission rates the correct number of expected infections per age category could be generated for the first epidemic outbreak, furthermore an epidemic disease cycle was observed. The transmission rate is in line with what was expected, since the transmission rate for influenza is 0.2. Influenza is transmitted similarly as pertussis, so transmission rates around this value are seen as realistic.

5 VALIDATION, ANALYSIS AND RESULTS

This chapter splits into two parts, the validation of the model (5.1) in which the performance of the model will compared with the results of an existing model for pertussis; and a discussion of the effects of the eight vaccination strategies (5.2). As explained in section 3.2.4 these intervention strategies are hypothetically conducted by the health units of the Netherlands, hence the health units would be modelled as agents. Due to time limitations the vaccination intervention is not agent-based, but is simulated via a static method, where vaccination occurs at pre-defined percentages and times.

5.1 Model validation

Before testing different intervention scenarios, the pertussis model is compared to a model developed by Van Rie & Hethcote (2004). These researchers investigated five new vaccination strategies through the mathematical modelling of different age groups, whose contacts are defined by a WAIFW matrix. To validate the model used in this thesis, two of their strategies will be regenerated.

5.1.1 GENERAL BEHAVIOR MODEL

To investigate the model's behavior in response to re-occurring vaccination of adults, a first intervention experiment is conducted in which every 10 years the age group of 25 year and older (including the age groups 25-35, 35-50, 50-65 and 65+) is vaccinated with a pre-defined percentage of vaccination. The chosen vaccination rates of 25%, 50% and 80% are added to the regular adult immunity (by vaccinating a percentage of the susceptible adult population). The current childhood vaccination is not taken into account in these runs. This experiment is limited to a single municipality (Utrecht), and because of the limited spatial extent no commuting is included.

When looking at the total number of infections (Table 5.1), it shows that more vaccination in the adult age groups leads to a reduction in total number of infections compared to the current vaccination strategy. In the strategies with 50% and 80% coverage, a reduction of 54% and 72% of pertussis cases is perceived at the third epidemic peak. In the strategy with 25% coverage the highest reduction is reached at the second peak of 33%. Vaccination of adults has a substantial effect on the total number of pertussis cases.

Table 5.1: *Number of infections in Utrecht municipality specified by adult vaccination percentage for three consecutive peaks.*

Vaccination strategy	Total infected peak 1	Difference with current, peak 1	Total infected peak 2	Difference with current, peak 2	Total infected peak 3	Difference with current, peak 3
Current	8033		7055		3987	
Adults 25%	7359	-8.39%	4678	-33.69%	3527	-11.54%
Adults 50%	6805	-15.29%	4664	-33.89%	1828	-54.15%
Adults 80%	6348	-20.85%	3390	-51.95%	1106	-72.26%

When looking at the relative distribution of infections over age groups (Figure 5.1 and Figure 5.2), a very different figure is seen when vaccinating adults instead of children. All three vaccination rates show similar results: high percentage of pertussis cases in the age group 5-12 years during the first two years, followed by a peak in all other age groups after 2 to 3 years, and a peak in the adult (25-35 age) group after 4 to 5 years. These results can be explained in the following way. The adult age group is by far the largest group. A reduction in this age group leads to a shift in the relative number of cases per age group but still leave a large number of people susceptible (enough for a new peak). The peak of the 25-35 age group appears to happen 4-5 years after the vaccination took place, this is the moment the immunity wanes. The duration of immunity is set to twelve years in the model, this does not mean that everybody remains immune during this period. After one year $1/12^{th}$ of the immune population has become susceptible again. Apparently, the number of susceptible individuals is high enough to generate a new peak after 4-5 years. The fact that the 25-35 group seems to be more effected (peak) can possibly be explained by the fact that this is the group including most parents of young children, and therefore have a higher chance of infection.

At year 10, a new intervention takes place in the adult strategies, and a reduction in the adult age groups can be observed due to vaccination. The pertussis burden in the younger age groups (except for 0-5 months) is hereby relatively increased. Two years after vaccination, another outbreak can be observed in the 25-35 year age group, albeit less extreme than in year 4.

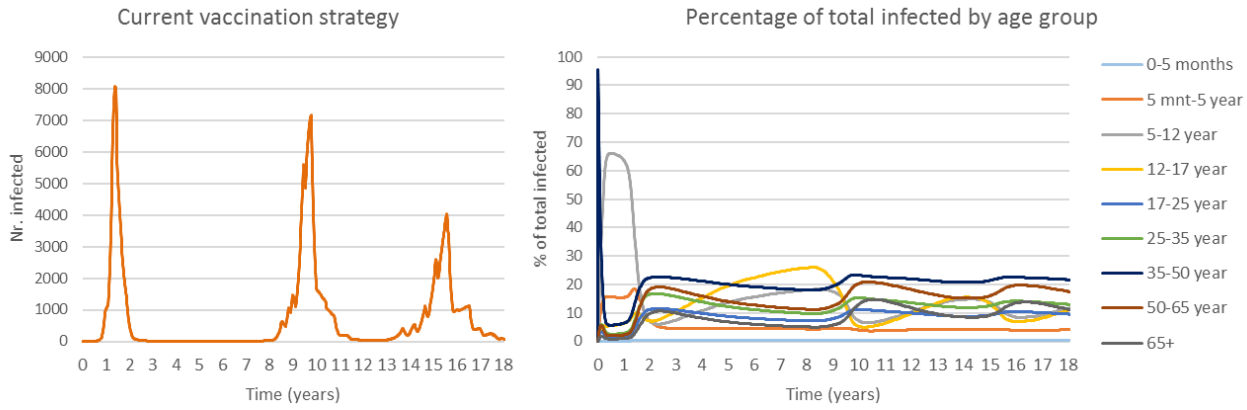


Figure 5.1: *Total infections and infections relative to age group of the current childhood vaccination strategy (for Utrecht municipality).*

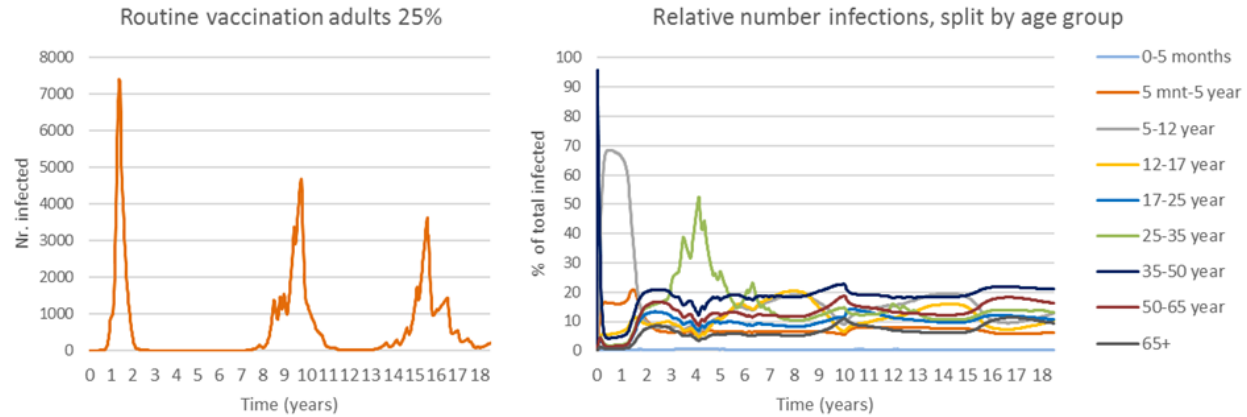


Figure 5.2*: (Continued on next page) Total infections and infections relative to age group where 25%, 50%, and 80% of the adults are vaccinated (for Utrecht municipality).*

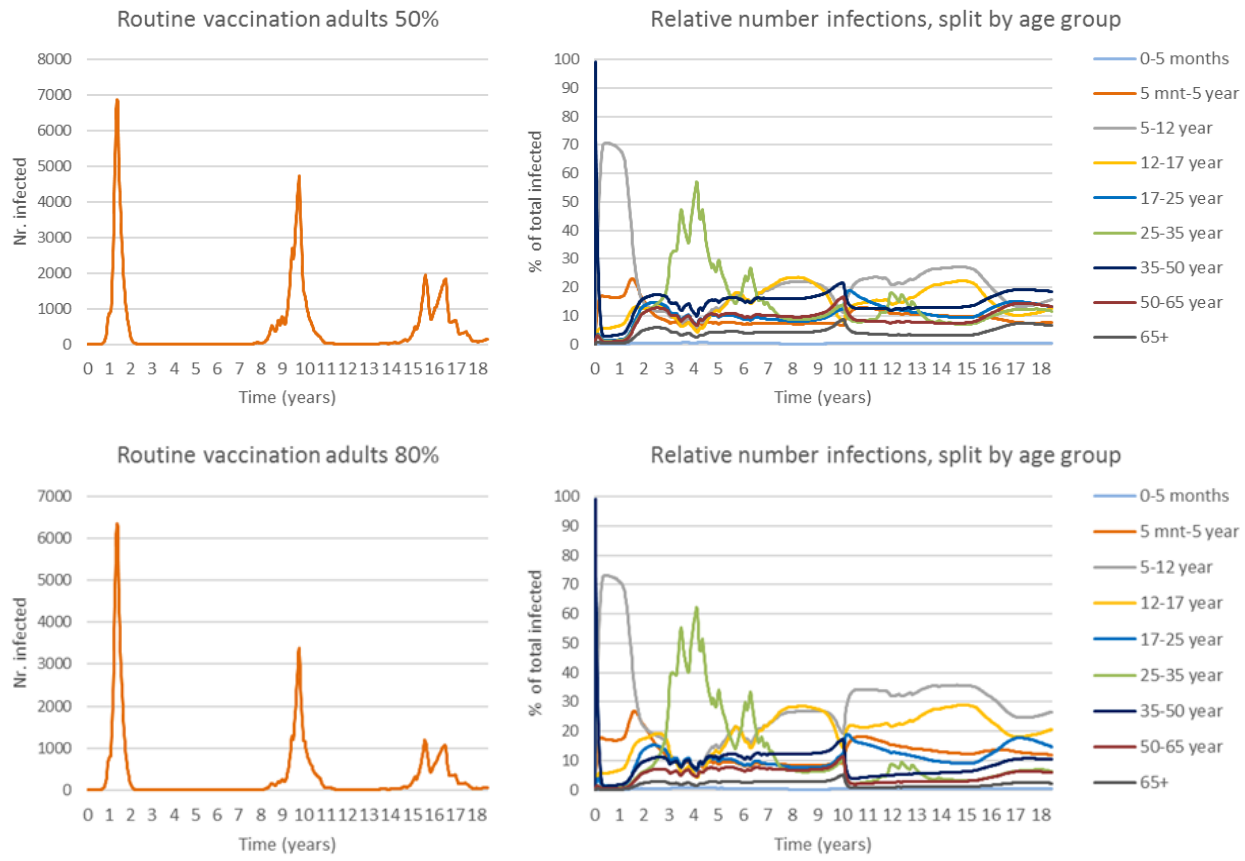


***Figure 5.2**: Total infections and infections relative to age group where 25%, 50%, and 80% of the adults are vaccinated (for Utrecht municipality).*

5.1.2 COMPARISON OF STRATEGIES

Van Rie & Hethcote (2004) test five new vaccination strategies in comparison with the current childhood vaccination scheme in the US. These five strategies are:

1. Current vaccination + routine vaccination of adolescents at age 12 (with 75% coverage).
2. Routine vaccination of adolescents at age 12 (with 75% coverage) + routine vaccination of adults every ten years starting at age 20 (with 60% coverage).
3. Current vaccination + selective vaccination of household contacts of newborns (with 90% coverage).
4. Combination of strategy 1 and 3.
5. Combination of strategy 2 and 3.

Strategy 1 and 2 will be simulated, with the current coverage of the Netherlands (complete country including commuting), and for the new strategies the same coverages as in the research of Van Rie & Hethcote (2004). These strategies will be tested on the municipality of Utrecht only (without commuting).

5.1.2.1 Strategy 1 for Utrecht

Strategy 1, simulated with the model created for this thesis, leads to a minor reduction in pertussis cases at the first outbreak (of 1%), in the second and third simulated outbreak an increase in infections is seen, respectively of 16% and 1% (Table 5.2). When comparing the relative distribution

of infections per age group of this strategy with the current strategy, not much difference is seen (Figure 5.1 and Figure 5.3). As a direct result of vaccination in the teenage age group (12-17 year) a reduction of infections is seen in this group. The expected decrease of pertussis burden in the age groups between 0 and 4 year, due to herd immunity, are not observed in this model output. The decrease in pertussis in the 12-17 age group leads to a small relative increase of pertussis in the groups 35-50 year, 50-65 year, and 65 year and older.

Table 5.2: *Number infections in Utrecht municipality (with a total population of 324 723) with the current vaccination strategy, and with two simulated strategies adopted from Van Rie & Hethcote (2004). During the runtime three outbreaks were simulated.*

Vaccination strategy	Total infected peak 1	Difference with current, peak 1	Total infected peak 2	Difference with current, peak 2	Total infected peak 3	Difference with current, peak 3
Current	8033		7055		3987	
Strategy 1	7940	-1.15%	8198	+16.20%	4027	+1.00%
Strategy 2	6544	-18.54%	4023	-42.98%	1755	-55.98%

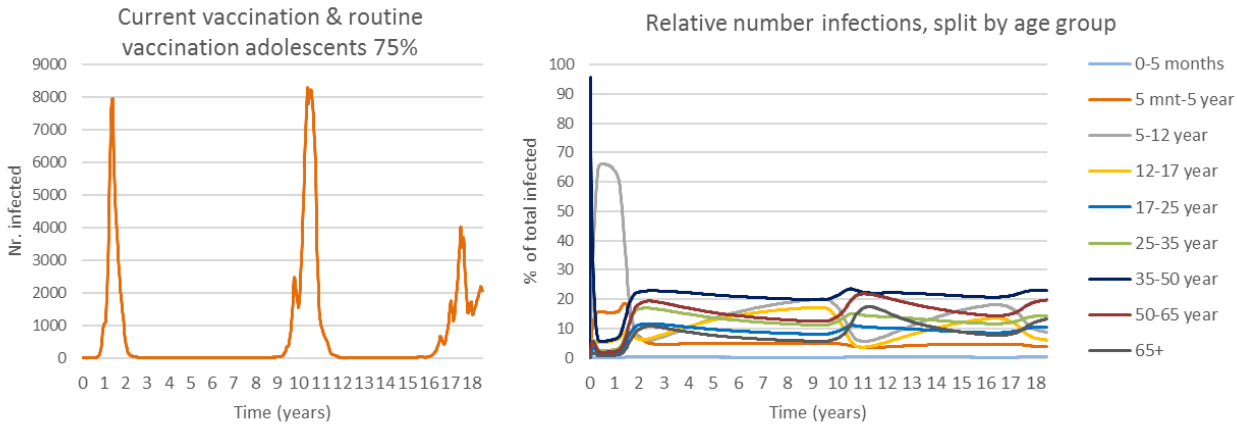


Figure 5.3*: Total infections and infections relative to age group of strategy 1 (for Utrecht municipality).*

In the research of Van Rie & Hethcote (2004) strategy 1 leads to an overall decline of pertussis of 19%, most of this reduction is seen in the group in which extra vaccination takes place (12-17 year). However, it also leads to some herd immunity in children, in a way that the pertussis burden is decreased in the ages between 0 and 4 year. This is not seen in Dutch situation. A possible explanation is the different school sizes in the US and the Netherlands. In the US it is more regular to educate children of a larger age range in the same building as in the Netherlands. Where children above age 12 structurally go to a different school(building). So there is less contact between teenagers and children in the Netherlands, hence there is less effect on children when vaccinating teenagers.

5.1.2.2 Strategy 2 for Utrecht

Strategy 2 leads to a continuous decrease of infections over time, a decrease of 18% at the first outbreak, 43% at the second outbreak, and 56% at the third outbreak. When looking at the temporal evolution of the epidemic per age group, a similar figure is observed as the adult vaccination

strategies explained earlier this section (Figure 5.4). About 4 to 5 years after vaccination of adults an outbreak is observed in the 25-35 year age group, which leads to a relative increase of infections in the age groups 5-12 and 12-17, even though there is also vaccinated in the 12-17 year group. The expected indirect effect, of pertussis reduction, in the age groups below 5 year are not observed.

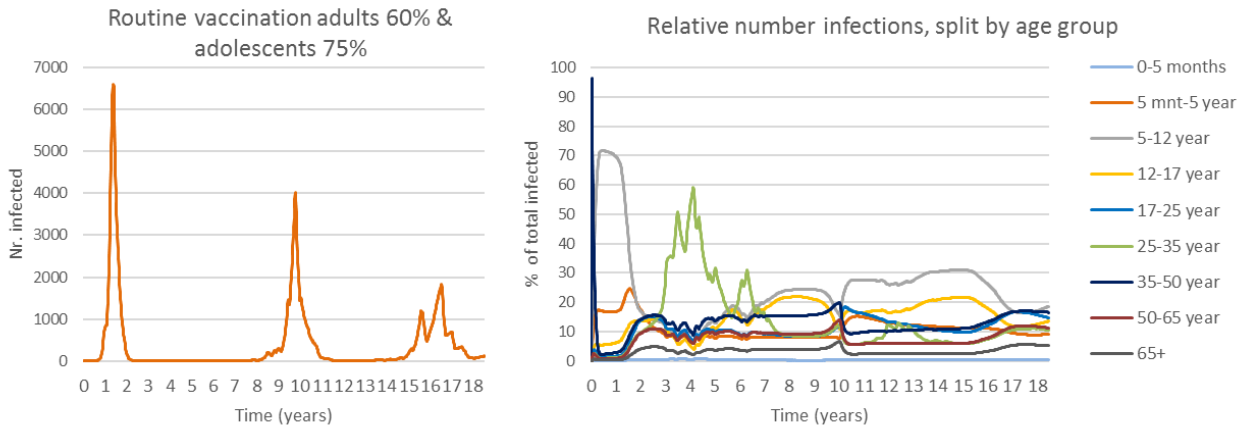


***Figure 5.4**: Total infections and infections relative to age group of strategy 2 (for Utrecht municipality).*

In the research of Van Rie & Hethcote (2004) strategy 2 leads to an overall reduction in pertussis cases of 37%. Not only a substantial effect is seen in the adolescent and adult age groups, also a sizeable indirect effect is observed in the age groups between 0 and 4 year.

5.1.2.3 Strategy 1 for the complete country

The output of strategy 1 can be seen in Figure 5.6. This figure is a lot like the figure of the current vaccination strategy (depicted in Figure 5.5). The main differences are the relative number of infections in the 35-50 year age group being about 5% higher, the age group 50-65 year has a pertussis burden of about 5% lower, the number of infections in the 25-35 year group are slightly higher, and the number of infections in the 12-17 year group are slightly lower. In both the current and the strategy 1 scenario the number of infections in the 12-17 year group shows oscillations, with a peak about every 3 to 4 year. When looking at the total number of infections generated, an increase in infections of 1.10% is observed in strategy 1 compared to the current situation.

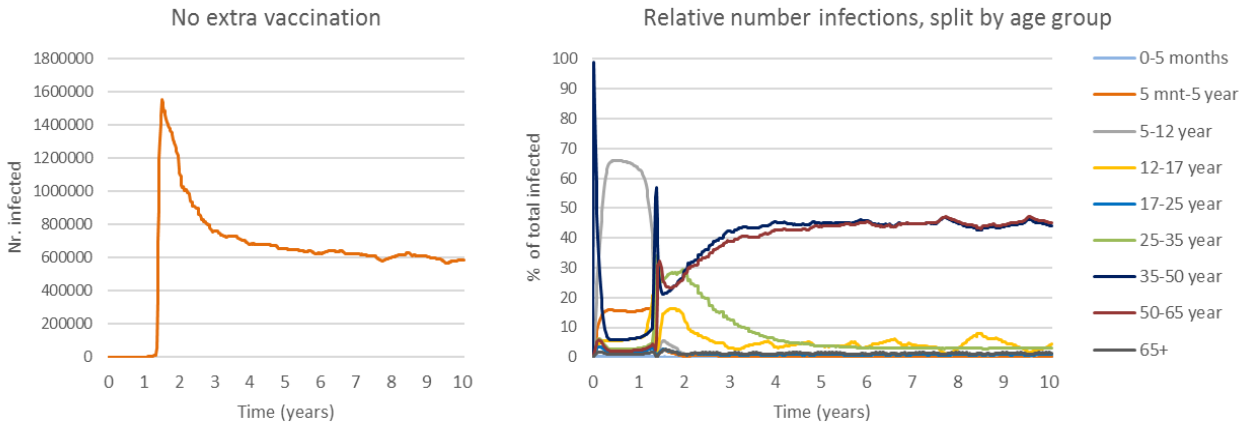


***Figure 5.5:** The total number of infections and the relative number of infections per age group for the current situation in the Netherlands - only childhood vaccination.*

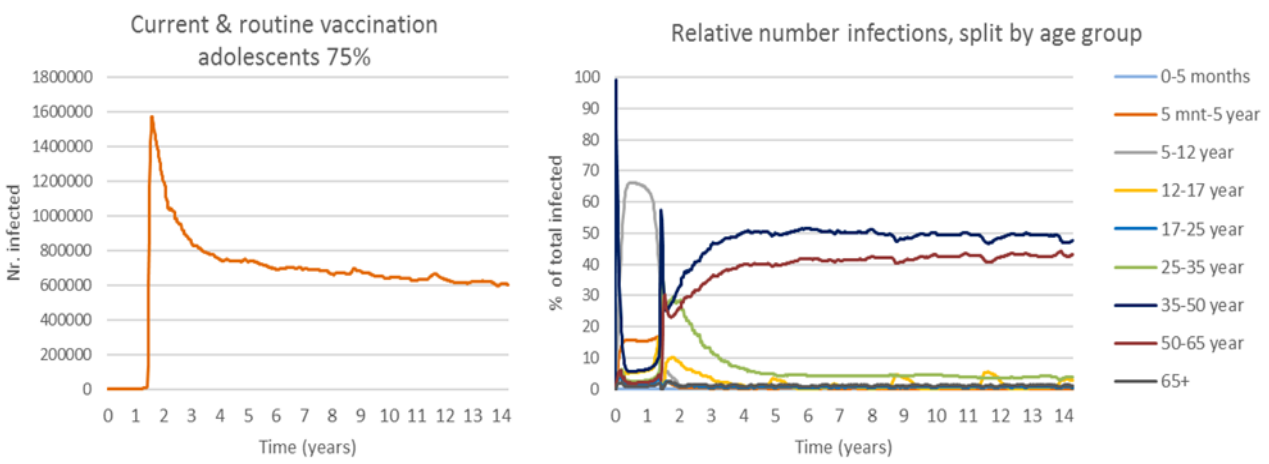


***Figure 5.6**: Total infections and infections relative to age group of strategy 1 (with commuting).*

5.1.2.4 Strategy 2 for the complete country

When running this strategy, where adults are vaccinated, with commuting a problem occurs. At the time where an outbreak occurs in the 25-35 year age group (as can be observed in Figure 5.2 and Figure 5.4) the model crashes with the error *"math operation produced a number too large for NetLogo"*. It is thought that this is caused by the large outbreak in the 25-35 year group, which will be enhanced by commuting, however this cannot be verified due to the model's crashing.

5.2 Scenarios

In the analysis part of this research the model was used to compare the network intervention scenario with the maternal vaccination scenario. Due to limitations by the long runtime of the model the wanted time span of 40 years will not be fully analyzed.

The model will be run for eight different situations, in all situations both job- and school commuting is taken into account. Four runs are performed to test the network based vaccination strategy, and four runs to test the maternal vaccination strategy. Since the model is deterministic differences in results are fully related to these differences in vaccination strategies.

5.2.1 NETWORK INTERVENTION

By vaccinating in certain locations that are linked with many other locations it is examined if it is possible to influence the number of disease cases and/or the spatial-temporal diffusion pattern of pertussis. One of the hypotheses concerning network based vaccination was that there might be several 'network' cities that link the different urban networks of the Netherlands (see section 2.4 Network based vaccination). When visualizing the commuter flows and urban networks in one figure (see Figure 5.7), one can see that there is no such thing as a 'network' city that links two or more urban networks. The urban networks are directly linked with each other via daily commuter flows. Every day there are at least 1000 commuters travelling back and forth between Randstad Holland and Groningen-Assen, Randstad Holland and Zuid-Limburg, Randstad Holland and Brabantstad, Randstad Holland and Arnhem-Nijmegen, and between Arnhem-Nijmegen and Brabantstad. The only urban network that is not directly linked (with more than 1000 commuters a day) with another region is Twente. Especially Randstad Holland plays a big role in connecting all regions of the Netherlands. This does not come as a surprise, since Randstad Holland is being identified as "the

political, administrative, social and cultural heart of the Netherlands and the main area of economy, logistics, business and financial services, and tourism" (Ministerie van VROM et al., 2005, p. 66). Furthermore, four of the biggest cities of the Netherlands are located in Randstad Holland.

Since there are no network cities identified, another strategy will be used to test network based vaccination. Instead of targeting cities that link urban networks, the impact of increased vaccination in cities that have many links and the impact of increased vaccination in large cities will be the focus of these experiments. These selected cities with many links are Zoetermeer and Haarlemmermeer, and Rotterdam and Amsterdam are selected as the big cities for this vaccination strategy (Figure 5.7). Vaccination coverage in these cities will be derived from data about vaccination rates per municipality for the standard childhood vaccinations, and the strategy will be tested as a one-time intervention.

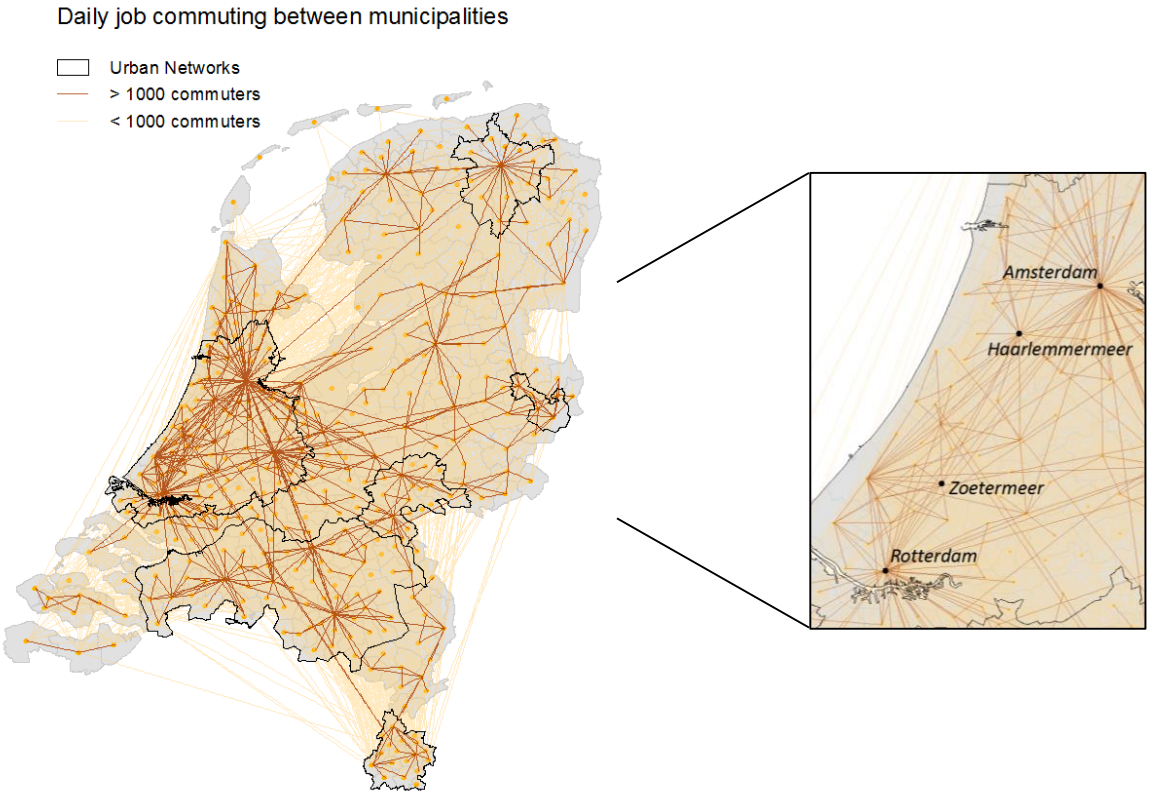


Figure 5.7: (Left) *Daily job commuter flows and the urban networks of the Netherlands (2013). (Right) The four chosen cities for network vaccination, located in Randstad Holland.*

5.2.2 MATERNAL INTERVENTION

Maternal vaccination is seen as a promising method to decrease the number of pertussis infections in infants, the most vulnerable group for pertussis. Women in the Netherlands are advised to vaccinate themselves against pertussis when they are pregnant. In this research vaccinating pregnant women will be modelled in different ways: via a municipality specific percentage, via a one-time vaccination and using a similar number to the network scenario.

As a first method the most ideal situation will be tested. There will be a continuous program running in the Netherlands to vaccinate pregnant women. Every week a municipality specific percentage of (susceptible) pregnant women is vaccinated in all municipalities in the Netherlands.

This percentage is derived from data about vaccination rates per municipality for the standard childhood vaccinations. It is assumed that mothers who let their children be vaccinated against pertussis, will want to get vaccinated against pertussis when they are pregnant.

The second method comprises a one-time vaccination intervention for pregnant women in all municipalities, again the vaccination rate is derived from the vaccination rate of childhood vaccinations per municipality.

To be able to make a comparison between the maternal vaccination and network vaccination a third method will be performed. In this method the number vaccinated pregnant women in total will be the same as the number vaccinated people in the network cities (of the network vaccination strategy). How many people are vaccinated in the network cities determines the intervention for the maternal vaccination. The vaccination rate per municipality is set to a national rate so that the number of vaccinated pregnant women is the same as in the network city. For Amsterdam and Rotterdam this proved to be impossible, since the number of vaccinated people in these cities exceeds the number of pregnant women in the Netherlands (see Table 5.3). For Zoetermeer and Haarlemmermeer this is possible, and runs have been performed. For each vaccinated pregnant women an infant that is introduced in the population model is immune.

Table 5.3: *Number of vaccinated people per network city. The total number of pregnant women in the start population is 171 510. The number of vaccinated people in Amsterdam and Rotterdam exceeds this number. For Zoetermeer the national vaccination rate is set to 70.05% to vaccinate the same amount of pregnant women as are vaccinated in Zoetermeer in total. For Haarlemmermeer the vaccination rate is set to 81.21%.*

City	Total population	Vaccination rate (%)	Vaccinated people
Amsterdam	799 278	99.3	793 683
Rotterdam	616 294	91.7	565 142
Zoetermeer	123 092	97.6	120 138
Haarlemmermeer	149 679	93.1	139 276

5.3 Results of the scenarios

In this section the results of the performed analysis will be discussed. The impact of the different vaccination strategies will be analyzed by looking at the total number of infections, the number of infected infants, and the spatial diffusion of pertussis.

5.3.1 NUMBER INFECTIONS

The first measurement of the influence of the vaccination strategies is the number of infections per age category. The benchmark will be the results of the run performed without any new vaccination strategies. Results are shown in Figure 5.5. The maximum number of infections is 1 553 940, which is being reached halfway in the second year, after an infection has been introduced. After the first epidemic outbreak the number of infections declines until it reaches an endemic state oscillating around 600 000 infections. When looking at the age groups in which most people are infected, an interesting figure can be seen (Figure 5.5). The infection is introduced in the age group 35-50 year. At the beginning of the model all infections are thus seen in this age group, resulting in a peak of 100 percent. After this the biggest increase in infections is seen in the age groups 5-12 year and 5 months-5 year, which can be explained by the high contact rate among 35-50 year olds (parents) and children. It can be noticed that the epidemic peak, a bit later than one year after the first infection is introduced in the population, seems to be caused by an enormous increase of infections in the age

group 35-50 years, and in a smaller amount 50-65 year. After this initial increase in these age groups, the number of infections is rising in the age groups 25-35 year, and 12-17 year as well. In the other age groups a small increase is seen, however these groups do not account for more than 10 percent of the total number of infections. When the disease reaches its' endemic state, around 45 percent of the infections are seen in both the age groups 35-50 year and 50-65 year. After these age groups, most infections are seen in the 12-17 year olds, and 25-35 year olds. However, both already account for less than 10 percent of the total number of infections, the rest of the age groups for even less.

On a side note, this shows that the calibration performed in section 4.4, does not fully result in an expected outcome in terms of the relative number of infections per age group. Most infections were expected in the age group 5-12 year. This is only the case between the introduction of the infection and the outbreak of the epidemic. The developed model, however, does not simulate symptomatic versus a-symptomatic results and also not notified versus un-notified cases. A comparison between notified cases and simulated cases is always difficult. The large share of infections in the age groups 35-50 and 50-60 year supports the expectation that the endemic state of the disease cycle is caused by the number of commuters (see section 4.2.3).

5.3.1.1 Network vaccination

For the network vaccination strategy interventions have been tested in Amsterdam, Rotterdam, Zoetermeer and Haarlemmermeer. It is notable to see that the general figure of the network vaccination strategy is the same as the figure of the current vaccination strategy. This is the case for all four tested cities as location for vaccination (see Appendix E for the individual figures of these intervention strategies). There are some differences in the number of infections when comparing the base run and the four intervention methods. The bigger the city, the lower the maximum number of infections (Table 5.4). Which is a logical result, since the bigger the city the more people are vaccinated, hence the less people will get infected with pertussis. It is, however, striking to see that it is not necessarily the case that more vaccinating leads to less infections. Vaccinating in Zoetermeer and Haarlemmermeer even led to an increase in the maximum number of infections, and in the endemic number of infections when comparing it with the base run.

The time it takes for an epidemic to reach its highest point does not change when vaccinating in certain network locations. It can be said that vaccinating in network locations does have some effect on the number of infections, however, not necessarily a positive effect.

Table 5.4: *The maximum number of infections, at which time the peak of the epidemic outbreak is reached, and around which number the number of infections is oscillating in the endemic state.*

Intervention in	Max. nr. infections	Reached at time (years)	Endemic nr. infections
Non – base run	1 553 940	1.57	600 000
Amsterdam	1 437 615	1.57	580 000
Rotterdam	1 499 049	1.57	600 000
Zoetermeer	1 561 966	1.57	650 000
Haarlemmermeer	1 567 947	1.57	650 000

5.3.1.2 Maternal vaccination

For the maternal vaccination strategy, also four scenarios are tested. Again the general figure of the number of infections, in total and relative by age group, strongly resemble the figure of the base run performed (see Figure 5.8 for one of the four maternal strategies, for the rest of the figures see

Appendix E). The biggest difference is the change in the 35-50 year olds and 50-65 year olds. Whereas the relative number of infections is almost the same in both age groups in the base run, for all maternal vaccination strategies the number of infections in the age group 50-65 year is lower than the number of infections in the age group 35-50 year. Even though the extra vaccination is aimed at the age group 25-35 year, the age pregnant women are assumed to be, no large difference is seen in this age group.

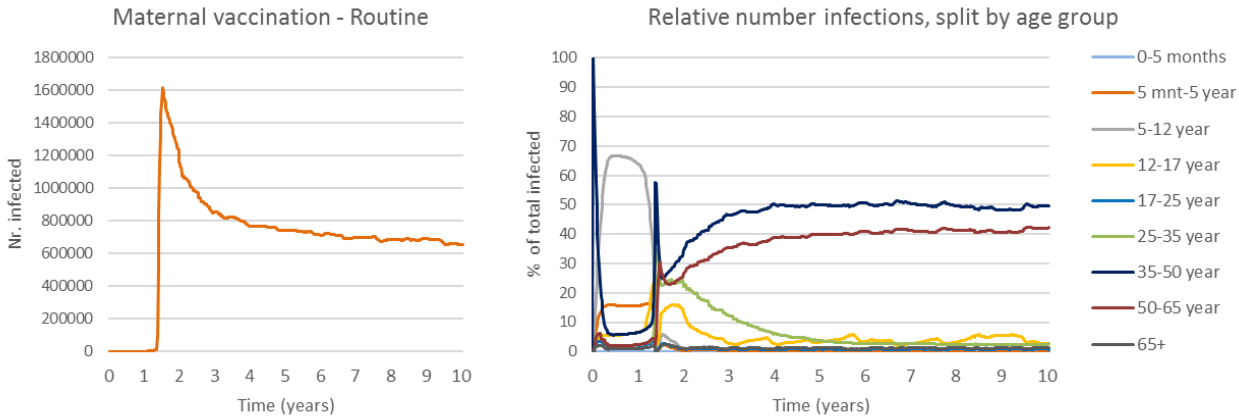


Figure 5.8: *The total number of infections and the relative number of infections per age group for routine maternal vaccination.*

When looking at the maximum number of infections reached at the epidemic peak, the Zoetermeer maternal vaccination strategy (the same number of vaccinated pregnant women compared to the total vaccinated population in Zoetermeer) results in the lowest number of infections of the four maternal vaccination strategies. This is an unexpected result, since this strategy vaccinates the least pregnant women. What is striking to see is that all strategies result in more infections than the base run (Table 5.5).

For comparability reasons the same number of pregnant women have been vaccinated throughout the Netherlands as people were vaccinated in Zoetermeer and Haarlemmermeer. When comparing Table 5.4 and Table 5.5 it can be seen that the network vaccination strategies of Zoetermeer and Haarlemmermeer result in less infections than the maternal strategies. According to this outcome it looks like network vaccination might mean less total infections. However, still more than the number of infections generated by the base run.

The time at which the epidemic peak is reached is the same for all vaccination strategies. The only differences occur at the total number of infections, and the number around which the endemic situation oscillates. This number is the highest in all four maternal vaccination strategies (Table 5.5).

Table 5.5: *The maximum number of infections, at which time the peak of the epidemic outbreak is reached, and around which number the number of infections is oscillating in the endemic state.*

Intervention method	Max. nr. Infections	Reached at time (years)	Endemic nr. infections
Non - baserun	1 553 940	1.57	600 000
One time intervention	1 636 306	1.57	700 000
Routine intervention	1 618 150	1.57	700 000
Nr. Zoetermeer	1 568 805	1.57	650 000
Nr. Haarlemmermeer	1 650 978	1.57	800 000

5.3.1.3 Infected infants

Since infants are the most vulnerable for pertussis, this age group should benefit most from the new vaccination strategies. Therefore, the number of infected infants in each vaccination strategy is compared (Figure 5.9). A broad distinction can be made between the strategies that do affect the number of infected infants and those that do not. The only strategies that prevent infants from infection are routine maternal vaccination, one-time maternal vaccination and the same amount vaccination as Haarlemmermeer (nr. Haarlemmermeer maternal strategy). These three strategies result in less than 10 infected infants for more than six years.

The other vaccination strategies do not decrease the number of infected infants. Only the Rotterdam network- and Amsterdam network strategy result in a slightly lower number of infected infants in the first outbreak. What is interesting to see, is that although the Zoetermeer maternal strategy results in the least total number of infections of all four maternal strategies, the method is not effective in reducing the number of infected infants, but this was also not expected. For the Zoetermeer strategy the lowest vaccination rate of the four maternal strategies has been used: 70.05% of all pregnant women and their infants in each municipality is vaccinated. For the Haarlemmermeer strategy this percentage is 81.21%, and for the one-time and routine strategy these percentages deviate per municipality, but fluctuate between 60% and 99%, of which most around 95%. It seems like there is a tipping point somewhere between a vaccination rate of 70% and 81% in which the difference is made. Either there is enough immunity among mothers and infants to keep the level of infections below 10, or there is too little immunity and the number of infected infants reaches the same levels as non-infant targeting strategies.

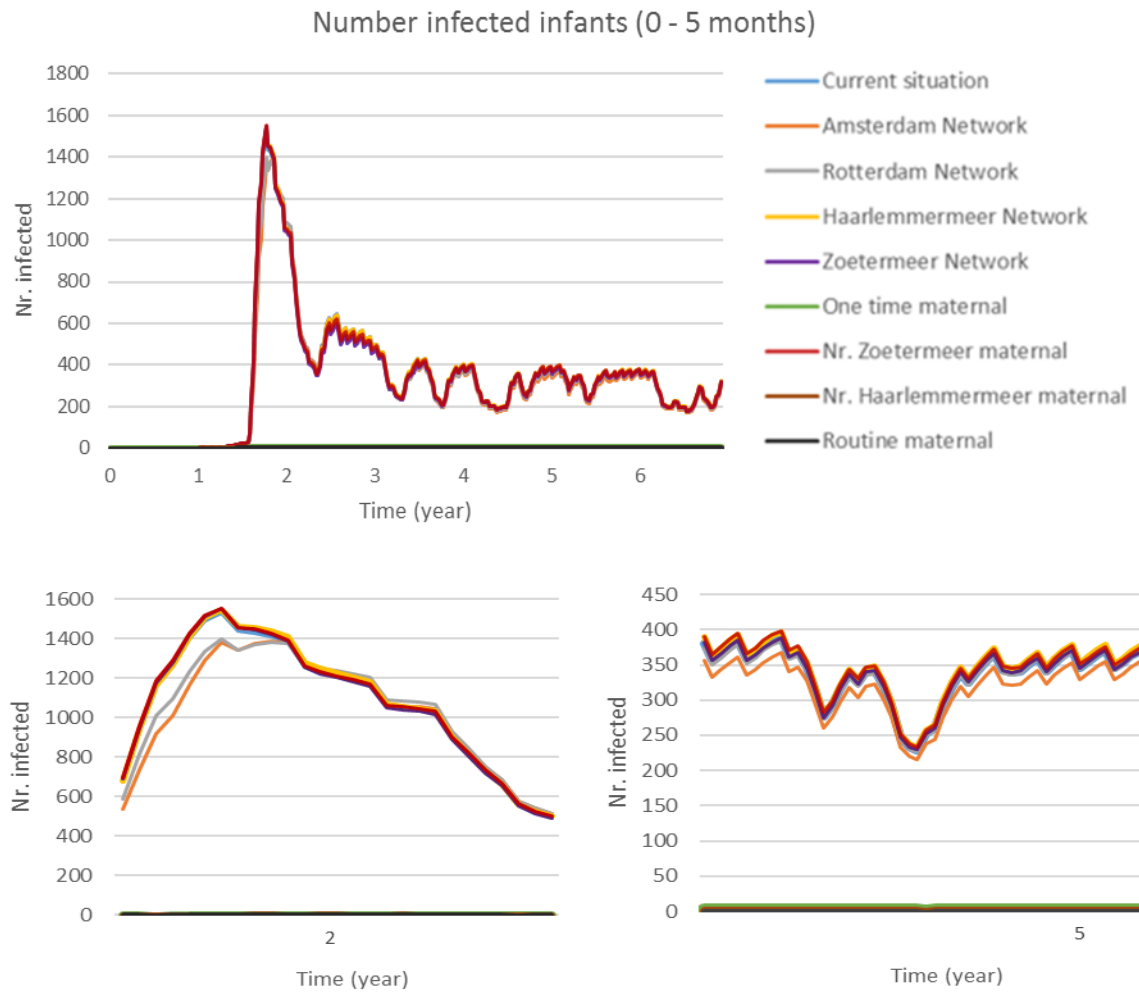


Figure 5.9: *The total number of infected infants per vaccination strategy. The lines at the very bottom of the figure belong to the strategies One time maternal, Nr. Haarlemmermeer maternal and routine maternal.*

5.3.2 EFFECTS ON DISEASE DIFFUSION

The idea behind network vaccinating is that a disease will not spread to new regions of the country. When looking at the spread of pertussis throughout the Netherlands in the current scenario, the base run, it can be seen that the disease spreads to the neighbouring municipalities of Utrecht first (Figure 5.11). The spread of pertussis starts in the 72nd week after one infectious person has been introduced in Utrecht (see Appendix F for an extended lapse of diffusion maps). In the 73rd week the disease starts spreading to further municipalities in the south east as well. The south-western and north-eastern regions are infected the latest. In the 76th week the disease has reached every municipality of the Netherlands. The figure shows that the locations where the number of infections reaches more than 10 percent of the population, are the bigger cities in first instance, like Amsterdam and Rotterdam, or cities close to big cities, like Bunnik and Hilversum. At the 82nd week the number of infections is the highest in the largest number of municipalities. After this week the disease retreats in a similar way as it came to all municipalities. The northern and south-eastern municipalities show the first signs of a declining number of infections. In the endemic state of the disease, pertussis is seen in all regions of the Netherlands, the lowest percentages are seen in the north and south, most infections are seen in the middle regions of the Netherlands.

When looking at the different intervention strategies in network cities, not a lot of difference can be seen (Figure 5.11). The cities in which vaccination takes place keep having lower percentage infections for a longer period than in the base run. Eventually the infections start to rise in those municipalities as well. Except for Haarlemmermeer, this municipality stays within the 5 percent limit. Some minor differences can be seen in terms of spatial differences, and in number infections at certain locations.

When vaccinating in Amsterdam pertussis infections rise slower in the south, in week 74 of the base run some municipalities further south of Utrecht have reached 1-5% infections, when vaccinating in Amsterdam these municipalities are within the 0.5-1% class. In week 75 the figures are, however, almost identical again. One week later the number of municipalities that have reached the 1-5% class are about the same. In the base run these municipalities are more located in Noord-Holland, whereas for intervention in Amsterdam more municipalities in Friesland reached this state. Most of the municipalities of the most northern line of municipalities of the Netherlands do not reach the class 5-10% of the population infected in this vaccination strategy. After week 82 both the current scenario and the intervention in Amsterdam scenario see a declining number of infections in a similar way.

The scenario where there is vaccinated in Rotterdam shows a similar diffusion as vaccinating in Amsterdam in the beginning, with less spreading to the south. In week 82 it is surprising to see that there are more municipalities that reach the > 10% infected state. These municipalities are mainly located in the mid-east of the Netherlands, and municipalities around Amsterdam. After week 82 this scenario also knows a similar decline of pertussis cases as in the current - and Amsterdam scenario.

When vaccinating in Zoetermeer the figures are almost identical to vaccinating in Rotterdam. The biggest difference is the location of municipalities with > 10 percent infections. In this scenario these highly infected municipalities are more located in the middle of the country. Besides, the northern municipalities stay in a lower class of percentage infected. Just like when vaccinating in Amsterdam.

The last network intervention is tested in Haarlemmermeer. It is noticeable that Haarlemmermeer itself stays in a lower class of percentage infected population than the other cities where was vaccinated. Furthermore, the pattern resembles the pattern of vaccinating in Rotterdam the most. Another difference can be seen in the endemic state of the disease (see Appendix F), more municipalities are in the 5-10 percent infected class when the disease has reached its endemic state than in the base run as in the other network vaccination strategies.

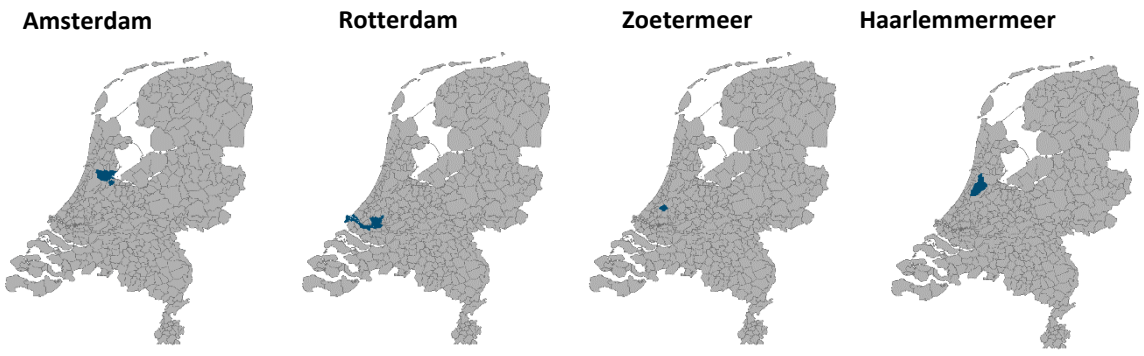


***Figure 5.10**: Locations of vaccination in the network vaccination strategy.*

Figure 5.11: *Pertussis diffusion for different locations of vaccination.*

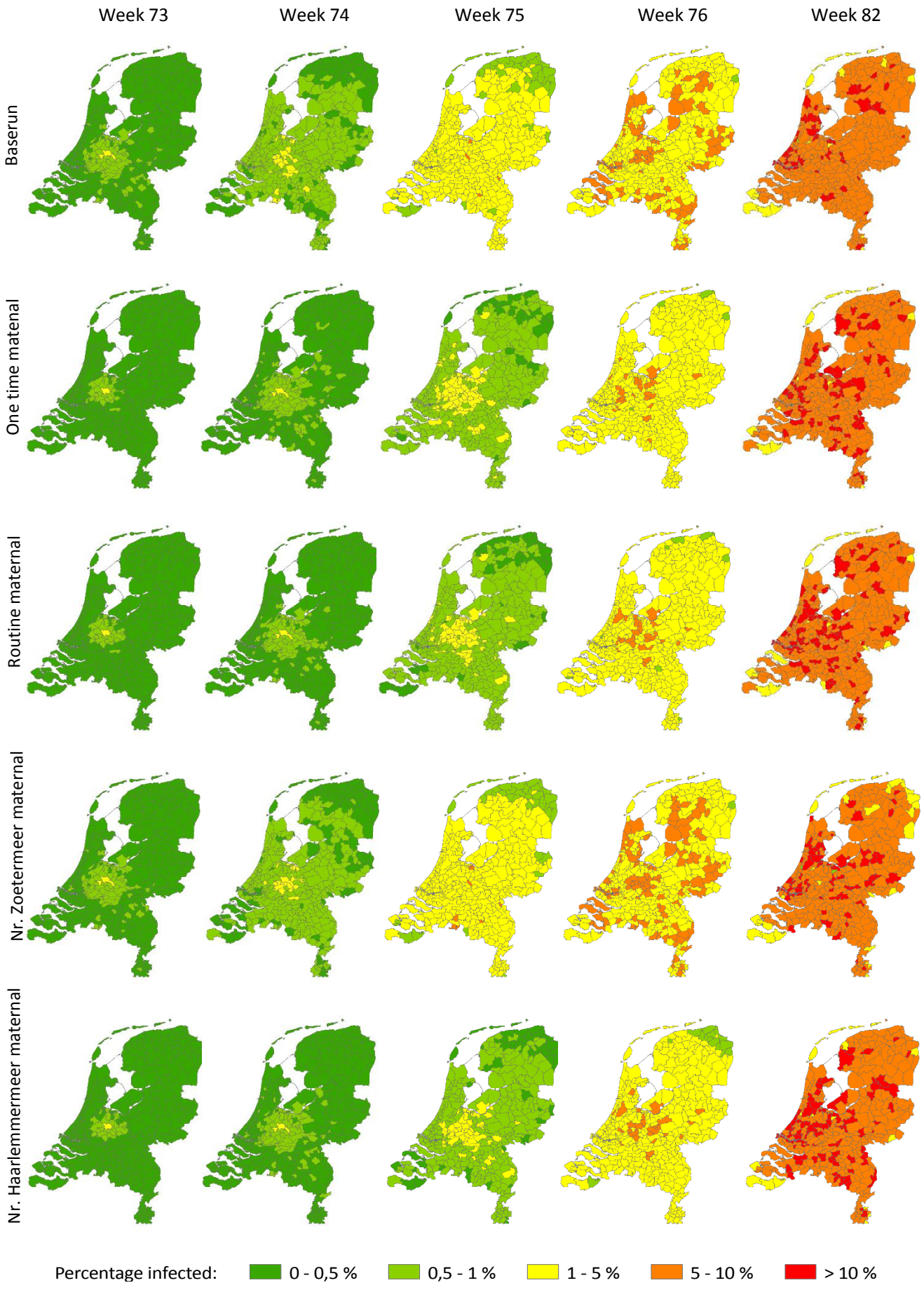


Figure 5.12: *Pertussis diffusion for different strategies of maternal vaccination.*

The second vaccination strategy, maternal vaccination, results in more differences in spatial diffusion of pertussis. The first noticeable difference is the divergent output of the Zoetermeer strategy, compared to the other maternal vaccination strategies. The maternal Zoetermeer strategy strongly resembles the diffusion of the base run, and of the network vaccination strategies. The other three maternal strategies result in a different figure than the base run. The time it takes before the majority of the municipalities has 1-5 percent of its' population infected with pertussis is longer in these strategies than in the base run (Figure 5.12). It takes longer for the disease to spread, however, at week 77 the figure is about the same for all maternal strategies and the base run (see Appendix E). After this week there are more municipalities with more than 10 percent infections in the maternal vaccination strategy scenarios than in the current scenario. It thus takes longer for the disease to spread, however at a later stage the disease has reached all municipalities, and results in even more infections in those municipalities.

Of these four maternal strategies, the Zoetermeer strategy has the lowest vaccination rate. This vaccination rate of 70% for pregnant women seems to be too low to make a difference in the diffusion of pertussis. As already explained in 5.2.1.3 there might be a tipping point in vaccination rate, where at a certain level the amount of immunity is just high enough to delay the diffusion of pertussis.

5.4 Discussion

In this section the calibration, validation and results will be critically evaluated. As discussed in chapter 4, the calibration showed that the model produced a realistic number of disease cases, compared to values reported in other research and in comparison to the available empirical data. For example, the model generated 753 adult (20-50) disease cases per 100.000 inhabitants in Utrecht. This is slightly higher than the estimates of 337 mentioned by Ward et al. (2000) and 400-700 of Strebel et al. (2001). Besides, the cases generated by the model are within the expected range of the actual number of disease cases. This range is defined with the knowledge that the number of reported cases is just 0.3% to 2% of the total number of infections in a population (Mcdonald et al., 2014; Van Der Maas, 2013).

The model's vaccination strategies have been validated by simulating vaccination strategies of research performed by Van Rie & Hethcote (2004). Their strategies of vaccinating adolescents next to the current vaccination strategy, and vaccinating adolescents and adults have been compared with the outcomes of their research. Interestingly, the total impact of the first strategy was lower for the developed model than the results of Van Rie & Hethcote. Where these researchers note a reduction of 19%, the developed model shows only a small decrease in the number of disease cases (1%). This deviation can partly be explained by the fact that the results of Van Rie & Hethcote were measured over a 38 year period (from 2000 to 2040) in contrast to the results of the developed model, which are measured over 14 years. Furthermore, the model of Van Rie & Hethcote is developed for the US, opposed to this model created for the Netherlands. In addition to the previously mentioned deviation, the effect of adolescent vaccination on disease prevalence in younger age groups that was found by Van Rie & Hethcote could not be detected. On the other hand, Van Rie & Hethcote's observation that the routine adolescent vaccination mostly has a direct impact on the vaccinated group matched the results of this research.

A comparison between Van Rie & Hethcote's results generated with strategy 2 and those of this thesis' model, show that the age group 25-35 has a completely different temporal pattern than

those of the other age groups. This deviation underlines the relevance of age specific analysis of the results. It also shows the importance of the parent group in the diffusion process. As Van Rie & Hethcote indicate, "*Different vaccination strategies have diverse direct and indirect (herd immunity) effects on specific age groups"* (p.3163). Similar effects occurred in this thesis' model, as extra vaccination in one age group did not always lead to a reduction of the total disease burden.

Maternal vaccination, for instance, did not result in less population-wide infections. However, it did slow the diffusion of pertussis down in three of the four maternal strategies. For all maternal interventions, reducing the number of infections in infants was the primary aim. For this, the best tactic seems to be to achieve a maternal vaccination rate of above 70%. Network vaccination was conducted to check if the spatial-temporal diffusion pattern of the disease can be influenced. However, this did not turn out to be so. This is most probably caused by internal workings of the model, as will be explained in the next chapter.

6 CONCLUSION AND RECOMMENDATIONS

The main goal of this thesis was to create a model with which different vaccination strategies for pertussis could be tested. The base model consists of a SEIR model in which the pertussis diffusion of the Netherlands is simulated. Here, an individual is either Susceptible, Exposed, Infected, or Removed from the disease cycle. The basic SEIR model has been enhanced by the additional creation of age groups, and by taking job- and school commuting into account. In the latter category, work related commuting rates were based on actual daily travel, and for school commuting information on secondary schools was used.

For the SEIR model to represent a realistic epidemic curve with re-occurring peaks, seasonal forcing has been implemented. The infectivity of pertussis was made to change with the seasons. A so-called contact matrix, depicting the chance of contact, has been derived from research of the RIVM (the National Institute for Public Health and Environment of the Netherlands). The transmission rates have been set to 0.4 for summer, 0.2 for spring and autumn, and 0.1 for winter.

Initially, the heterogeneous behavior of health units in the Netherlands was planned to be integrated as the agent-based part of this model. However, due to time limitations, this step was not achieved. Experiments were therefore conducted by vaccinating population groups in a static manner. However, this leads to homogeneous interventions (the same for the complete country). Although the impact of this simplification on the results cannot be completely assessed at this moment, it may have had an influence on the results.

The problem in combining a population model with a network commuting model was that a certain fraction of the commuters population group is always infected, leading to a constant diffusion of the disease to new areas. The effect of a threshold has been investigated, however, this did not have a significant impact. As only data is available about job commuting, for school commuting an estimate has been made. Job and school commuting are just a fraction of all movements of a population. People also move around for family visits, leisure and sports activities. Information about these flows are difficult to capture in data, and are therefore not taken into account. It might be better to model movement in a totally different way. One way to do this is by looking at contact networks or proxies of network structures (Del Valle et al., 2007; Tizzoni et al., 2014).

Earlier in this research it was stated that the mathematical SEIR model might not be able to grasp the large amount of daily commuters. The SEIR model is created for a closed system (Rock et al., 2014), the Netherlands as a whole functions as a closed system in the developed model. The individual municipalities are subsystems, that are not closed due to commuting, hence this might be what causes the problem. This can also be substantiated by the larger effect of unexpected number of infections in big cities, where more commuting takes place.

Before starting with running the model for results, the model has been calibrated. The outcomes of this calibration were promising. The method of calibration was, however, not ideal. There has only been calibrated on Utrecht municipality without taking commuter flows into account. This is done because the models' behavior could not be validated when taking commuter flows into account. In an ideal situation the model would be calibrated by first calculating the basic reproduction number (R0) and subsequently run the model, including commuter flows, with the corresponding transmission rates. That the calibration is not ideal lies also in not calibrating on vaccinating in a population.

After the model calibration the model has been run with different vaccination rates to test the model's general behavior. This showed that the model is able to generate a lower pertussis burden with a higher vaccination rate. Validation experiments were performed comparing the model to another existing pertussis model, however it was not straightforward to compare the results. Some of the problems in this comparison were due to differences between the two models. Where the pertussis model for the Netherlands includes commuting this is not the case for the model of Van Rie & Hethcote (2004). However, their model differentiates between the disease severity (typical, mild and a-symptomatic cases). Within the time period it was impossible to run all the scenarios and also the time period of the experiments in this research were much shorter (14 years) than the experiments of van Van Rie & Hethcote (38 years) hindering comparison.

Most unexpected behavior has been observed in the age group 25-35 year, the only group divided in male and female. Besides vaccination of pregnant women, the gender division does not play an important role in the model, but as a result of this division small population groups occur. The model is programmed in such a way that SEIR calculations stop if the number of susceptible individuals is below 0.5, to prevent negative values in population groups. Even though a population group with a number of susceptible individuals below 0.5 sounds unrealistic, in very small population groups, with just 5 people, this is a possibility. When the SEIR calculations are stopped in these population groups it might be that the proportions become imbalanced, which might lead to unexpected behavior.

The current model has a long runtime which is due to the many different population groups. Experiments were conducted to check if the SEIR model should be converted into a SIR model. This did not lead to a significantly shorter runtime but eventually may be advisable because of the fact that it limits the number of agents preventing runtime errors. The complexity of this model is at the limit of what can be achieved within NetLogo, which is a serious consideration for further model development.

In this thesis a comparison is made between maternal vaccination, an effective strategy to protect infants, the most vulnerable population group to pertussis and network based vaccination. Via network vaccination the spatial diffusion of pertussis may be influenced and ultimately vaccination at tactical locations might be able to prevent pertussis from diffusion. Results were evaluated based on number of pertussis cases, disease prevalence per age group and on the spatial diffusion of pertussis.

Running the model led to unexpected outcomes. More vaccination led to more infections in both maternal and network vaccinating. Some differences can be seen. Maternal strategies slow the process of disease diffusion down. Besides, the three maternal strategies with the highest vaccination rate resulted in less infections in infants. According to this model, the best way to reduce the total number of infections in the population is by vaccinating a large population in Amsterdam, or Rotterdam, two of the biggest cities of the Netherlands. Vaccinating in smaller amounts, but all over the Netherlands slows pertussis diffusion down, which can buy time to start targeted interventions at non-infected places. And maternal vaccination with a high vaccination rate prevents infants from infection. These outcomes generated by the model are not seen as realistic. A problem occurs in the model, most likely in the job-commuting part of the model. This is the only part of the model that could not be validated, but does have the biggest impact on the outcomes of the model, since it accounts for most of the population movement.

The model proved the possibility of modelling spatial diffusion of a disease. With these model outcomes it is, however, not possible to identify one of the vaccination strategies as best. To

be able to do this further research is needed. Results indicate the importance of commuting in the diffusion process and therefore it is recommended to further improve and validate the commuting model. Results also underline the differences between the age groups and the importance to study both short term and longer term effects of different vaccination strategies.

The model did not generate any results that are of direct societal use, but it has contributed to our understanding of the geographic diffusion of pertussis. Even though epidemics is a widely known topic of research, the geographic component in this has been underdeveloped. This thesis has shown that it is possible to look at geographic spread via mathematical modelling. The vaccination strategies did not work as expected, however it is still possible to derive some spatial information from the outputs. It can, for example, be distilled that the northern and south-western municipalities suffer less from pertussis infections than the municipalities located in the middle of the Netherlands. This shows potential to look further into modelling spatial diffusion of pertussis, or other epidemics. Further research should be conducted on modelling this spatial diffusion, and subsequently on testing vaccination strategies in such models. This research has formed a basic, but showed that using actual commuting data might not be the best way to model population movement. Therefore, there should be looked into different ways of modelling movement in the Netherlands. Furthermore, a more extensive research should be done on modelling the heterogeneous behavior of the health units, and its' influence on the diffusion of infectious diseases.

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APPENDICES

Appendix A – Population model

Nr	Gender	Age	Commuter	Pregnant	Household	SEIR	UniqueID
1	no	0 - 5 months	non	no	yes	S	1.1.1.1.2.1
2	no	0 - 5 months	non	no	yes	E	1.1.1.1.2.2
3	no	0 - 5 months	non	no	yes	I	1.1.1.1.2.3
4	no	0 - 5 months	non	no	yes	R	1.1.1.1.2.4
5	no	5 mnt - 5 yrs	non	no	yes	S	1.2.1.1.2.1
6	no	5 mnt - 5 yrs	non	no	yes	E	1.2.1.1.2.2
7	no	5 mnt - 5 yrs	non	no	yes	I	1.2.1.1.2.3
8	no	5 mnt - 5 yrs	non	no	yes	R	1.2.1.1.2.4
9	no	5 - 12 yrs	non	no	yes	S	1.3.1.1.2.1
10	no	5 - 12 yrs	non	no	yes	E	1.3.1.1.2.2
11	no	5 - 12 yrs	non	no	yes	I	1.3.1.1.2.3
12	no	5 - 12 yrs	non	no	yes	R	1.3.1.1.2.4
13	no	12 - 17 yrs	school	no	yes	S	1.4.2.1.2.1
14	no	12 - 17 yrs	school	no	yes	E	1.4.2.1.2.2
15	no	12 - 17 yrs	school	no	yes	I	1.4.2.1.2.3
16	no	12 - 17 yrs	school	no	yes	R	1.4.2.1.2.4
17	no	12 - 17 yrs	non	no	yes	S	1.4.1.1.2.1
18	no	12 - 17 yrs	non	no	yes	E	1.4.1.1.2.2
19	no	12 - 17 yrs	non	no	yes	I	1.4.1.1.2.3
20	no	12 - 17 yrs	non	no	yes	R	1.4.1.1.2.4
21	no	17 - 25 yrs	non	no	no	S	1.5.1.1.1.1
22	no	17 - 25 yrs	non	no	no	E	1.5.1.1.1.2
23	no	17 - 25 yrs	non	no	no	I	1.5.1.1.1.3
24	no	17 - 25 yrs	non	no	no	R	1.5.1.1.1.4
25	male	25 - 35 yrs	job	no	no	S	2.6.3.1.1.1
26	male	25 - 35 yrs	job	no	no	E	2.6.3.1.1.2
27	male	25 - 35 yrs	job	no	no	I	2.6.3.1.1.3
28	male	25 - 35 yrs	job	no	no	R	2.6.3.1.1.4
29	male	25 - 35 yrs	job	no	yes	S	2.6.3.1.2.1
30	male	25 - 35 yrs	job	no	yes	E	2.6.3.1.2.2
31	male	25 - 35 yrs	job	no	yes	I	2.6.3.1.2.3
32	male	25 - 35 yrs	job	no	yes	R	2.6.3.1.2.4
33	male	25 - 35 yrs	non	no	no	S	2.6.1.1.1.1
34	male	25 - 35 yrs	non	no	no	E	2.6.1.1.1.2
35	male	25 - 35 yrs	non	no	no	I	2.6.1.1.1.3
36	male	25 - 35 yrs	non	no	no	R	2.6.1.1.1.4
37	male	25 - 35 yrs	non	no	yes	S	2.6.1.1.2.1
38	male	25 - 35 yrs	non	no	yes	E	2.6.1.1.2.2

39	male	25 - 35 yrs	non	no	yes	I	2.6.1.1.2.3
40	male	25 - 35 yrs	non	no	yes	R	2.6.1.1.2.4
41	female	25 - 35 yrs	job	yes	yes	S	3.6.3.2.2.1
42	female	25 - 35 yrs	job	yes	yes	E	3.6.3.2.2.2
43	female	25 - 35 yrs	job	yes	yes	I	3.6.3.2.2.3
44	female	25 - 35 yrs	job	yes	yes	R	3.6.3.2.2.4
45	female	25 - 35 yrs	job	no	no	S	3.6.3.1.1.1
46	female	25 - 35 yrs	job	no	no	E	3.6.3.1.1.2
47	female	25 - 35 yrs	job	no	no	I	3.6.3.1.1.3
48	female	25 - 35 yrs	job	no	no	R	3.6.3.1.1.4
49	female	25 - 35 yrs	job	no	yes	S	3.6.3.1.2.1
50	female	25 - 35 yrs	job	no	yes	E	3.6.3.1.2.2
51	female	25 - 35 yrs	job	no	yes	I	3.6.3.1.2.3
52	female	25 - 35 yrs	job	no	yes	R	3.6.3.1.2.4
53	female	25 - 35 yrs	non	yes	yes	S	3.6.1.2.2.1
54	female	25 - 35 yrs	non	yes	yes	E	3.6.1.2.2.2
55	female	25 - 35 yrs	non	yes	yes	I	3.6.1.2.2.3
56	female	25 - 35 yrs	non	yes	yes	R	3.6.1.2.2.4
57	female	25 - 35 yrs	non	no	no	S	3.6.1.1.1.1
58	female	25 - 35 yrs	non	no	no	E	3.6.1.1.1.2
59	female	25 - 35 yrs	non	no	no	I	3.6.1.1.1.3
60	female	25 - 35 yrs	non	no	no	R	3.6.1.1.1.4
61	female	25 - 35 yrs	non	no	yes	S	3.6.1.1.2.1
62	female	25 - 35 yrs	non	no	yes	E	3.6.1.1.2.2
63	female	25 - 35 yrs	non	no	yes	I	3.6.1.1.2.3
64	female	25 - 35 yrs	non	no	yes	R	3.6.1.1.2.4
65	no	35 - 50 yrs	job	no	no	S	1.7.3.1.1.1
66	no	35 - 50 yrs	job	no	no	E	1.7.3.1.1.2
67	no	35 - 50 yrs	job	no	no	I	1.7.3.1.1.3
68	no	35 - 50 yrs	job	no	no	R	1.7.3.1.1.4
69	no	35 - 50 yrs	job	no	yes	S	1.7.3.1.2.1
70	no	35 - 50 yrs	job	no	yes	E	1.7.3.1.2.2
71	no	35 - 50 yrs	job	no	yes	I	1.7.3.1.2.3
72	no	35 - 50 yrs	job	no	yes	R	1.7.3.1.2.4
73	no	35 - 50 yrs	non	no	no	S	1.7.1.1.1.1
74	no	35 - 50 yrs	non	no	no	E	1.7.1.1.1.2
75	no	35 - 50 yrs	non	no	no	I	1.7.1.1.1.3
76	no	35 - 50 yrs	non	no	no	R	1.7.1.1.1.4
77	no	35 - 50 yrs	non	no	yes	S	1.7.1.1.2.1
78	no	35 - 50 yrs	non	no	yes	E	1.7.1.1.2.2
79	no	35 - 50 yrs	non	no	yes	I	1.7.1.1.2.3
80	no	35 - 50 yrs	non	no	yes	R	1.7.1.1.2.4
81	no	50 - 65 yrs	job	no	no	S	1.8.3.1.1.1
82	no	50 - 65 yrs	job	no	no	E	1.8.3.1.1.2
83	no	50 - 65 yrs	job	no	no	I	1.8.3.1.1.3

84	no	50 - 65 yrs	job	no	no	R	1.8.3.1.1.4
85	no	50 - 65 yrs	job	no	yes	S	1.8.3.1.2.1
86	no	50 - 65 yrs	job	no	yes	E	1.8.3.1.2.2
87	no	50 - 65 yrs	job	no	yes	I	1.8.3.1.2.3
88	no	50 - 65 yrs	job	no	yes	R	1.8.3.1.2.4
89	no	50 - 65 yrs	non	no	no	S	1.8.1.1.1.1
90	no	50 - 65 yrs	non	no	no	E	1.8.1.1.1.2
91	no	50 - 65 yrs	non	no	no	I	1.8.1.1.1.3
92	no	50 - 65 yrs	non	no	no	R	1.8.1.1.1.4
93	no	50 - 65 yrs	non	no	yes	S	1.8.1.1.2.1
94	no	50 - 65 yrs	non	no	yes	E	1.8.1.1.2.2
95	no	50 - 65 yrs	non	no	yes	I	1.8.1.1.2.3
96	no	50 - 65 yrs	non	no	yes	R	1.8.1.1.2.4
97	no	65+ yrs	non	no	no	S	1.9.1.1.1.1
98	no	65+ yrs	non	no	no	E	1.9.1.1.1.2
99	no	65+ yrs	non	no	no	I	1.9.1.1.1.3
100	no	65+ yrs	non	no	no	R	1.9.1.1.1.4

Appendix B – Contact matrices

Contact matrix used for SIR calculations within municipalities

Average number of contacts per day in the Netherlands

Contact from Y-axis (i) to X-axis (j).

Yij is the average number of people in age category j that is being contacted by 1 person in age category i during one day, divided by the total population in age category j.

Within MUNI	1.1.1.1.2.1	1.2.1.1.2.1	1.3.1.1.2.1	1.4.2.1.2.1	1.4.1.1.2.1	1.5.1.1.1.1	2.6.3.1.1.1	2.6.3.1.2.1	2.6.1.1.1.1	2.6.1.1.2.1	3.6.3.2.2.1	3.6.3.1.1.1
1.1.1.1.2.3	2,61E-06	1,05E-06	2,00E-07	7,71E-08	7,71E-08	1,63E-07	7,71E-07	1,17E-06	7,71E-07	1,17E-06	1,17E-06	7,71E-07
1.2.1.1.2.3	1,05E-06	4,77E-06	1,31E-06	1,38E-07	1,38E-07	1,75E-07	6,16E-07	1,02E-06	6,16E-07	1,02E-06	1,02E-06	6,16E-07
1.3.1.1.2.3	2,00E-07	1,31E-06	6,71E-06	1,40E-06	1,40E-06	2,37E-07	2,65E-07	6,65E-07	2,65E-07	6,65E-07	6,65E-07	2,65E-07
1.4.2.1.2.3	3,86E-08	1,38E-07	1,40E-06	8,78E-06	8,78E-06	1,09E-06	3,43E-07	3,43E-07	3,43E-07	3,43E-07	3,43E-07	3,43E-07
1.4.1.1.2.3	3,86E-08	1,38E-07	1,40E-06	8,78E-06	8,78E-06	1,09E-06	3,43E-07	3,43E-07	3,43E-07	3,43E-07	3,43E-07	3,43E-07
1.5.1.1.1.3	1,63E-07	1,75E-07	2,38E-07	3,43E-07	3,43E-07	2,51E-06	8,62E-07	8,62E-07	8,62E-07	8,62E-07	8,62E-07	8,62E-07
2.6.3.1.1.3	7,71E-07	6,16E-07	2,65E-07	3,43E-07	3,43E-07	8,62E-07	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06
2.6.3.1.2.3	1,17E-06	1,02E-06	6,65E-07	3,43E-07	3,43E-07	8,62E-07	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06
2.6.1.1.1.3	7,71E-07	6,16E-07	2,65E-07	3,43E-07	3,43E-07	8,62E-07	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06
2.6.1.1.2.3	1,17E-06	1,02E-06	6,65E-07	3,43E-07	3,43E-07	8,62E-07	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06
3.6.3.2.2.3	1,17E-06	1,02E-06	6,65E-07	3,43E-07	3,43E-07	8,62E-07	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06
3.6.3.1.1.3	7,71E-07	6,16E-07	2,65E-07	3,43E-07	3,43E-07	8,62E-07	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06
3.6.3.1.2.3	1,17E-06	1,02E-06	6,65E-07	3,43E-07	3,43E-07	8,62E-07	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06
3.6.1.2.2.3	1,17E-06	1,02E-06	6,65E-07	3,43E-07	3,43E-07	8,62E-07	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06
3.6.1.1.1.3	7,71E-07	6,16E-07	2,65E-07	3,43E-07	3,43E-07	8,62E-07	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06
3.6.1.1.2.3	1,17E-06	1,02E-06	6,65E-07	3,43E-07	3,43E-07	8,62E-07	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,86E-06
1.7.3.1.1.3	1,68E-07	4,05E-07	6,77E-07	7,53E-07	7,53E-07	6,98E-07	1,01E-06	1,01E-06	1,01E-06	1,01E-06	1,01E-06	1,01E-06
1.7.3.1.2.3	5,68E-07	8,05E-07	1,08E-06	7,53E-07	7,53E-07	6,98E-07	1,01E-06	1,01E-06	1,01E-06	1,01E-06	1,01E-06	1,01E-06
1.7.1.1.1.3	1,68E-07	4,05E-07	6,77E-07	7,53E-07	7,53E-07	6,98E-07	1,01E-06	1,01E-06	1,01E-06	1,01E-06	1,01E-06	1,01E-06
1.7.1.1.2.3	5,68E-07	8,05E-07	1,08E-06	7,53E-07	7,53E-07	6,98E-07	1,01E-06	1,01E-06	1,01E-06	1,01E-06	1,01E-06	1,01E-06
1.8.3.1.1.3	3,21E-07	3,00E-07	2,66E-07	3,52E-07	3,52E-07	6,11E-07	7,12E-07	7,12E-07	7,12E-07	7,12E-07	7,12E-07	7,12E-07
1.8.3.1.2.3	3,21E-07	3,00E-07	2,66E-07	3,52E-07	3,52E-07	6,11E-07	7,12E-07	7,12E-07	7,12E-07	7,12E-07	7,12E-07	7,12E-07
1.8.1.1.1.3	3,21E-07	3,00E-07	2,66E-07	3,52E-07	3,52E-07	6,11E-07	7,12E-07	7,12E-07	7,12E-07	7,12E-07	7,12E-07	7,12E-07
1.8.1.1.2.3	3,21E-07	3,00E-07	2,66E-07	3,52E-07	3,52E-07	6,11E-07	7,12E-07	7,12E-07	7,12E-07	7,12E-07	7,12E-07	7,12E-07
1.9.1.1.1.3	1,36E-07	1,69E-07	2,14E-07	2,32E-07	2,32E-07	2,88E-07	3,04E-07	3,04E-07	3,04E-07	3,04E-07	3,04E-07	3,04E-07

Within MUNI	3.6.3.1.2.1	3.6.1.2.2.1	3.6.1.1.1.1	3.6.1.1.2.1	1.7.3.1.1.1	1.7.3.1.2.1	1.7.1.1.1.1	1.7.1.1.2.1	1.8.3.1.1.1	1.8.3.1.2.1	1.8.1.1.1.1	1.8.1.1.2.1	1.9.1.1.1.1
1.1.1.1.2.3	1,17E-06	1,17E-06	7,71E-07	1,17E-06	3,68E-07	3,68E-07	3,68E-07	3,68E-07	3,21E-07	3,21E-07	3,21E-07	3,21E-07	1,36E-07
1.2.1.1.2.3	1,02E-06	1,02E-06	6,16E-07	1,02E-06	4,05E-07	8,05E-07	4,05E-07	8,05E-07	3,00E-07	3,00E-07	3,00E-07	3,00E-07	1,69E-07
1.3.1.1.2.3	6,65E-07	6,65E-07	2,65E-07	6,65E-07	6,76E-07	1,08E-06	6,76E-07	1,08E-06	2,66E-07	2,66E-07	2,66E-07	2,66E-07	2,14E-07
1.4.2.1.2.3	3,43E-07	3,43E-07	3,43E-07	3,43E-07	7,53E-07	7,53E-07	7,53E-07	7,53E-07	3,52E-07	3,52E-07	3,52E-07	3,52E-07	2,32E-07
1.4.1.1.2.3	3,43E-07	3,43E-07	3,43E-07	3,43E-07	7,53E-07	7,53E-07	7,53E-07	7,53E-07	3,52E-07	3,52E-07	3,52E-07	3,52E-07	2,32E-07
1.5.1.1.1.3	8,62E-07	8,62E-07	8,62E-07	8,62E-07	6,98E-07	6,98E-07	6,98E-07	6,98E-07	6,11E-07	6,11E-07	6,11E-07	6,11E-07	2,88E-07
2.6.3.1.1.3	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,01E-06	1,01E-06	1,01E-06	1,01E-06	7,12E-07	7,12E-07	7,12E-07	7,12E-07	3,04E-07
2.6.3.1.2.3	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,01E-06	1,01E-06	1,01E-06	1,01E-06	7,12E-07	7,12E-07	7,12E-07	7,12E-07	3,04E-07
2.6.1.1.1.3	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,01E-06	1,01E-06	1,01E-06	1,01E-06	7,12E-07	7,12E-07	7,12E-07	7,12E-07	3,04E-07
2.6.1.1.2.3	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,01E-06	1,01E-06	1,01E-06	1,01E-06	7,12E-07	7,12E-07	7,12E-07	7,12E-07	3,04E-07
3.6.3.2.2.3	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,01E-06	1,01E-06	1,01E-06	1,01E-06	7,12E-07	7,12E-07	7,12E-07	7,12E-07	3,04E-07
3.6.3.1.1.3	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,01E-06	1,01E-06	1,01E-06	1,01E-06	7,12E-07	7,12E-07	7,12E-07	7,12E-07	3,04E-07
3.6.3.1.2.3	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,01E-06	1,01E-06	1,01E-06	1,01E-06	7,12E-07	7,12E-07	7,12E-07	7,12E-07	3,04E-07
3.6.1.2.2.3	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,01E-06	1,01E-06	1,01E-06	1,01E-06	7,12E-07	7,12E-07	7,12E-07	7,12E-07	3,04E-07
3.6.1.1.1.3	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,01E-06	1,01E-06	1,01E-06	1,01E-06	7,12E-07	7,12E-07	7,12E-07	7,12E-07	3,04E-07
3.6.1.1.2.3	1,86E-06	1,86E-06	1,86E-06	1,86E-06	1,01E-06	1,01E-06	1,01E-06	1,01E-06	7,12E-07	7,12E-07	7,12E-07	7,12E-07	3,04E-07
1.7.3.1.1.3	1,01E-06	1,01E-06	1,01E-06	1,01E-06	1,49E-06	1,49E-06	1,49E-06	1,49E-06	7,20E-07	7,20E-07	7,20E-07	7,20E-07	3,89E-07
1.7.3.1.2.3	1,01E-06	1,01E-06	1,01E-06	1,01E-06	1,49E-06	1,49E-06	1,49E-06	1,49E-06	7,20E-07	7,20E-07	7,20E-07	7,20E-07	3,89E-07
1.7.1.1.1.3	1,01E-06	1,01E-06	1,01E-06	1,01E-06	1,49E-06	1,49E-06	1,49E-06	1,49E-06	7,20E-07	7,20E-07	7,20E-07	7,20E-07	3,89E-07
1.7.1.1.2.3	1,01E-06	1,01E-06	1,01E-06	1,01E-06	1,49E-06	1,49E-06	1,49E-06	1,49E-06	7,20E-07	7,20E-07	7,20E-07	7,20E-07	3,89E-07
1.8.3.1.1.3	7,12E-07	7,12E-07	7,12E-07	7,12E-07	7,19E-07	7,19E-07	7,19E-07	7,19E-07	1,07E-06	1,07E-06	1,07E-06	1,07E-06	5,05E-07
1.8.3.1.2.3	7,12E-07	7,12E-07	7,12E-07	7,12E-07	7,19E-07	7,19E-07	7,19E-07	7,19E-07	1,07E-06	1,07E-06	1,07E-06	1,07E-06	5,05E-07
1.8.1.1.1.3	7,12E-07	7,12E-07	7,12E-07	7,12E-07	7,19E-07	7,19E-07	7,19E-07	7,19E-07	1,07E-06	1,07E-06	1,07E-06	1,07E-06	5,05E-07
1.8.1.1.2.3	7,12E-07	7,12E-07	7,12E-07	7,12E-07	7,19E-07	7,19E-07	7,19E-07	7,19E-07	1,07E-06	1,07E-06	1,07E-06	1,07E-06	5,05E-07
1.9.1.1.1.3	3,04E-07	3,04E-07	3,04E-07	3,04E-07	3,89E-07	3,89E-07	3,89E-07	3,89E-07	5,05E-07	5,05E-07	5,05E-07	5,05E-07	1,29E-06

(Derived by personal contact with the RIVM, January 19, 2016)

Average duration of contacts in hours per day (Tij)

Within MUNI	1.1.1.1.2.1	1.2.1.1.2.1	1.3.1.1.2.1	1.4.2.1.2.1	1.4.1.1.2.1	1.5.1.1.1.1	2.6.3.1.1.1	2.6.3.1.2.1	2.6.1.1.1.1	2.6.1.1.2.1	3.6.3.2.2.1	3.6.3.1.1.1
1.1.1.1.2.3	4	4	7,5	3	3	3	1,5	7,5	1,5	7,5	7,5	1,5
1.2.1.1.2.3	4	4	7,5	3	3	3	1,5	7,5	1,5	7,5	7,5	1,5
1.3.1.1.2.3	7	7	4,5	4,5	4,5	3,5	2	7,5	2	7,5	7,5	2
1.4.2.1.2.3	3	3	4,5	6	6	4	6,5	6,5	6,5	6,5	6,5	6,5
1.4.1.1.2.3	3	3	4,5	6	6	4	6,5	6,5	6,5	6,5	6,5	6,5
1.5.1.1.1.3	5	5	4	2	2	5	3	3	3	3	3	3
2.6.3.1.1.3	1,5	1,5	1,5	1,5	1,5	3,5	4,5	4,5	4,5	4,5	4,5	4,5
2.6.3.1.2.3	7,5	7,5	7,5	5,5	5,5	3,5	4,5	4,5	4,5	4,5	4,5	4,5
2.6.1.1.1.3	1,5	1,5	1,5	1,5	1,5	3,5	4,5	4,5	4,5	4,5	4,5	4,5
2.6.1.1.2.3	7,5	7,5	7,5	5,5	5,5	3,5	4,5	4,5	4,5	4,5	4,5	4,5
3.6.3.2.2.3	7,5	7,5	7,5	5,5	5,5	3,5	4,5	4,5	4,5	4,5	4,5	4,5
3.6.3.1.1.3	1,5	1,5	1,5	1,5	1,5	3,5	4,5	4,5	4,5	4,5	4,5	4,5
3.6.3.1.2.3	7,5	7,5	7,5	5,5	5,5	3,5	4,5	4,5	4,5	4,5	4,5	4,5
3.6.1.2.2.3	7,5	7,5	7,5	5,5	5,5	3,5	4,5	4,5	4,5	4,5	4,5	4,5
3.6.1.1.1.3	1,5	1,5	1,5	1,5	1,5	3,5	4,5	4,5	4,5	4,5	4,5	4,5
3.6.1.1.2.3	7,5	7,5	7,5	5,5	5,5	3,5	4,5	4,5	4,5	4,5	4,5	4,5
1.7.3.1.1.3	1,5	1,5	1,5	1,5	1,5	3	2	2	2	2	2	2
1.7.3.1.2.3	6,5	6,5	7,5	7,5	7,5	3	2	2	2	2	2	2
1.7.1.1.1.3	1,5	1,5	1,5	1,5	1,5	3	2	2	2	2	2	2
1.7.1.1.2.3	6,5	6,5	7,5	7,5	7,5	3	2	2	2	2	2	2
1.8.3.1.1.3	1	1	1,5	2	2	2	2	2	2	2	2	2
1.8.3.1.2.3	1	1	1,5	2	2	2	2	2	2	2	2	2
1.8.1.1.1.3	1	1	1,5	2	2	2	2	2	2	2	2	2
1.8.1.1.2.3	1	1	1,5	2	2	2	2	2	2	2	2	2
1.9.1.1.1.3	1	1	1	1	1	1	1,5	1,5	1,5	1,5	1,5	1,5

Within MUNI	3.6.3.1.2.1	3.6.1.2.2.1	3.6.1.1.1.1	3.6.1.1.2.1	1.7.3.1.1.1	1.7.3.1.2.1	1.7.1.1.1.1	1.7.1.1.2.1	1.8.3.1.1.1	1.8.3.1.2.1	1.8.1.1.1.1	1.8.1.1.2.1	1.9.1.1.1.1
1.1.1.1.2.3	7,5	7,5	1,5	7,5	1,5	6,5	1,5	6,5	1,5	1,5	1,5	1,5	1
1.2.1.1.2.3	7,5	7,5	1,5	7,5	1,5	6,5	1,5	6,5	1,5	1,5	1,5	1,5	1
1.3.1.1.2.3	7,5	7,5	2	7,5	2	7,5	2	7,5	2	2	2	2	1
1.4.2.1.2.3	6,5	6,5	6,5	6,5	7,5	7,5	7,5	7,5	2	2	2	2	1
1.4.1.1.2.3	6,5	6,5	6,5	6,5	7,5	7,5	7,5	7,5	2	2	2	2	1
1.5.1.1.1.3	3	3	3	3	4	4	4	4	3	3	3	3	1
2.6.3.1.1.3	4,5	4,5	4,5	4,5	3	3	3	3	2,5	2,5	2,5	2,5	1
2.6.3.1.2.3	4,5	4,5	4,5	4,5	3	3	3	3	2,5	2,5	2,5	2,5	1
2.6.1.1.1.3	4,5	4,5	4,5	4,5	3	3	3	3	2,5	2,5	2,5	2,5	1
2.6.1.1.2.3	4,5	4,5	4,5	4,5	3	3	3	3	2,5	2,5	2,5	2,5	1
3.6.3.2.2.3	4,5	4,5	4,5	4,5	3	3	3	3	2,5	2,5	2,5	2,5	1
3.6.3.1.1.3	4,5	4,5	4,5	4,5	3	3	3	3	2,5	2,5	2,5	2,5	1
3.6.3.1.2.3	4,5	4,5	4,5	4,5	3	3	3	3	2,5	2,5	2,5	2,5	1
3.6.1.2.2.3	4,5	4,5	4,5	4,5	3	3	3	3	2,5	2,5	2,5	2,5	1
3.6.1.1.1.3	4,5	4,5	4,5	4,5	3	3	3	3	2,5	2,5	2,5	2,5	1
3.6.1.1.2.3	4,5	4,5	4,5	4,5	3	3	3	3	2,5	2,5	2,5	2,5	1
1.7.3.1.1.3	2	2	2	2	4,5	4,5	4,5	4,5	2,5	2,5	2,5	2,5	1
1.7.3.1.2.3	2	2	2	2	4,5	4,5	4,5	4,5	2,5	2,5	2,5	2,5	1
1.7.1.1.1.3	2	2	2	2	4,5	4,5	4,5	4,5	2,5	2,5	2,5	2,5	1
1.7.1.1.2.3	2	2	2	2	4,5	4,5	4,5	4,5	2,5	2,5	2,5	2,5	1
1.8.3.1.1.3	2	2	2	2	3	3	3	3	5,5	5,5	5,5	5,5	2
1.8.3.1.2.3	2	2	2	2	3	3	3	3	5,5	5,5	5,5	5,5	2
1.8.1.1.1.3	2	2	2	2	3	3	3	3	5,5	5,5	5,5	5,5	2
1.8.1.1.2.3	2	2	2	2	3	3	3	3	5,5	5,5	5,5	5,5	2
1.9.1.1.1.3	1,5	1,5	1,5	1,5	1,5	1,5	1,5	1,5	3	3	3	3	6

(Derived from Del Valle et al., 2007)

Matrices serve as input for the following equations:

$$P_{ij} = 1 - e^{-\sigma T_{ij}}$$

$$\beta_{ij} = \gamma_{ij} \times P_{ij}$$

Contact matrix used for SIR calculations among municipalities

Average number of contacts per day in the Netherlands

Contact from Y-axis (i) to X-axis (j).

Yij is the average number of people in age category j that is being contacted by 1 person in age category i during one day, divided by the total population in age category j.

Infected School commuters TO susceptible non commuters of same age

Infected Job commuters TO Susceptible non commuters working age

(The transmission rates for susceptible (school) commuters traveling to municipalities with infected non commuters are the same as the ones depicted in this matrix)

Among MUNI	1.1.1.1.2.1	1.2.1.1.2.1	1.3.1.1.2.1	1.4.2.1.2.1	1.4.1.1.2.1	1.5.1.1.1.1	2.6.3.1.1.1	2.6.3.1.2.1	2.6.1.1.1.1	2.6.1.1.2.1	3.6.3.2.2.1	3.6.3.1.1.1
1.1.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0
1.2.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0
1.3.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0
1.4.2.1.2.3	0	0	0	0	8,78E-06	0	0	0	0	0	0	0
1.4.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0
1.5.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0
2.6.3.1.1.3	0	0	0	0	0	0	0	0	1,86E-06	1,86E-06	0	0
2.6.3.1.2.3	0	0	0	0	0	0	0	0	1,86E-06	1,86E-06	0	0
2.6.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0
2.6.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0
3.6.3.2.2.3	0	0	0	0	0	0	0	0	1,86E-06	1,86E-06	0	0
3.6.3.1.1.3	0	0	0	0	0	0	0	0	1,86E-06	1,86E-06	0	0
3.6.3.1.2.3	0	0	0	0	0	0	0	0	1,86E-06	1,86E-06	0	0
3.6.1.2.2.3	0	0	0	0	0	0	0	0	0	0	0	0
3.6.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0
3.6.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0
1.7.3.1.1.3	0	0	0	0	0	0	0	0	1,01E-06	1,01E-06	0	0
1.7.3.1.2.3	0	0	0	0	0	0	0	0	1,01E-06	1,01E-06	0	0
1.7.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0
1.7.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0
1.8.3.1.1.3	0	0	0	0	0	0	0	0	7,12E-07	7,12E-07	0	0
1.8.3.1.2.3	0	0	0	0	0	0	0	0	7,12E-07	7,12E-07	0	0
1.8.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0
1.8.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0
1.9.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0

Among MUNI	3.6.3.1.2.1	3.6.1.2.2.1	3.6.1.1.1.1	3.6.1.1.2.1	1.7.3.1.1.1	1.7.3.1.2.1	1.7.1.1.1.1	1.7.1.1.2.1	1.8.3.1.1.1	1.8.3.1.2.1	1.8.1.1.1.1	1.8.1.1.2.1	1.9.1.1.1.1
1.1.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.2.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.3.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.4.2.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.4.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.5.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0	0
2.6.3.1.1.3	0	1,86E-06	1,86E-06	1,86E-06	0	0	1,01E-06	1,01E-06	0	0	7,12E-07	7,12E-07	0
2.6.3.1.2.3	0	1,86E-06	1,86E-06	1,86E-06	0	0	1,01E-06	1,01E-06	0	0	7,12E-07	7,12E-07	0
2.6.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0	0
2.6.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
3.6.3.2.2.3	0	1,86E-06	1,86E-06	1,86E-06	0	0	1,01E-06	1,01E-06	0	0	7,12E-07	7,12E-07	0
3.6.3.1.1.3	0	1,86E-06	1,86E-06	1,86E-06	0	0	1,01E-06	1,01E-06	0	0	7,12E-07	7,12E-07	0
3.6.3.1.2.3	0	1,86E-06	1,86E-06	1,86E-06	0	0	1,01E-06	1,01E-06	0	0	7,12E-07	7,12E-07	0
3.6.1.2.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
3.6.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0	0
3.6.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.7.3.1.1.3	0	1,01E-06	1,01E-06	1,01E-06	0	0	1,49E-06	1,49E-06	0	0	7,19E-07	7,19E-07	0
1.7.3.1.2.3	0	1,01E-06	1,01E-06	1,01E-06	0	0	1,49E-06	1,49E-06	0	0	7,19E-07	7,19E-07	0
1.7.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.7.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.8.3.1.1.3	0	7,12E-07	7,12E-07	7,12E-07	0	0	7,19E-07	7,19E-07	0	0	1,07E-06	1,07E-06	0
1.8.3.1.2.3	0	7,12E-07	7,12E-07	7,12E-07	0	0	7,19E-07	7,19E-07	0	0	1,07E-06	1,07E-06	0
1.8.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.8.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.9.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0	0

Average duration of contacts in hours per day (Tij)

Among MUNI	1.1.1.1.2.1	1.2.1.1.2.1	1.3.1.1.2.1	1.4.2.1.2.1	1.4.1.1.2.1	1.5.1.1.1.1	2.6.3.1.1.1	2.6.3.1.2.1	2.6.1.1.1.1	2.6.1.1.2.1	3.6.3.2.2.1	3.6.3.1.1.1
1.1.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0
1.2.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0
1.3.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0
1.4.2.1.2.3	0	0	0	0	3,75	0	0	0	0	0	0	0
1.4.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0
1.5.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0
2.6.3.1.1.3	0	0	0	0	0	0	0	0	3,75	3,75	0	0
2.6.3.1.2.3	0	0	0	0	0	0	0	0	3,75	3,75	0	0
2.6.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0
2.6.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0
3.6.3.2.2.3	0	0	0	0	0	0	0	0	3,75	3,75	0	0
3.6.3.1.1.3	0	0	0	0	0	0	0	0	3,75	3,75	0	0
3.6.3.1.2.3	0	0	0	0	0	0	0	0	3,75	3,75	0	0
3.6.1.2.2.3	0	0	0	0	0	0	0	0	0	0	0	0
3.6.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0
3.6.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0
1.7.3.1.1.3	0	0	0	0	0	0	0	0	3,75	3,75	0	0
1.7.3.1.2.3	0	0	0	0	0	0	0	0	3,75	3,75	0	0
1.7.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0
1.7.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0
1.8.3.1.1.3	0	0	0	0	0	0	0	0	0,1	0,1	0	0
1.8.3.1.2.3	0	0	0	0	0	0	0	0	0,1	0,1	0	0
1.8.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0
1.8.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0
1.9.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0

Among MUNI	3.6.3.1.2.1	3.6.1.2.2.1	3.6.1.1.1.1	3.6.1.1.2.1	1.7.3.1.1.1	1.7.3.1.2.1	1.7.1.1.1.1	1.7.1.1.2.1	1.8.3.1.1.1	1.8.3.1.2.1	1.8.1.1.1.1	1.8.1.1.2.1	1.9.1.1.1.1
1.1.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.2.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.3.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.4.2.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.4.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.5.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0	0
2.6.3.1.1.3	0	3,75	3,75	3,75	0	0	3,75	3,75	0	0	0,1	0,1	0
2.6.3.1.2.3	0	3,75	3,75	3,75	0	0	3,75	3,75	0	0	0,1	0,1	0
2.6.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0	0
2.6.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
3.6.3.2.2.3	0	3,75	3,75	3,75	0	0	3,75	3,75	0	0	0,1	0,1	0
3.6.3.1.1.3	0	3,75	3,75	3,75	0	0	3,75	3,75	0	0	0,1	0,1	0
3.6.3.1.2.3	0	3,75	3,75	3,75	0	0	3,75	3,75	0	0	0,1	0,1	0
3.6.1.2.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
3.6.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0	0
3.6.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.7.3.1.1.3	0	3,75	3,75	3,75	0	0	3,75	3,75	0	0	0,1	0,1	0
1.7.3.1.2.3	0	3,75	3,75	3,75	0	0	3,75	3,75	0	0	0,1	0,1	0
1.7.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.7.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.8.3.1.1.3	0	0,1	0,1	0,1	0	0	0,1	0,1	0	0	0,1	0,1	0
1.8.3.1.2.3	0	0,1	0,1	0,1	0	0	0,1	0,1	0	0	0,1	0,1	0
1.8.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.8.1.1.2.3	0	0	0	0	0	0	0	0	0	0	0	0	0
1.9.1.1.1.3	0	0	0	0	0	0	0	0	0	0	0	0	0

(Derived from Del Valle et al., 2007)

Matrices serve as input for the following equations:

$$P_{ij} = 1 - e^{-\sigma T_{ij}}$$

$$\beta_{ij} = \gamma_{ij} \times P_{ij}$$

Appendix C – Duration of the model (NetLogo Profiler)

Run times per sub model over 50 time steps.

	SEIR model		**SIR model**	
Model part	**Calls**	**Time (ms)**	**Calls**	**Time (ms)**
Go	50	10753.525	50	10100.265
Job-Commuting-Model	19800	61.700	19800	45.551
Normal-Commuting	19800	540727.931	19800	690200.320
S(E)IR-Model	19800	22657.940	19800	11270.229
School-Commuting-Model	19800	47.437	19800	39.432
Normal-Schoolcommuting	19800	7407.184	19800	10654.852
Population-Model-Plus	19800	1844.181	19800	1237.733
Population-Model-Min	19800	1816.096	19800	1227.775
Recolor-Municipalities	19800	65.948	19800	69.344
Municipality-Infections	19800	19.698	19800	14.769
Winter	51	0.166	51	0.162
Summer	1	0.004	1	0.004
Spring	1	0.004	1	0.004
Autumn	1	0.003	1	0.004
Total		**585401.815**		**724860.444**

Appendix D – Validation and calibration

Tried input parameters for taking **school- and job commuting** into account

Transmission rate	**R**	**I**	**% R start**	**Nr new infections introduced**	**Run till tick**	**Epidemic?**	**Max. Infections**	**At tick**	**Notes**
1.0, 0.2, 0.04	12	21	70%	none (start 1)	540	crash	crash		Infection rate too high
1.0, 0.067, 0.2	12	21	90%	none (start 1) Utrecht	900	No	1	2	Infection rate too low
1.0, 0.067, 0.2	12	21	90%	none (start 1) Cuijk	960	No	1	2	Infection rate too low
1.0, 0.067, 0.2	12	21	70%	none (start 1) Cuijk	1380	No	1	2	Infection rate too low
0.6, 0.2, 0.067	12	21	70%	none (start 1) Cuijk	1330	No	1	2	Infection rate too low
0.8, 0.2, 0.05	12	21	70%	none (start 10) Cuijk	320	crash	crash		Infection rate too high
0.8, 0.2, 0.05	12	21	70%	none (start 1) Utrecht	2430	crash	crash		Infection rate too high
0.6, 0.2, 0.067	12	21	70%	none (start 10) Cuijk	1085	No	3740000	238	-
0.6, 0.2, 0.067	12	21	70%	none (start 10) Utrecht	939	No	3320000	185	-
0.6, 0.2, 0.067	12	21	90%	none (start 10) Utrecht	1324	No	1480000	205	Endemic
0.6, 0.2, 0.02	12	21	90%	none (start 10) Utrecht	1176	No	1470000	209	Endemic
0.029, 0.04, 0.2	4	21	70%	none (start 10) Utrecht	904	No	2070000	205	-
0.029, 0.04, 0.2	20	21	90%	none (start 10) Utrecht	1569	No	702000	466	-
0.029, 0.04, 0.2	4	21	90%	none (start 10) Utrecht	1554	No	1480000	239	-
0.1, 0.2, 0.4	12	21	70%	none (start 1) Utrecht	8219	No	1410000	260	Endemic
0.020, 0.029, 0.2	20	21	90%	none (start 10) Utrecht	4082	No	348000	390	-
0.020, 0.029, 0.2	4	21	90%	none (start 10) Utrecht	4208	No	703800	260	-

Tried input parameters for taking **school- and job commuting** into account, and looking at commuter **thresholds**

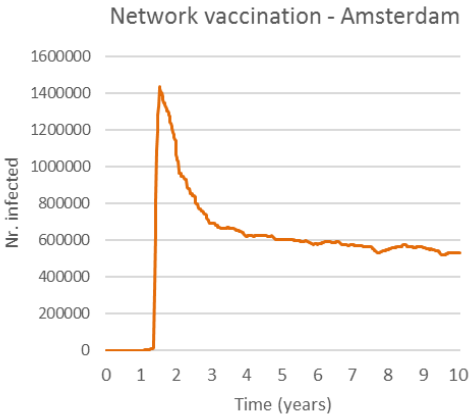
Infectionrate	**R**	**Threshold job/school**	**% R start**	**Nr new infections introduced**	**Run till tick**	**Epidemic?**	**Max. Infections**	**At tick**	**Notes**
0.6, 0.2, 0.067	12	50/25	70%	none (start 10) Cuijk	980	No	1	2	Threshold too high
0.6, 0.2, 0.067	12	10/5	70%	none (start 10) Cuijk	1043	No	1	2	Threshold too high
0.6, 0.2, 0.067	12	50/25	70%	none (start 10) Utrecht	939	No	3380000	244	Endemic
0.6, 0.2, 0.067	12	10/5	70%	none (start 10) Utrecht	1009	No	3930000	226	Endemic

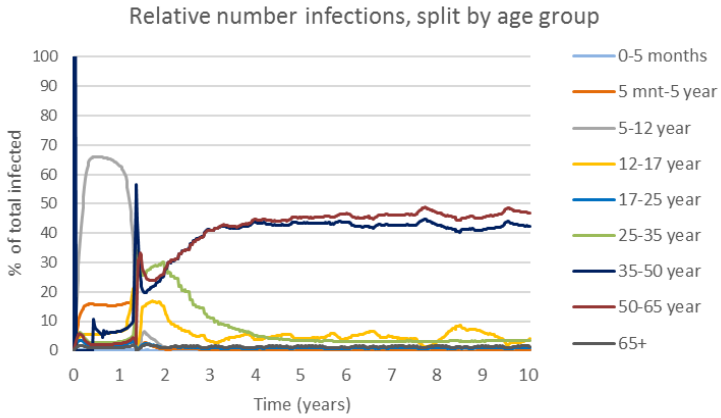
Tried input parameters for **calibration**

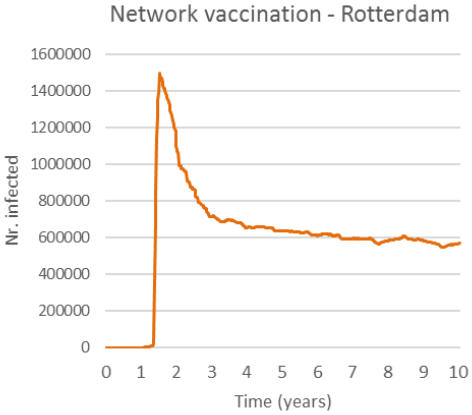
Transmission rate summer	**Transmission rate spring/autumn**	**Transmission rate winter**	**Max. infections**
0.067	0.05	0.04	No outbreak
0.2	0.10	0.067	1180
0.4	0.2	0.1	8057
0.3	0.2	0.1	10400
0.1	0.067	0.05	No outbreak
0.3	0.1	0.067	2410
0.4	0.1	0.067	680
0.4	0.2	0.067	7574

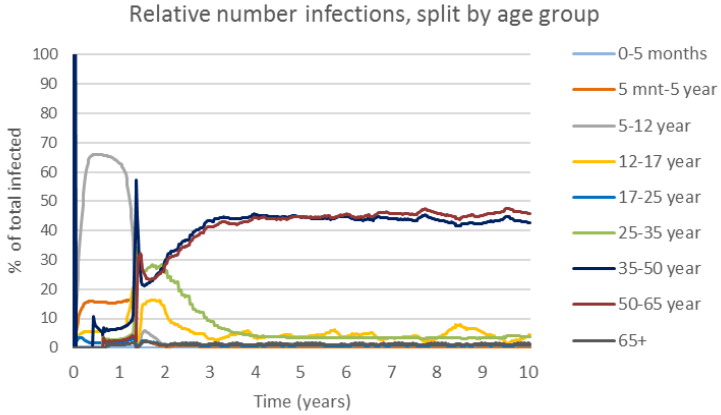
Appendix E – Figures of number of infections

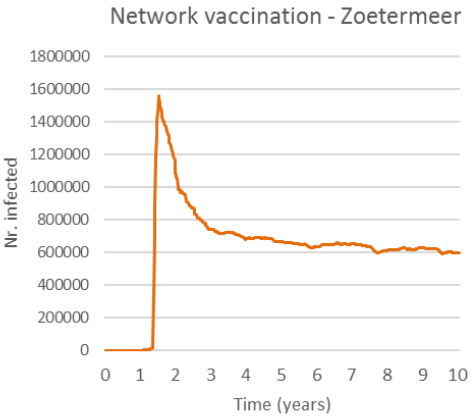
Network vaccination

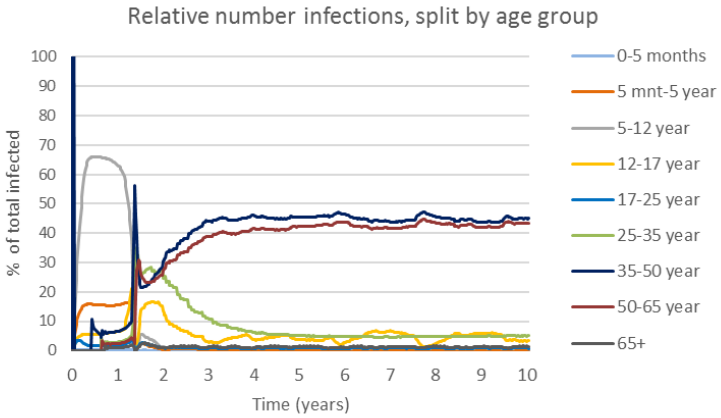


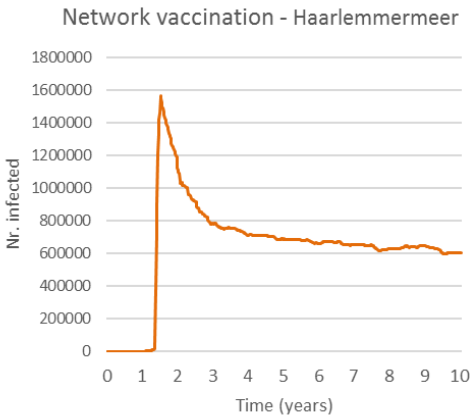


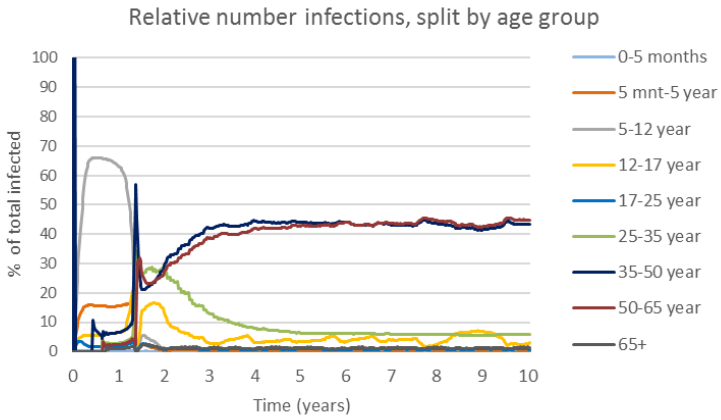




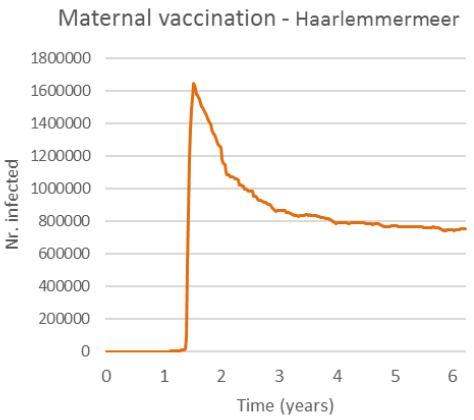


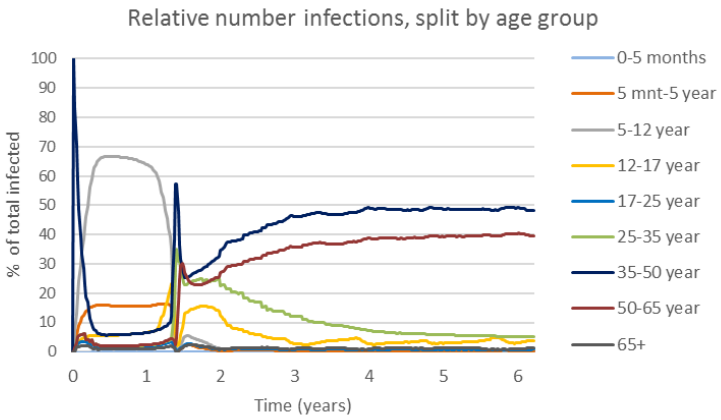


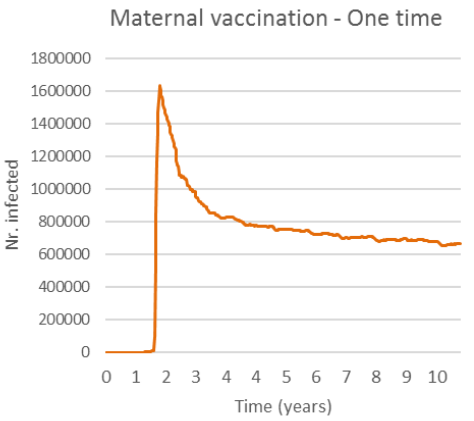


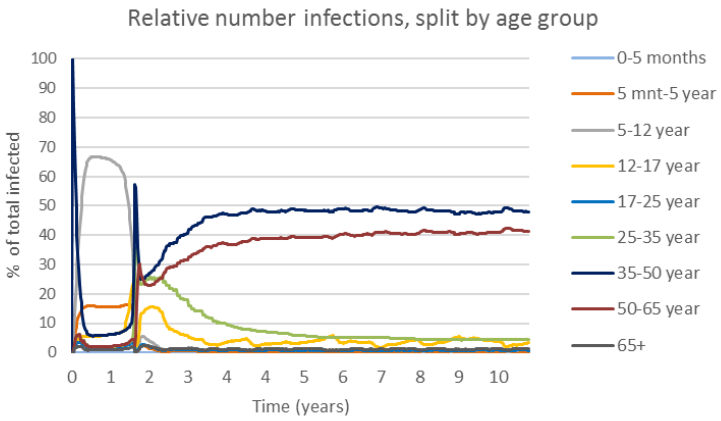


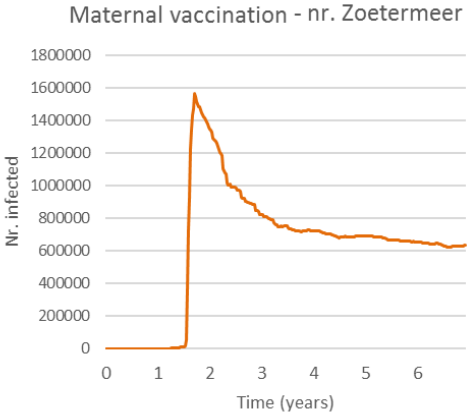
Maternal vaccination

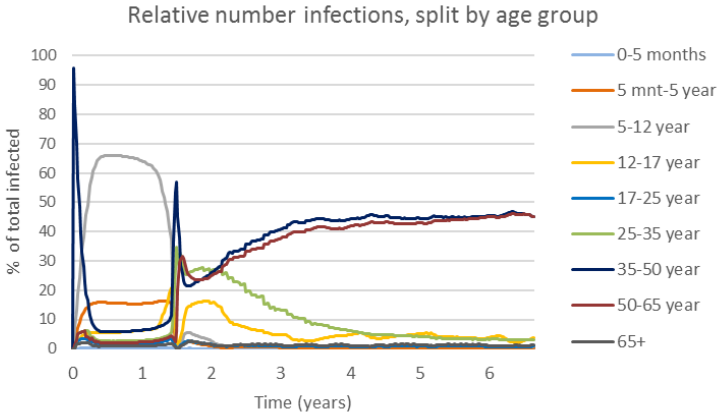






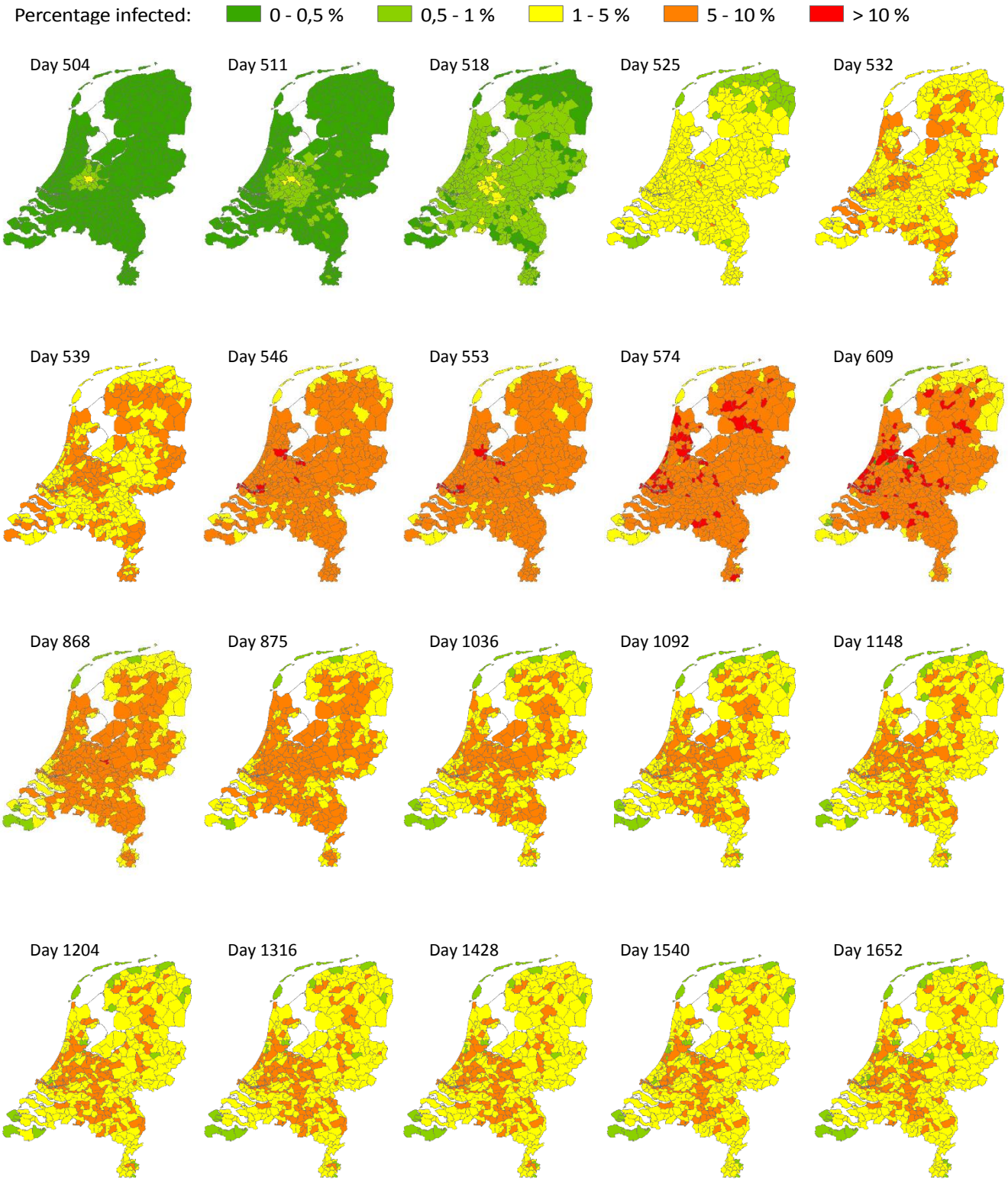




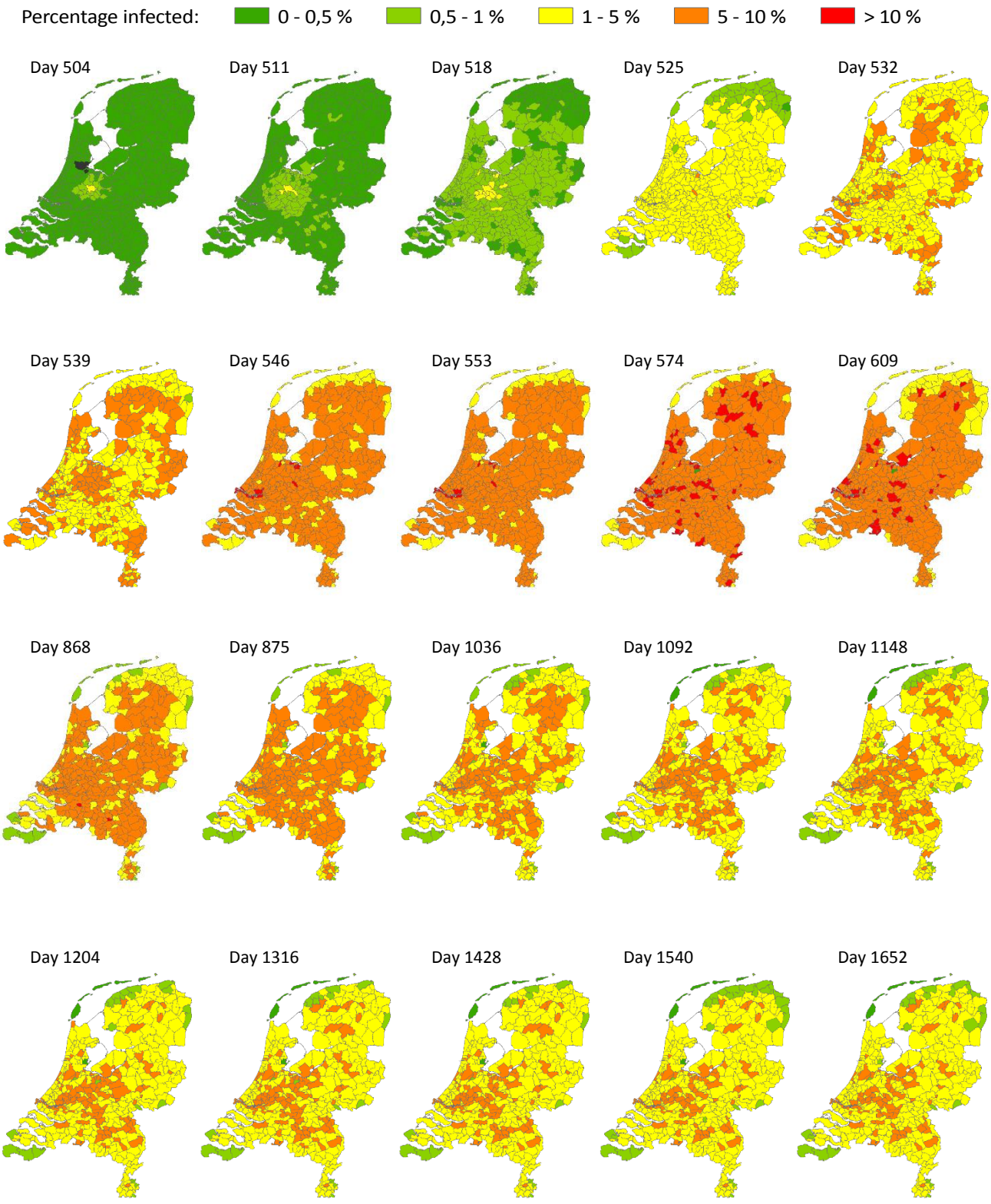


Appendix F - Disease diffusion maps

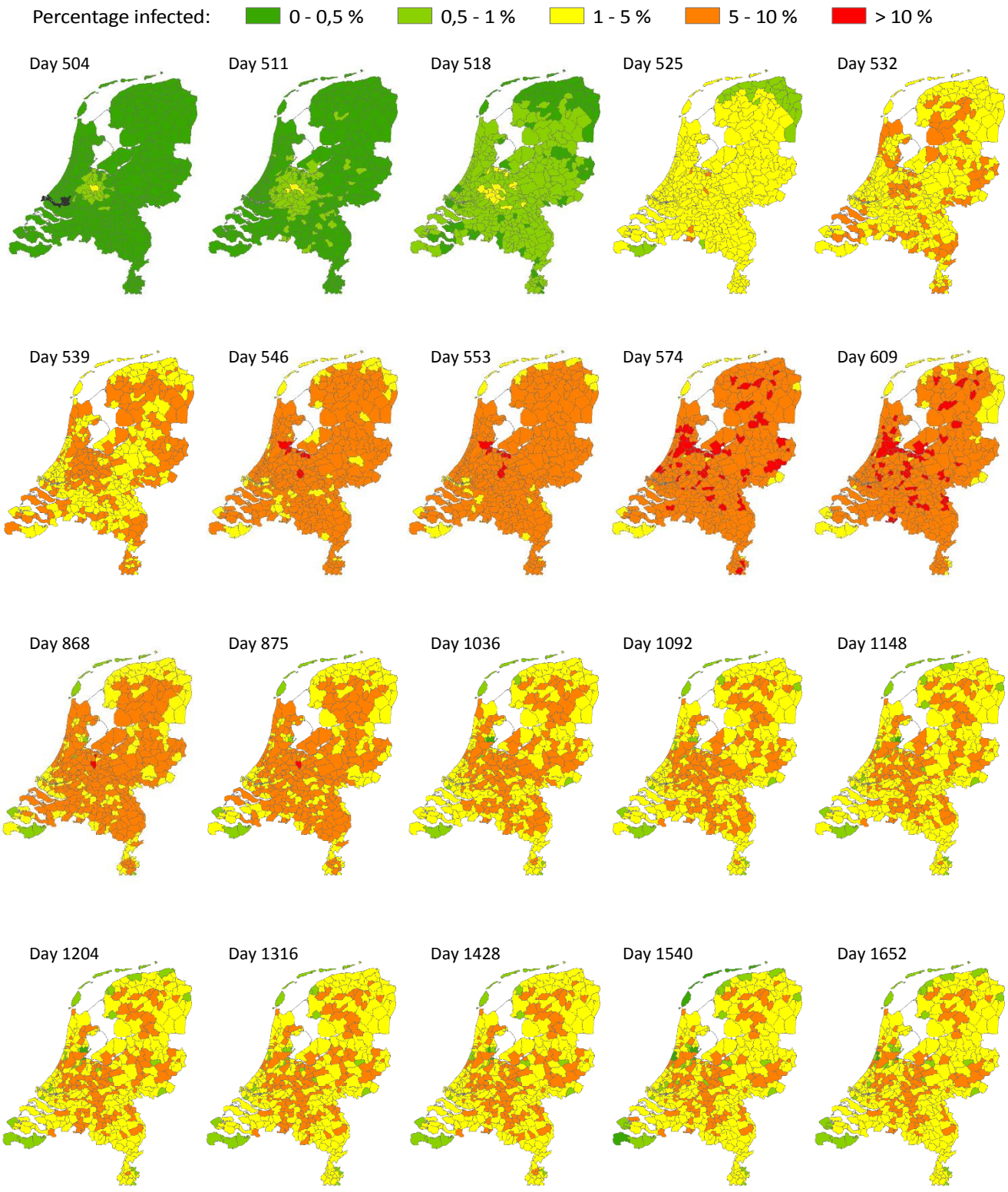
Baserun commuting:



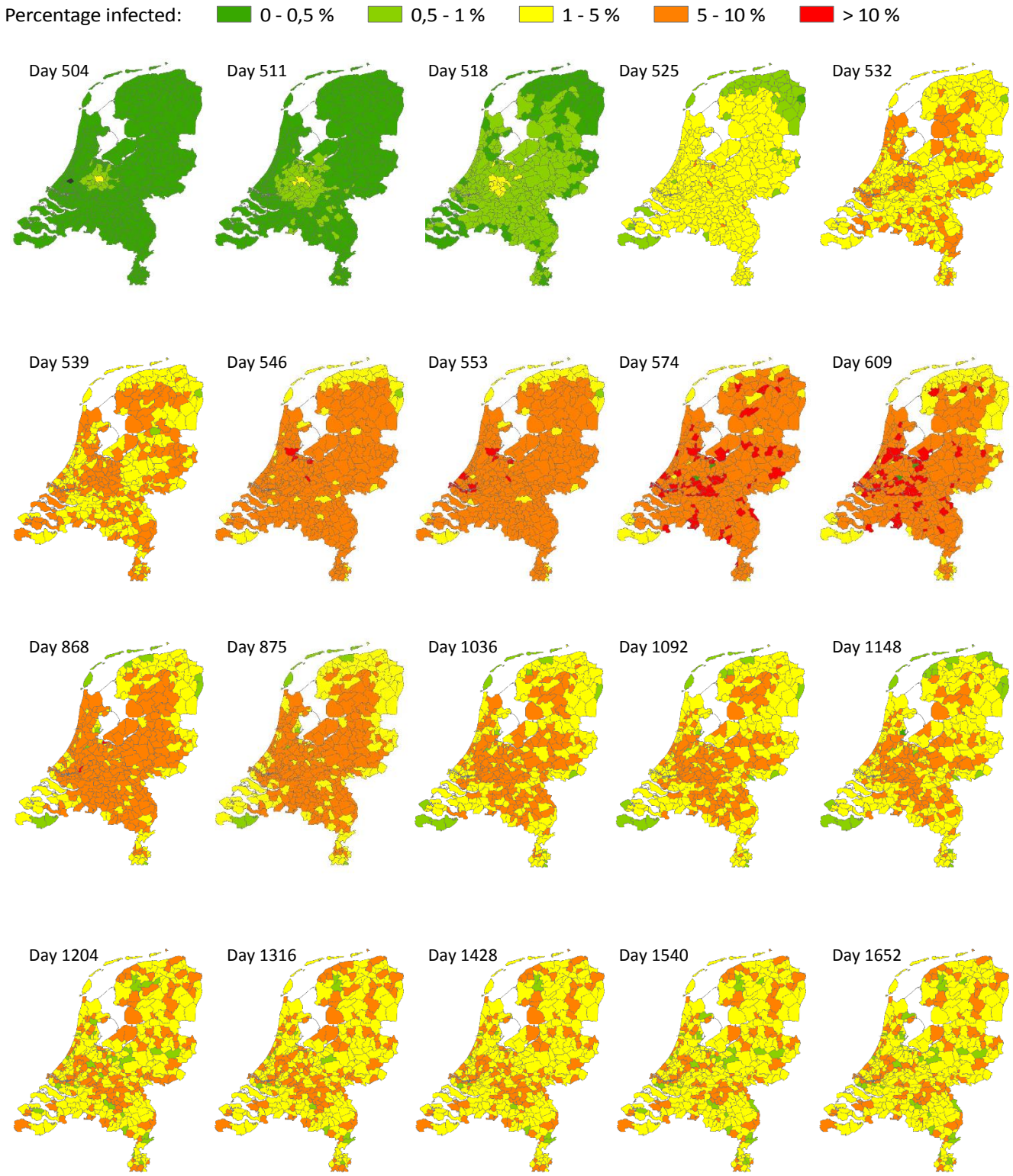
Amsterdam network vaccination:



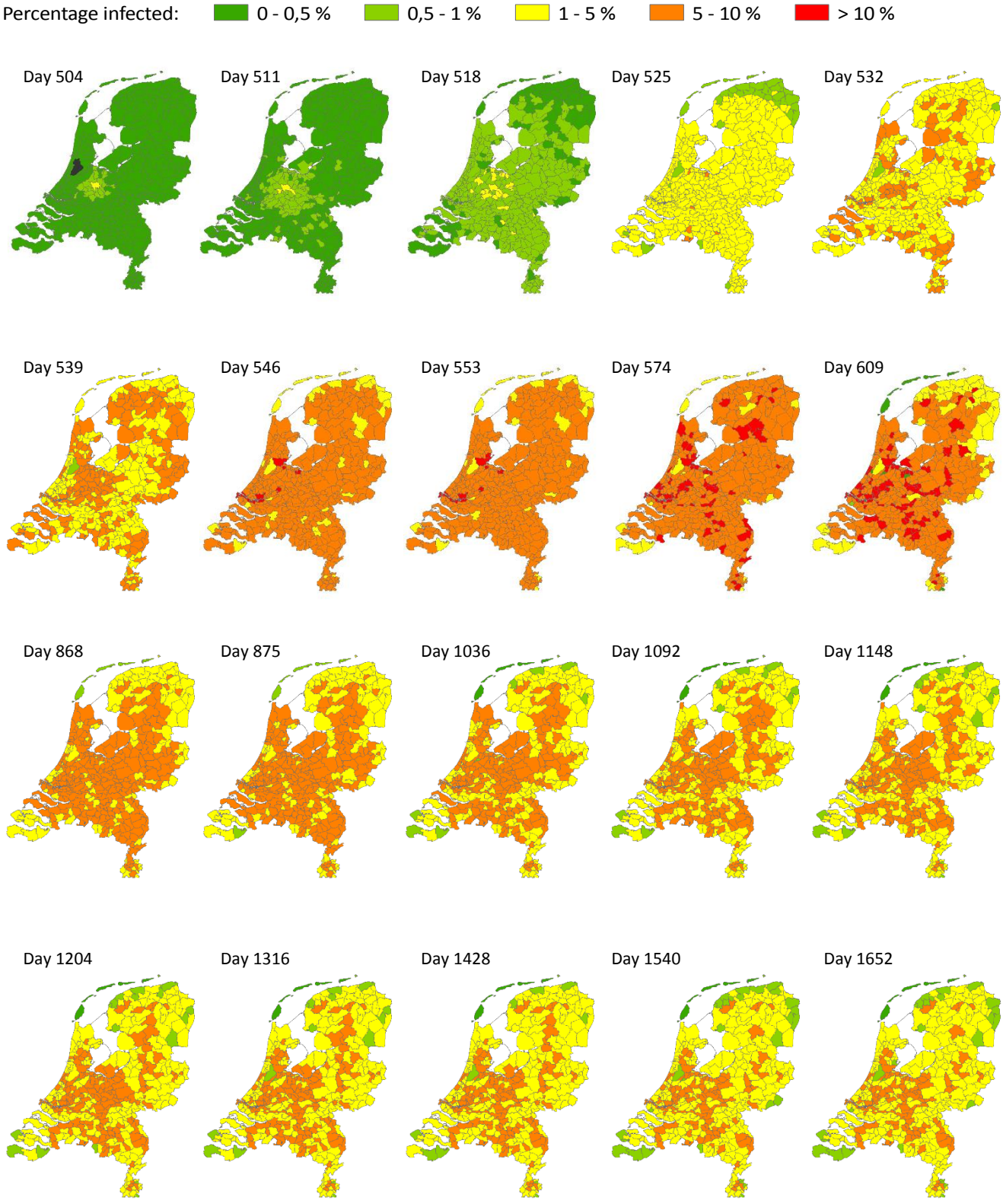
Rotterdam network vaccination:



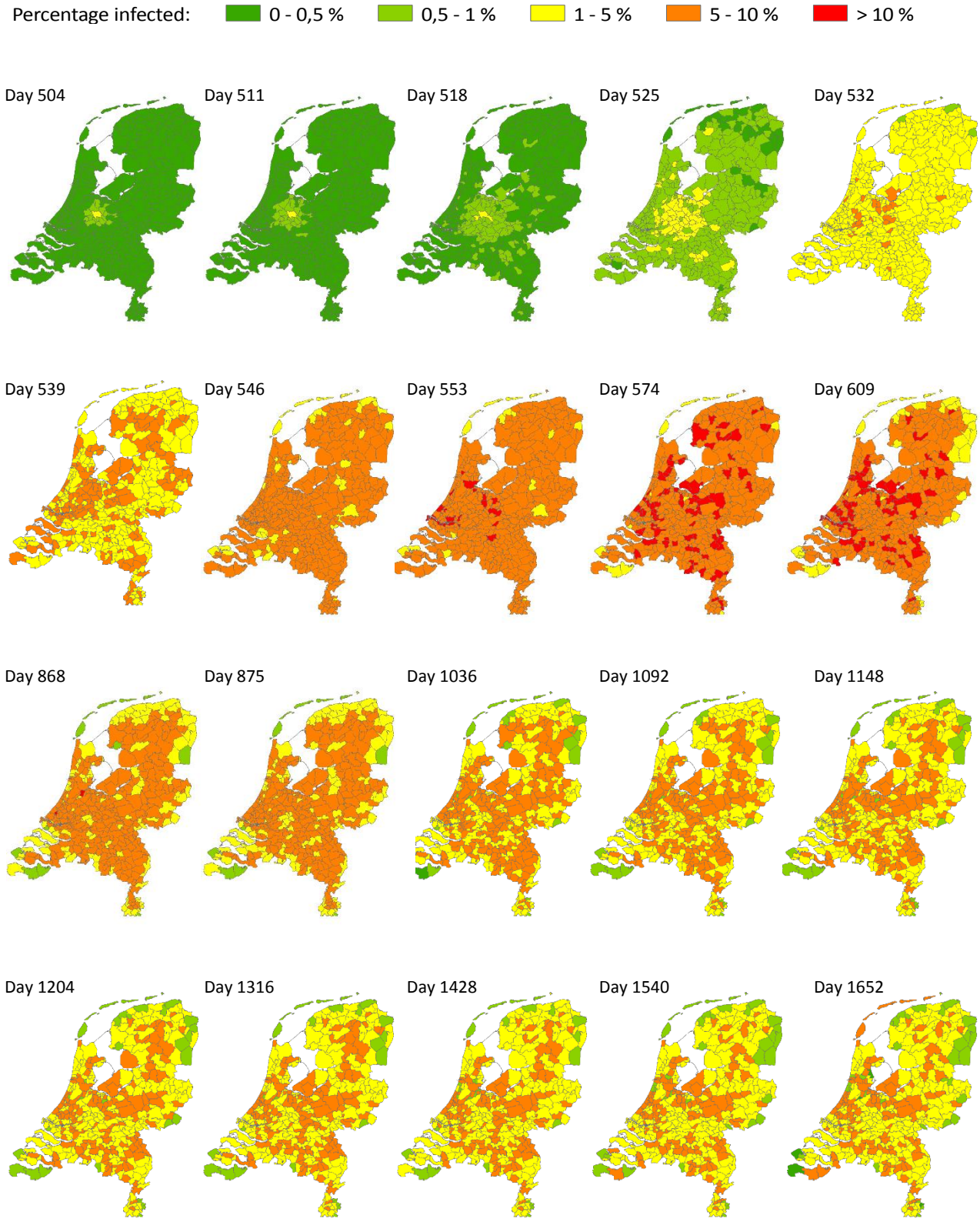
Zoetermeer network vaccination:



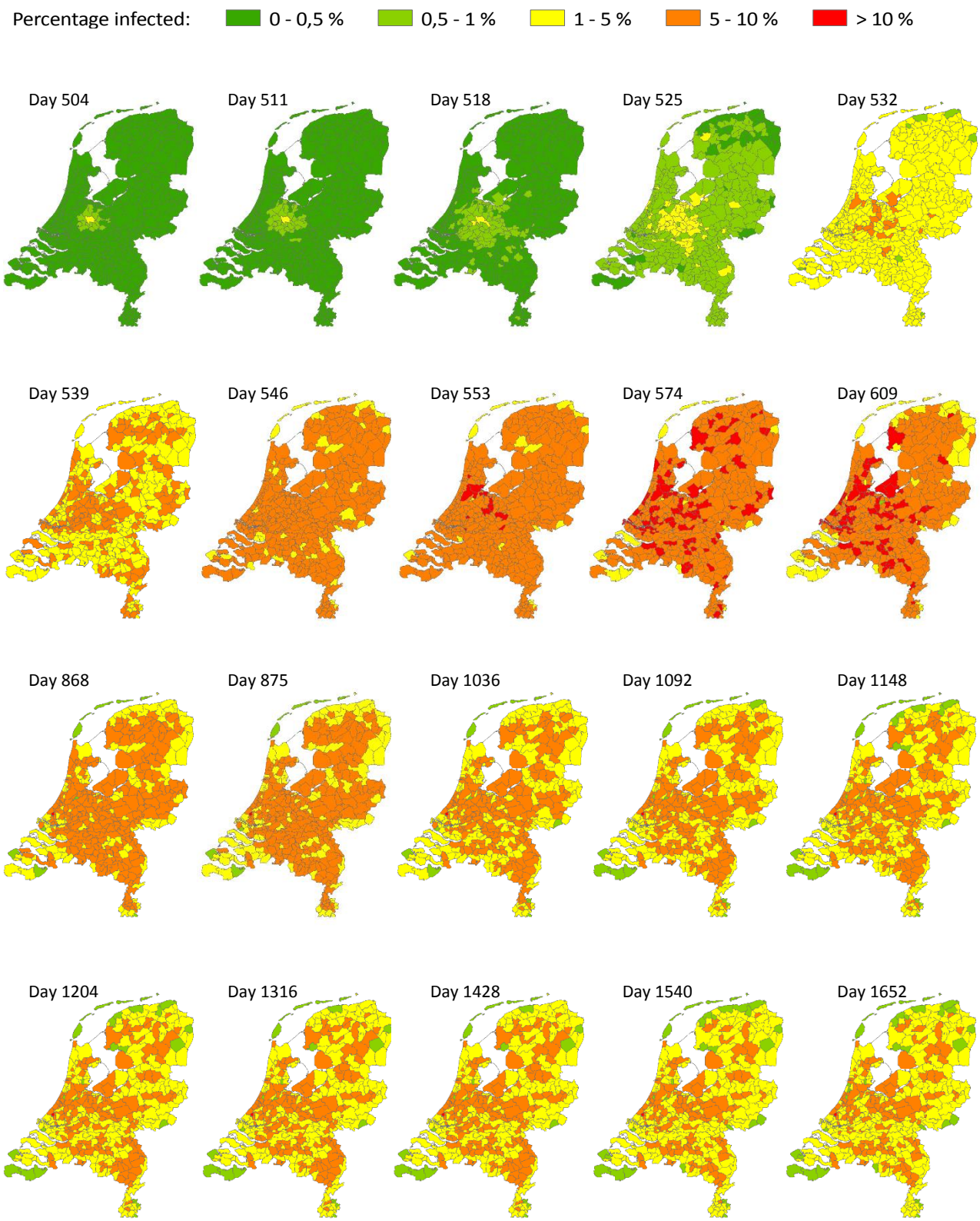
Haarlemmermeer network vaccination:



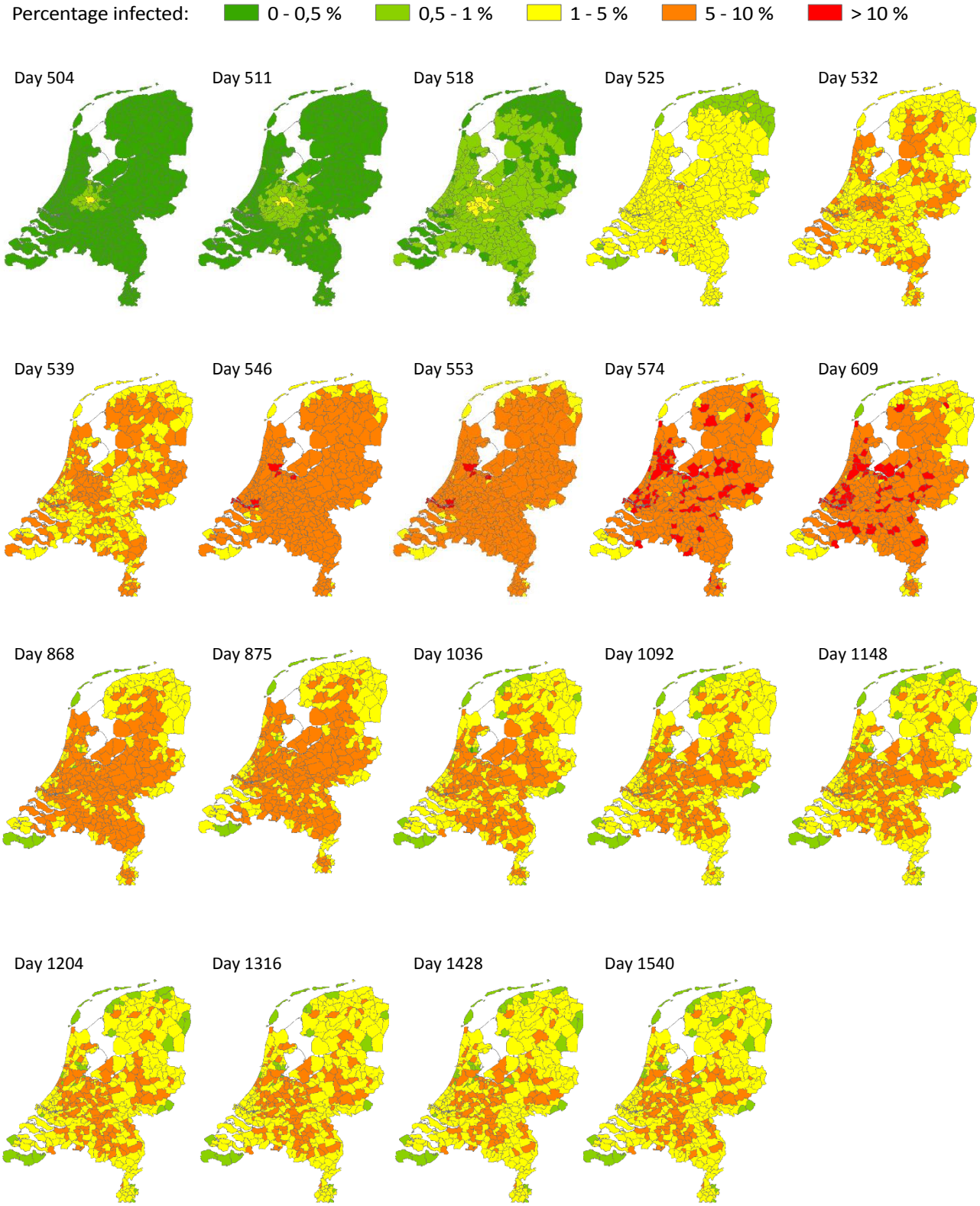
One-time maternal vaccination:



Routine maternal vaccination:



Maternal vaccination, nr. Zoetermeer:



Maternal vaccination, nr. Haarlemmermeer: