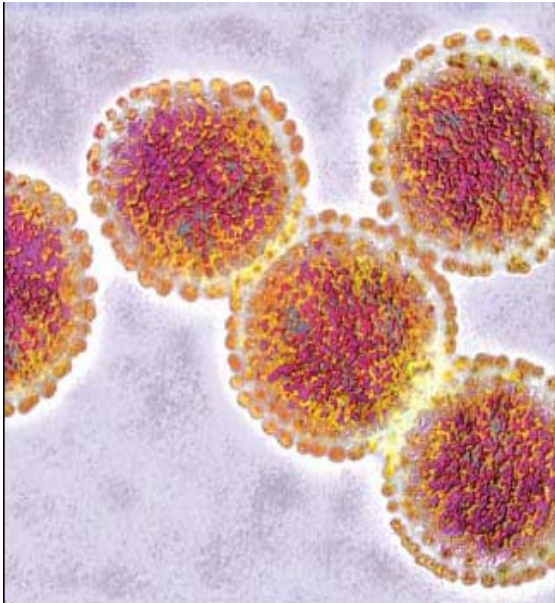


# Pandemic Influenza and mathematical modelling



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# ABSTRACT

The outbreaks of Avian Influenza H5N1 the recent years has increased our attention to a possible Pandemic Influenza. Mindful of the last century's pandemics, we fear that changes in the virus' surface antigens can cause a new virus capable of transmitting between humans. Statisticians use mathematical modelling as an instrument for predicting the pattern and intensity of the spreading of a pandemic; models can also help estimating the effects of measures such as antiviral drugs, vaccination and quarantines. Though simplified models have their limitations, it is obvious that even simple models can be a powerful tool in pandemic preparations. How should the governments and health care workers prepare for a possible pandemic? A lot of studies try to answer this, some using mathematical modelling. In this paper, I will review some of the debate on this subject. It seems to be generally agreed that we still need to learn more about influenza, and the WHO urges all countries to prepare plans for the handling of a possible pandemic. Secondly, I report the results of attempts to estimate  $R_0$ -values from outbreaks of Norwegian seasonal influenza epidemics. My estimations show expected values of  $R_0$ , but unexpectedly small values of latency and infectious periods. Finally, I have made an SEIR-model to simulate a possible pandemic, illustrating how differences in the viral pathogenicity and our efforts to reduce spread might alter the course of the pandemic.

# INTRODUCTION

## Influenza virus

Influenza virus is a virus in the orthomyxoviridea family. To replicate, all virus depend on the machinery and metabolism of cells in other organisms. Virus have developed ways to enter and infect cells, while organisms have evolved defence mechanisms to withstand infection. In fact, the species and microbes are involved in the same coevolutionary struggle, sometimes called 'a war', to develop the best mechanisms of replication and survival (24).

Because of the ability of the immune defence to change and adapt to pathogens, and then memorize that specific pathogen, the microbes are also forced to constantly change their pathogenicity to survive. Influenza viruses is continuously subjected to *antigenic drift*, i.e. mutations in the viral genome as the virus' genetic material is being reproduced inside infected host cells. Most of these mutations are largely deleterious and the resulting virus will not be able to replicate (1). But some mutations improve the virus' survival and the more 'fit' virus will spread more easily in and between hosts, possibly to other species or survive in reservoirs.

Viral evolution is also dependent on another important mechanism. When different virus strains co-exist in an individual or animal, there might be reassortment and recombination of viral genomes (25, 29). This is called *antigenic shifts*, and may lead to a new virus subtype with dramatically altered pathogenicity.

The two major influenza virus subtypes affecting humans are Influenza A and Influenza B. Influenza B viruses is only present in human population (12, 25), and represent

far less numerous subtypes than influenza A. Antigenic shifts has never been seen, nor has surface antigenic diversity (30). Hence, there are less options for a major antigenic change leading to a subtype with pandemic potential. Influenza A virus, on the other hand, has a large natural reservoir in wild waterfowl, and also infects a variety of other species, including birds, domesticated fowl and poultry, pigs, horses, dogs and humans. The terminology and classification of Influenza A virus is based on its two most important surface antigens. Haemagglutinin (HA) is the viral attachment protein, it promotes attachment to the cell and entry into the cell by fusion of the cell membrane and the viral sheath. Neuraminidase (NA) cleaves proteins on the virus' surface and prevents clustering of viruses, cleaves proteins on the surfaces of cells and permits the spreading of newly synthesized virus (8). A total of 16 antigenically distinct variants of HA and 9 of NA has been identified (10). Influenza H5N1, for example, is influenza A virus with HA type 5 and NA type 1. In addition to HA and NA genes, influenza A virus also has 6 other genomic segments each coding for a protein of substantial importance for the virus' function.

Mutations, reassortments and recombinations in these different genomic segments, primarily in the HA and NA genes, lead to a rapid emergence of new viral subtypes, and a vast amount of different co-circulating subtypes, in many different species. When discussing today's pandemic threat, it is practical to distinguish three categories of influenza: Human epidemic influenza, Avian influenza and Pandemic influenza.

## HUMAN EPIDEMIC INFLUENZA

Often referred to as seasonal influenza, epidemic influenza is a well known disease; millions of cases reported each year, and an estimated yearly excess death toll of about 50 000 in the USA (16, 17). In Norway, the yearly excess death toll is estimated to 1300 (34). An epidemic is the occurrence in a community or region of a disease or condition clearly in excess of normal expectancy (33). The influenza epidemics are caused by Influenza A or Influenza B viruses, which is transmitted by droplets escaping the carrier by sneezing, coughing or breathing and then inhaled by another person.

Human influenza occur all over the world, in temperate countries as winter epidemics, in tropical regions as all-season epidemics. Because of viral evolution, different subtypes will dominate from season to season, each presenting different pathogenicity, resulting in varying size and intensity of the outbreaks. The three pandemics of the last century each introduced a novel subtype to circulate the following years. The H3N2 virus, for example, introduced as the Hong Kong Flu of 1968, is known to be among the more pathogenic (13). The circulation of H3N2 has often been associated with more severe disease and with excess pneumonia and influenza mortality (31). In individuals having gone through an infection, immunity often persists, at least partly, during the following few years (9). A vaccine is manufactured each year, based on which viral subtypes the scientists and researchers believe will be causing the next seasons epidemic. The surveillance work of The World Health Organization (WHO) and national centres for disease control and prevention is important in this process. Vaccines are administered to individuals prone to complications from influenza infection (e.g. people with chronic medical conditions or people older than 65 years) and to groups susceptible to infection and spreading (health care workers, teachers and others with many contacts). The vaccine will only yield partial immunity, depending on how well the WHO-decided strains used in vaccine production correspond to the subtypes eventually dominating that seasons outbreak. Antiviral medication is also important in fighting complications amongst the weak

and old; Oseltamivir, sold under the name Tamiflu, is effective in mildening an influenza infection (22).

## AVIAN INFLUENZA

Avian influenza is caused by influenza A virus subtypes transmissible between birds. These viruses are normally present in many wild birds without causing disease, especially water birds and ducks, while domesticated birds such as chickens, hens and turkeys are most vulnerable to disease. Indeed, avian influenza has caused an estimated loss of more than 250 million birds in the poultry industry, including those killed by humans in attempt to stop the spread (20). There has been outbreaks in 46 different countries. The route of transmission is by droplets/secretions between birds, and possibly through the faecal-oral route. Only a few subtypes have been able to become established in mammalian hosts, probably largely because of differences in receptor preferences (20, 25), discussed in the next paragraph.

The H5N1 influenza virus has been circulating in South-East Asia since 1997 and reached Europe in 2005 (9, 18). This subtype seem to cross the species barrier more readily (20), and until September 25th 2007 there had been 328 reported human cases in 12 different countries in Asia and Africa (28). The symptoms range from typical influenza symptoms - fever, cough, sore throat, muscle aches, eye infection, to more severe complications such as pneumonia, respiratory distress, diarrhea and multi organ failure (18,22,23). Many infected cases has received medical treatment, including the antivirals oseltamivir and zanamivir, antibiotics and fungicides against secondary infections and further therapy against systemic complications. Still mortality is high; H5N1 has caused 200 deaths, and most of them were young and otherwise healthy adults (20, 28). Infected persons have all been living close to birds and poultry, as working in markets with living chickens, participating in slaughtering, eating infected chicken etc. There has been no reports of transmission between humans (22).

## PANDEMIC THREAT

History reveals many examples of devastating plagues, epidemics and pandemics. A pandemic is a disease occurring over a wide geographical area and affecting an exceptionally high proportion of the population (33). It can occur when a virus transmissible between humans meets a population where few or no individuals are immune. Last century, the world witnessed three great influenza pandemics. The Spanish Flu from 1918 to 1920 probably affected more than half the worlds population of about two billions (14), caused an estimated 50 million excess deaths worldwide (25), and 13000 – 15000 excess deaths in Norway (2). The Asia Flu (1957-58) caused an estimated 1 million deaths, and the Hong Kong Flu (1968-70) at least 700,000 excess deaths (35). There was also at least three major epidemics, but too small to be called pandemics: a pseudopandemic in 1947 with low death rates, an epidemic called The Russian Flu in 1977 that was a pandemic in children, and an abortive epidemic of swine influenza in 1976 that was feared to have pandemic potential (13).

To enter respiratory epithelial cells, influenza virus' surface antigen haemagglutinin (HA) binds to receptor molecules on the cell surface. For instance, human epidemic influenza viruses bind to respiratory cell receptors named sialic acid (SA)  $\alpha$ -2,6-Gal-terminated saccharides abundant in the upper airways. Avian influenza virus, on the other hand, prefers SA  $\alpha$ -2,3-Gal-terminated saccharides, in humans only abundant in the lower airways (1). This explains why avian virus, including H5N1, does not readily infect humans (20, 25). It might also explain the relatively high proportions of fatal pneumonia among H5N1 infected

individuals (1, 25). Today's fear of pandemic influenza is primarily based on the fact that H5N1 could change its specificity to cell receptors in the upper respiratory tract through changes in the HA-gene. Such an *antigenic shift*, leading to a novel subtype of antigen on the surface of the virus can be caused by reassortment between avian and human influenza virus in the large reservoir of influenza viruses in waterfowl. It could also for example happen in swine, where infections with both human and avian subtypes occur (25). This mechanism, by which the virus can jump the "species barrier" is in fact believed to be the cause of the last century's three great pandemics. The introduction of human transmissible HA subtype 1 (H1) led to The Spanish Flu in 1918. Similarly, the introduction of subtype H2 led to The Asia Flu in 1957 and H3 to the The Hong Kong Flu in 1968 (3, 13). Some scientist, however, suggest the Spanish Flu resulted from adaptive mutations (25).

In theory, any avian virus might evolve to gaining transmissibility between humans. If such a virus emerges, the chances are big that few or no people would be immune, because of the lack of similarity with circulating human epidemic virus. Depending on the virus' ability to cause disease in humans it might lead to a pandemic. And depending on how well the society and its governments handle this threat, it could end as a highly pathogenic influenza pandemic causing substantial morbidity and mortality. The ongoing outbreaks of avian influenza H5N1 in Asia, and the sporadic human infections show that this virus probably is the one with biggest pandemic potential. The many million birds and some hundred humans infected with H5N1 the recent years has again drawn attention to the pandemic threat. According to some sources, it is inevitable that another influenza pandemic will occur (7) - it is merely a question of time.

The WHO and many national health authorities is constantly monitoring the corresponding threat of an influenza pandemic. A worldwide network, established by the WHO, handles the surveillance of epidemic influenza, human cases of avian influenza and the genetic evolution of the H5N1 virus. The goal of this surveillance is to identify new emerging viral subtypes, to learn more about the influenza viruses and to contribute to the selection of appropriate vaccine strains (28). The WHO and many national health authorities have also made detailed pandemic preparedness plans, to assure organized efforts to handle a pandemic. But because of today's high rate of travelling between cities and countries it will be challenging to contain and stop such a spread and it could easily affect hundreds of millions of people in different countries.

## **Mathematical modelling**

Preparing for a possible pandemic influenza is an important task involving people from many different professions - epidemiologists, statisticians, virologists, immunologists, health care workers and politicians among others. Mathematical modelling is a powerful tool in the field of emerging infectious diseases. Models of society is designed to represent the contact pattern between individuals and knowledge about the pathogens is applied to help understanding and predicting the spread.

There are many different ways to do mathematical modelling of infectious disease. The classic model is the SIR model, and its analogues. The SIR model has three states: S for susceptibles, I for infectious and R for removed or recovered. At any given time, there is a certain number of persons in each state. Alternatively, each state can have a certain proportion of the total population. The susceptibles consist of individuals who can catch the disease, while the infectious are the ones with disease capable of infecting the susceptibles. Individuals no longer infectious move to the removed state, either by recovering and gaining

immunity, die, or for example be placed in quarantine. Simple SIR models often deal with a constant population, no births or deaths are taken into account, and the R state is then usually called 'recovered'.

The SIR models are deterministic: An individual can only move from one state to the next and a set of differential equations describe how these movements occur as a function of time. The model is commonly dependent on two variables: the contact rate and the length of the infectious period. The contact rate is the product of the number of contacts per person per day and the average probability that a contact is sufficient for transmitting disease. Put another way, it is the average number of adequate contacts per person per day, where an adequate contact is a contact sufficient for transmission of the pathogen. This will vary among different individuals, populations and pathogens. To get unique solutions when calculating the differential equations, one also must give initial values for each of the states, e.g. the number of persons in each state at the beginning of the simulation.

All individuals are thought to have constant and average contact patterns and rates, and each individual is thought to have the same infectious period. Understandably, this is a major simplification of society and biology; in reality, contact patterns and inter-individual differences are unimaginably complex. However, models are always simplifications of reality, and the more complex a model is, the harder it is to understand. In the field of mathematical modelling of infectious disease, more sophisticated models are usually applied. One example is SIR-like models with multiple states and different subpopulations; another is network-modelling, which applies a more realistic representation of people's contact patterns. Complex models are often stochastic, in which there are probabilities at each time step of moving from one epidemiological class to another. The presentations of such models, however, is beyond the scope of this paper.

A crucial quantity in modelling infectious spread is  $R_0$  – the basic reproductive number. It is defined as the average number of secondary cases infected by a randomly selected infected individual introduced in a fully susceptible population. In a SIR model,  $R_0$  is the product of the contact rate and the length of the infectious period. If  $R_0 > 1$ , the outbreak will possibly lead to an epidemic, while if  $R_0 < 1$  it will 'die' out. The higher the  $R_0$ , the more rapidly the epidemic evolves and the more individuals will be infected. In humans, the current H5N1 virus has an  $R_0 < 1$ , as it is not known to transmit between humans. A typical seasonal influenza H3N2 has an estimated  $R_0$  of about 1.3 (15), while estimates for  $R_0$  under the Spanish Flu range from 1.8 (5) to 2.9 and between 3 and 4 (27).

$R_0$  depends on biological features of the pathogen and the susceptible hosts, but also on the contact pattern in the susceptible population. Consequently, a single pathogen will have different  $R_0$  values depending on the chosen population or subpopulation (26). Because of their positions or social behaviour, some people have contact patterns far above the average, these are often referred to as *superspreaders*. If initially involving many superspreaders, an infection might spread fast and far, even if the average  $R_0$  is low (1). As an epidemic evolves, some people will gain immunity, some will die, some might have immunity after vaccination, some protection through medication, some will be isolated, others will reduce their contact patterns; a lot of factors affect the numbers of secondary cases each infected will cause. In addition, during an epidemic, the pathogen itself will change; the way we change our behaviour will in turn influence the viral evolution. As the number of secondary infections change from case to case during the outbreak there is a quantity called  $R$  – the replacement number. This is the average number of secondary infections produced by an infectious throughout the whole outbreak. Although interesting,  $R$  cannot be calculated or estimated until the end of the outbreak because it depends on how the outbreak develops.

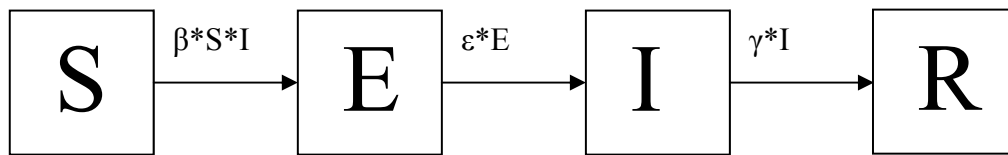
For the reasons stated above,  $R_0$  remains a theoretical value. According to its definition, it deals only with the very first round of spread in the population. Still, it is of great

value; it is one of the few ways to quantify the potency of an infectious disease to spread in a population. The  $R_0$  of a not yet emerged pandemic influenza virus is of course not known. But analysis of earlier pandemics and surveillance of the viral genomes and the mechanisms of mutations can provide estimates.

After having presented the SIR model and the concept of  $R_0$ , I will give a short mathematical presentation of the SEIR model. It is similar to the SIR model, but has one additional state. Later in this paper, I use the SEIR model in estimations and simulations.

**The SEIR - model:**

Four states: Susceptibles, Exposed, Infectious and Recovered.



**Variables:**

The contact rate,  $\beta$ , is the average number of adequate contacts per person per time unit where an adequate contact is a contact sufficient for transmission of the pathogen.  $\epsilon$  is the average number of individuals leaving E pr unit time;  $1/\epsilon$  is the average length of the latency period.  $\gamma$  is the average number of individuals leaving I pr unit time;  $1/\gamma$  is the average length of the infectious period. In such a model, where  $\beta$  and  $\gamma$  are constant,  $R_0$  is defined as:

$$R_0 = \beta / \gamma$$

**Equations:**

The following set of differential equations define the course of the epidemic as a function of time, given the variables mentioned above, as well as the initial conditions for each of the states.

$$\begin{aligned}
 s'(t) &= -\beta * i(t) * s(t) \\
 e'(t) &= \beta * i(t) * s(t) - \epsilon * e(t) \\
 i'(t) &= \epsilon * e(t) - \gamma * i(t) \\
 r'(t) &= \gamma * i(t)
 \end{aligned}$$

Mathematical and statistical programs can solve these equations, and produce solutions to simulate different scenarios.

(Reference for this paragraph: (36))



## **Fighting an outbreak**

We need to continue and intensify the work to understand and prepare for a pandemic, as it is probably only a question of time before it is here. In fact, many articles refer to a new pandemic influenza outbreak as *when*, not *if* (7). The role of the WHO and Centres for Disease Control and Prevention in different countries is central. Many countries have made detailed pandemic preparedness plans, describing how action should be taken during a Pandemic (26). The goal is to contain an outbreak at its source to gain time to produce vaccines in massive amounts. Alternatively one must reduce the spread of an already pandemic outbreak. In either way, a number of important measures need to be working swiftly:

- Effective monitoring of circulating virus, as well as surveillance for early identifying the first cases of a possible pandemic. Isolation and identification of the virus, and determining its properties.
- Well prepared measures for minimizing contact rates through transport restrictions, isolation, quarantines, etc.
- Sufficient and available amounts of antiviral drugs as well as plans for distribution and prioritization.
- A well developed industrial capacity to produce vaccines is also crucial to fight an outbreak in the long run.

It is convenient to categorize such efforts into three groups: Antiviral drugs, Vaccination and Social measures.

### **Antiviral Drugs**

Two classes of antiviral drugs is available against influenza virus: the adamantanes, for example amantadine and rimantadine, and the neuraminidase (NA) inhibitors, for example oseltamivir and zanamivir. The adamantanes work by targeting and inhibiting a proton channel (named M2) in the virus' surface necessary for replication. When used therapeutically, the adamantanes will often cause the influenza viruses to evolve and develop resistance. This is less often the case if used prophylactically; the amantadines could be used as part of a strategy where individuals more prone to infection gets prophylactic treatment to prevent illness. This is often referred to as "targeted antiviral prophylaxis" (4). The neuraminidase inhibitors, however, are rarely associated with viral resistance and can be used in both therapeutic as well as prophylactic strategies.

As the amount of antiviral drugs is limited, the question is of course what distribution strategy will most successfully reduce the outbreak. Prophylactic treatment of every person in a country, region or even city, will probably be unfeasible because of the vast amounts of drugs needed. Most articles conclude that a combination of therapeutic treatment of infected cases and targeted antiviral prophylaxis (TAP) is the most effective strategy (4,5,6). There are different types of TAP. In *social* targeting, prophylaxis is given to the network of people around the infected individual such as family members, friends, classmates, colleagues etc. In *geographical* targeting, the treatment includes a certain amount of people living geographically close to an infected individual. Therapeutic and prophylactic use of antiviral drugs is one of the first few options to contain or mitigate a pandemic; some countries has stockpiled large amounts, mostly oseltamivir, and health officials have made plans for how they should be distributed. The WHO has an international stockpile of at least 3 million treatment courses of the antiviral oseltamivir. These can quickly be flown to the centre of a potential pandemic to start programs of treatment and TAP, and could contribute to contain or

mitigate the outbreak. Especially for poor countries with little or no antiviral drugs of their own, such an international stockpile is of great importance (28). South-East Asia has been home to most of the human cases of H5N1, and it would not be surprising if the next pandemic begins there. But even the WHO stockpile might be too small if the outbreak grows to fast. Another problem is the possibility that the available antiviral drugs will be more or less ineffective in treating and protecting against the new pandemic virus. There has already been widespread circulation of adamantane resistant epidemic influenza (40), and resistance has been seen in increasing proportion of H5N1 subtypes. The NA inhibitor oseltamivir has been effective against most subtypes of influenza, but resistant virus has been seen, for example in immunocompromised hosts (19). Resistance to zanamivir is even more rare. However, as the virus is not yet here, we cannot know for sure anything about its abilities. A change in the genes coding for the NA antigen could in the worst case possibly render the NA inhibitors useless. A new virus might also be partially resistant, so that bigger doses of oseltamivir is required for one course, and stockpiles may not be sufficiently large. Manufacturers of antiviral drugs have committed to considerable increases in production over the next years (7).

Some studies have recently considered the use of antivirals in case of a new pandemic. Fergusson et al shows that containment of an emerging pandemic in Southeast Asia is possible with prophylactic use of antiviral medication combined with social distancing measures if  $R_0$  is below 1.8 (5). Another (Longini et al) says that targeted, prophylactic use of antiviral agents could contain a pandemic in rural Southeast Asia if  $R_0$  is below 1.6 and if the intervention took place 2 to 3 weeks after the first case appeared (6). Part of the conclusion of yet another study based on models for US and Great Britain is that household-based TAP coupled with reactive school closure could reduce clinical attack rates by 40-50%, given enough drugs for 50% of the population (11). The WHO urges all countries to develop preparedness plans (28), and further planning, research and investigation is still needed to find out what strategy will make these drugs most efficient (4).

## **Vaccines**

Influenza vaccines are produced by amplification of antigens from the surface of the virus (HA and NA) or attenuation of live virus. When a susceptible individual is vaccinated, an immunological response will produce high titres of antibodies against these specific antigens. The same manner a vaccine against human epidemic influenza is manufactured each season, health authorities and vaccine manufacturers plan to produce vaccines against a pandemic once the causing virus has been isolated (12). This calls for continuous surveillance and a great capacity for vaccine-production. But even if the virus could be isolated quickly, the production of enough vaccines in country after country will have to take time. Today, most vaccines are grown in chicken eggs, future research will possibly find others, more effective methods of production (8). Norwegian authorities have made an agreement with a vaccine-producer to deliver 4 million doses within 6 weeks of the start of production (26).

To mitigate the spread during this first period, other measures are crucial. Some studies show that, in a scenario of a quickly spreading, highly pathogenic influenza virus, the major wave of the outbreak might be over before considerable amounts of vaccines would be available (4, 11). The time for a vaccine to yield antibody response is also an important factor. According to literature, unimmunized individuals should receive two doses of vaccine one month apart, to yield a high amount of antibodies (12). As a result, vaccination will prevent disease and infectiousness, many studies estimating at least a 50% reduction (26). But because of the unknown pathogenicity of the not yet emerged virus more than one dose may be needed to immunize one person. This might strain the manufacturing capacity (12). The prioritization of

vaccines is important in such a setting; according to The Norwegian Plan for Pandemic Preparedness, groups important for vital functions of the society should gain priority (26). Given a delay in the spread, so that sufficient amount of vaccine could be produced, vaccination will be a powerful weapon to reduce the impact of a pandemic. A study by German et al concludes that in a pandemic influenza in the USA and for  $R_0 < 1.9$ , the rapid production and distribution of vaccines (within 2 weeks) could significantly slow disease spread and limit the number ill to  $< 10\%$  of the population (7). Another study by Fergusson et al shows that vaccines stockpiled in advance of a pandemic could significantly reduce attack rates even if of low efficacy (a 30% reduction in susceptibility is assumed) (11).

In 1976 in Fort Dix, New Jersey, there was an outbreak among soldiers of an H1 swine influenza. To prevent a possible catastrophic pandemic, the Government and Centre for Disease Control manufactured a vaccine and 43 million Americans were vaccinated. The outbreak turned out to be much more limited than expected, and when the vaccine proved to cause incidents of severe adverse effects, the immunization program was assailed as a fiasco (13). But as most scientists agree that it's just a matter of time before the next pandemic influenza hits us, this example illustrates the degree of sustained surveillance, resolute decisiveness and effective vaccine manufacturing such a vaccination program will need to be effective.

Some scientists call for a stronger focus on vaccines developing humoral defence against internal structures in the virus. This will possibly lead to a more powerful and long lasting vaccine because many internal structures are not subjected to such a strong mutational pressure as is the case with surface antigens (21). Others conclude that immunity against internal structures is either short lived or plays a relatively small role in resistance (12). The reason is that after having stopped circulating in 1957, the H1N1 virus reappeared in 1977, and significant disease was only seen in people born after 1957. People previously infected with H1N1 had antibodies against HA and NA surface antigens, and showed immunity to a large extent. Younger people, never infected with H1N1, but several times with other subtypes sharing the internal structures, had insignificant immunity (12).

## **Social measures**

As technological and economical development changes human lives all over the world, some of the many barriers reducing potential viral transmission is being changed. Ever growing urbanization will, at least in some parts of the population, increase the contact rates. Schools, public transport, social gatherings etc bring people closer together and facilitates transmission. While increased prosperity and wealth might increase the hygiene, increasing travel and trade can ease regional spread of virus. And the exploding increase in air travel has undoubtedly led to a greater risk for inter-regional and -continental spread (38).

In case of an emerging highly pathogenic avian influenza pandemic governments and health officials will have to introduce measures to reduce the contact rates in the population. Facing a possible emerging pandemic, people will also change their behaviour spontaneously and probably reduce the risk of transmission (5).

As with antiviral drugs and vaccination, the challenge regarding social measures is finding out which ones are the most effective. Economic loss and increased public expenses must also be taken under consideration.

Contact rates vary substantially from individual to individual, and among different age groups and subpopulations. Children are believed to have high contact rates, and the closing of schools and kindergartens might be an effective measure. But the result will be increased contact between children and adults, Fergusson et al assumes household and random contact rates to increase by 100% and 50%, respectively, for individuals no longer able to attend

school or work (5). There is also an economic cost having a large part of the adult population looking after kids at home. Another option is travel restrictions: reducing public transport, inter-regional or international travelling. In a setting of a severe pandemic, quarantines could be an alternative, Fergusson et al suggests quarantine zones, in which movements in and out of the affected area is restricted (5).

Other measures includes for example use of face masks, gloves, eye protection, increasing hygiene routines etc, especially relevant in hospitals. Simple measures such as thorough hand washing could be among the most efficient. It is hard to predict the effects of social measures (5). Although clinical data are limited, and expected levels of compliance is only moderate, studies conclude that social measures will work and should be subject to further investigation (37, 38). An important factor will in any case be the means of information and communication between officials and the people.

## **ATTEMPTS TO DETERMINE $R_0$ IN EPIDEMIC INFLUENZA IN NORWAY**

### **Method**

$R_0$  is an important value when modelling and simulating outbreaks of infectious disease. Almost every paper released in this subject relates at least part of their discussion to this quantity. Several studies aims at estimating  $R_0$ -values of the Flu Pandemics of the last century. This is of great interest, because  $R_0$  quantifies the potency of the pathogen to spread in the population under consideration. Knowledge of how earlier pandemic viruses spread can help us prepare for the next.

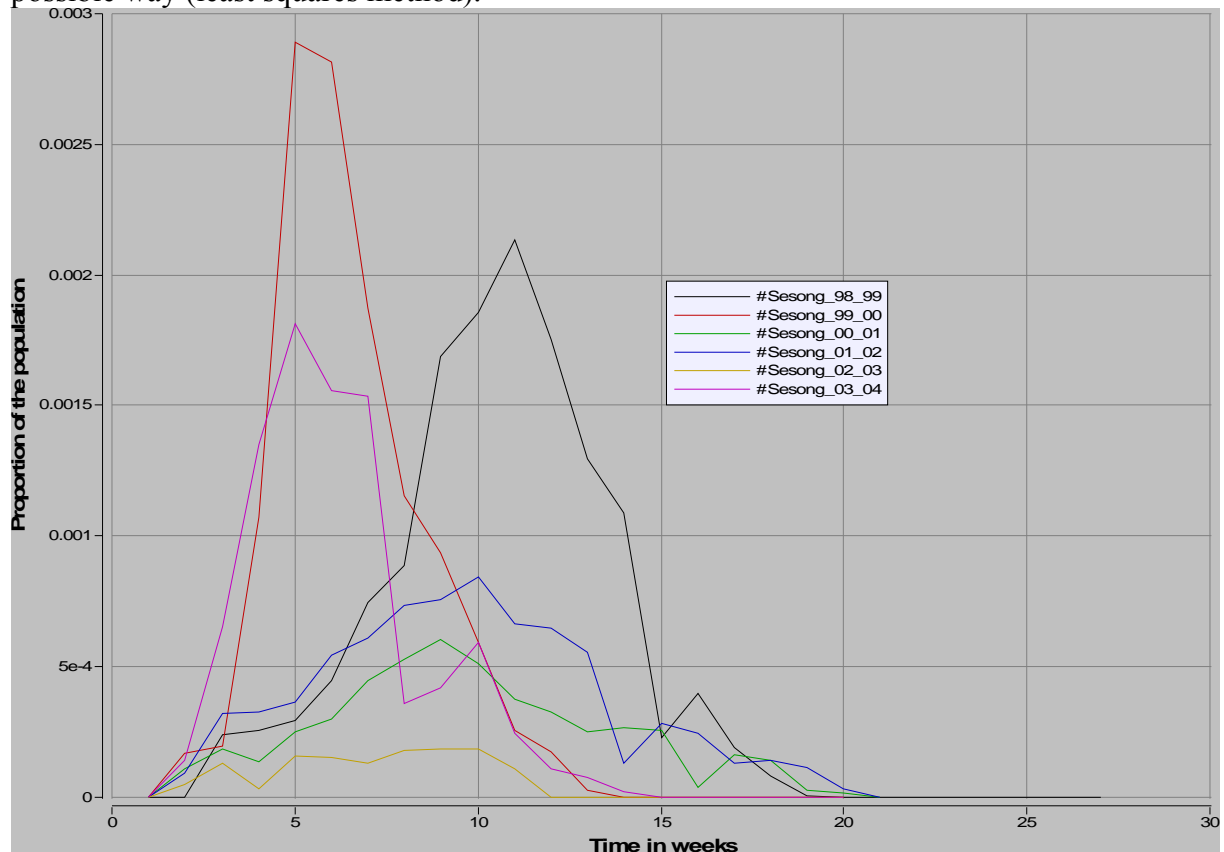
Trying to estimate  $R_0$ -values of seasonal influenza outbreaks is important as well; we have a lot of experience and data about seasonal outbreaks, and an estimation of  $R_0$  will help understanding these outbreaks. This, in turn, yields valuable information about how a pandemic virus will spread. At least in the beginning of an outbreak, a pandemic virus will probably meet the same conditions as seasonal influenza.

Norwegian Primary Physicians covering 15% of Norway's population reports statistics about influenza to FHI (Folkehelseinstituttet), the Norwegian Centre for Disease Control. Each physician report weekly the total numbers of consultations as well as the number of consultations where the patient had symptoms of Influenza Like Illness (ILI). These data was collected through six "influenza seasons" from 1998 through 2004, each season lasting from week 40 to week 20 the following year. We used these numbers to estimate the proportion of the population having influenza in the following way:

We summed up all ILI-numbers for each week and we summed up the total consultations each season. Throughout a year we assume that there is a certain number of consultations where the patient has ILI symptoms, but no actual influenza. For that reason, we subtracted a basal rate from each weekly total of ILI, so that the weekly number of ILI is close to zero at the beginning of the outbreak, as defined by the FHI. In all cases this was during late fall or winter.

Then we divided each adjusted number of weekly ILI with that seasons total consultations. In this estimate, the number of ILI-symptoms noted by the physician represents the number of influenza cases, and the total number of consultations represents the population.

Figure 1.1 shows these data, the curves reflecting each seasonal influenza outbreak. We imported these curves into a statistical program named Berkley-Madonna, and constructed an SEIR model as described above. The program (curve fitting) fitted the values infectious period, latency period, initially infected, initially immune and the contact rates so that the infectious curve from the SEIR model matched the curve from the data set the best possible way (least squares method).



*figure 1.1. Weekly numbers of each season's observed ILI, after having subtracted the basal rate, divided by the total number of consultations during the season.*

Figures 1.2 and 1.4 shows for the seasons 98-99 and 99-00, respectively, the results of this curve fitting and the estimated values of  $R_0$ , latency period and infectious period. Figures 1.3 and 1.5 shows for the same two seasons the number of susceptibles and cumulated infected throughout the modelled outbreak. Figure 1.6 shows the results of all six seasons.

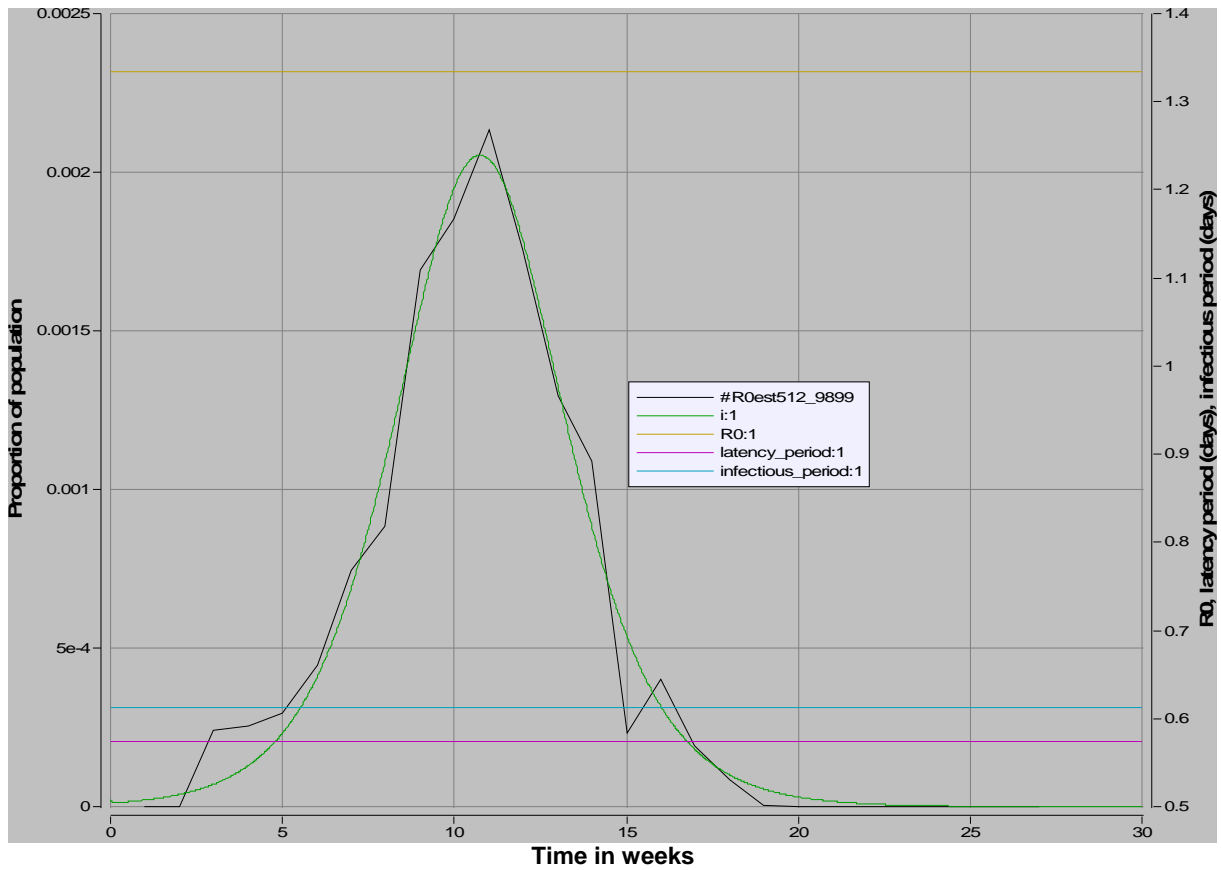


figure 1.2. ILI-data from the 98-99 season (black), the fitted curve in the SEIR-model (green) and the calculated values of  $R_0$  and latency and infectious periods.

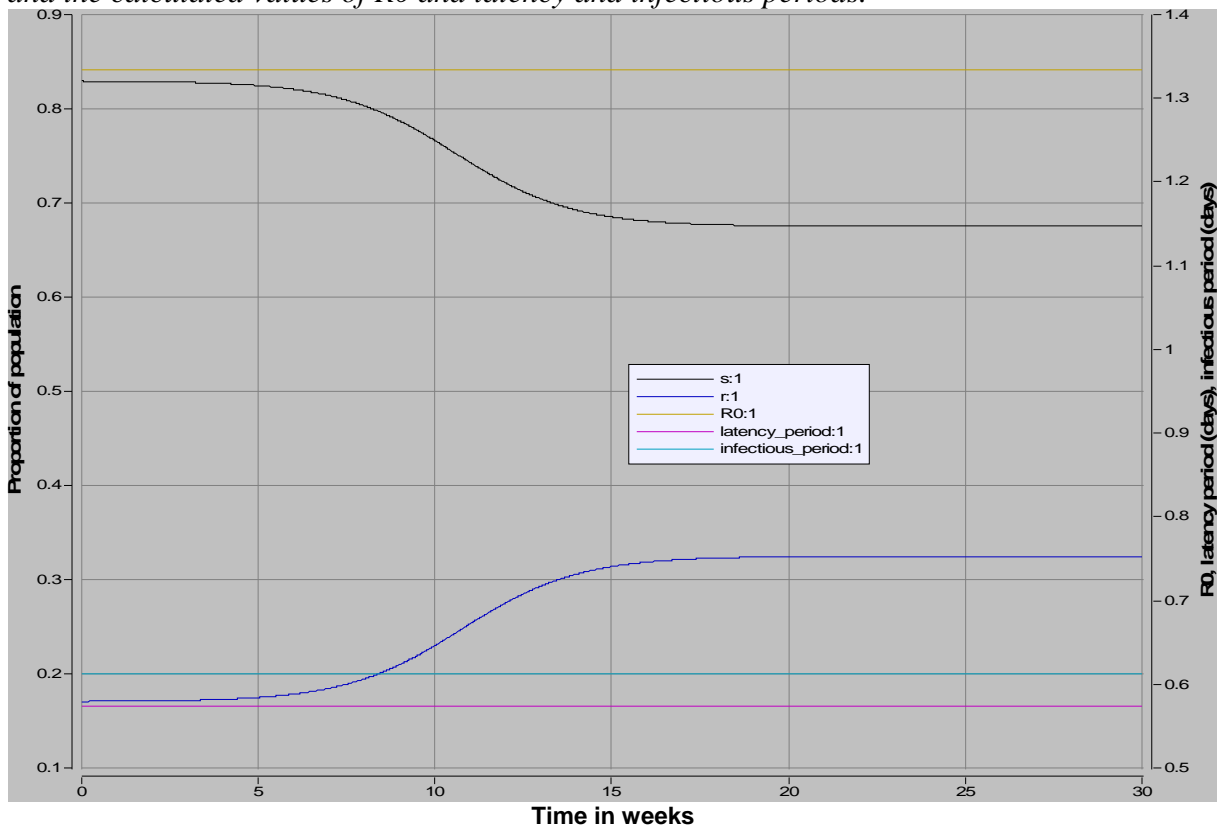


figure 1.3. The number of susceptibles (black) and cumulated infected (blue) throughout the modelled outbreak in the 98-99 season .

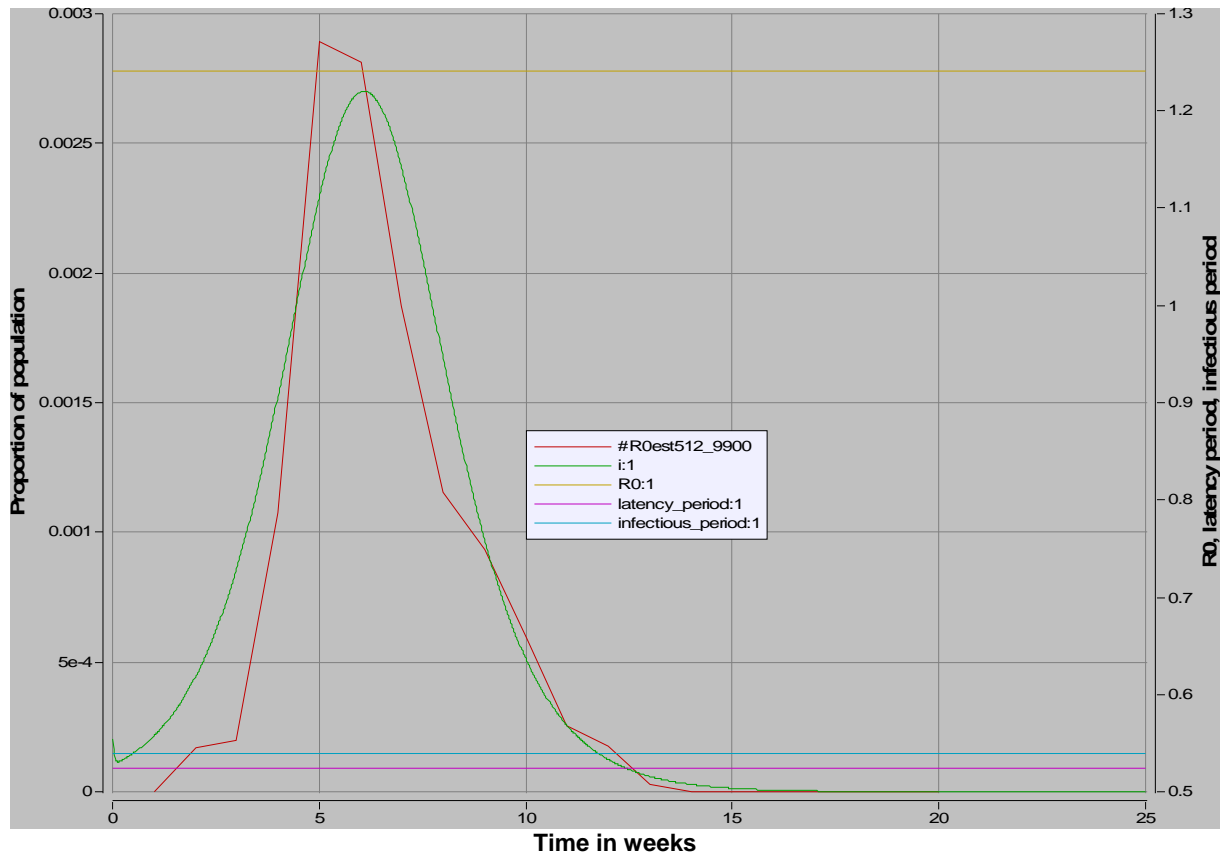


figure 1.4. ILI-data from the 99-00 season (red), the fitted curve in the SEIR-model(green) and the calculated values of  $R_0$  and latency and infectious periods.

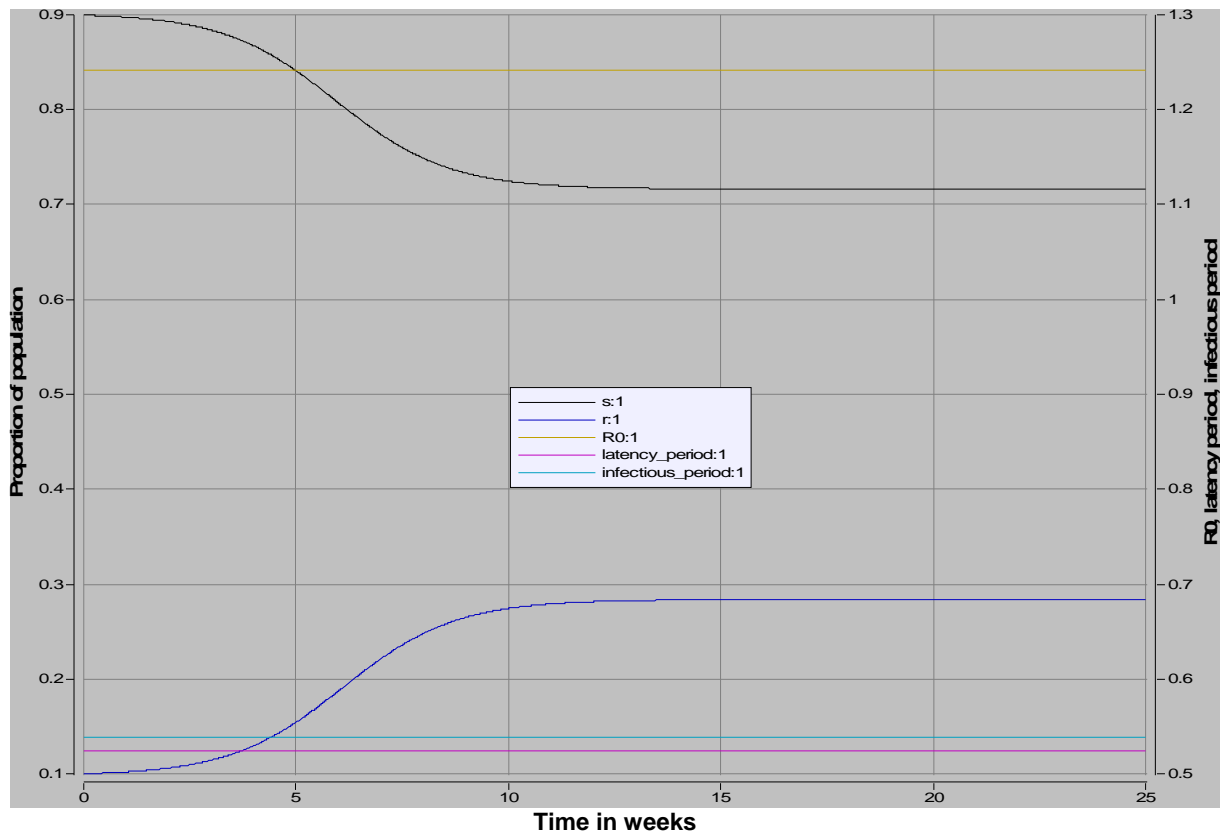


figure 1.5. The number of susceptibles (black) and cumulated infected (blue) throughout the modelled outbreak in the 99-00 season.

## **Results**

season	R0	latency period (days)	infectious period (days)	initially immune (%)	totally infected (%)
98-99	1.34	0.58	0.62	0.17	0.15
99-00	1.24	0.52	0.54	0.10	0.18
00-01	1.17	0.32	0.57	0.10	0.06
01-02	1.18	0.59	0.39	0.10	0.095
02-03	1.04	0.35	0.41	0.02	0.032
03-04	1.24	0.50	0.42	0.11	0.17

*Figure 1.6. Table showing the different seasons and estimated values from the SEIR models.*

## **Discussion**

The method described above for estimating R0 of epidemic influenza in Norway is not very robust. There are several factors contributing to possible errors. First I will discuss uncertainties about the data and how they are collected and treated.

Influenza is a well known disease, but it is not easy to diagnose it clinically. A lot of other conditions including for example other viral infections and allergy, can yield symptoms as coughing, sneezing, sore throat or fever, while headache, myalgia, nausea etc is mostly subjectively recognized. Hence, the physicians diagnosis of ILI does not have an optimal specificity as an estimate of true influenza incidence. This problem is possibly even larger during an influenza outbreak: when there is an increased focus on influenza, the physician and the patients will more often think that influenza causes the symptoms. It is believed that during an influenza season, there will be many sub-clinical cases not recognized by the doctor as influenza. Hence, the sensitivity is not optimal either.

Another problem is that far from all persons on a Primary Physicians list visit the doctor during a season. These are primarily healthy people, but even people with clinical influenza might not go see the doctor, and many cases of ILI will be left out. These effects might counter-balance each other, but this is still a source of great uncertainty.

The data-gathering might seem satisfactory if one considers the group of patients consulting the physician during the season as a representative part of all the persons on that physicians list. But even if that was true, there would still be the mentioned problem of specificity and sensitivity. Patients with more than one consultation will be counted more than once, and patients without ILI at their consultation might still have had ILI during the season.

To conclude, the ILI-registration system might not be a very good estimate of the total incidence of influenza, but so far, these are the best data available. The FHI also register the positive proportion of serological samples taken from patients with ILI by some physicians and hospitals, but this procedure does not yet include enough patients to be of any certain value.

The procedure of subtracting a basal rate from all the weekly ILI-numbers might also be a source of error. It is, however, believed that outside influenza season there are as good as no cases of influenza and the basal rate subtraction might therefore correct some of the mentioned lack of specificity.

Secondly, methods for modelling the spread and calculations of R0 might contribute to errors. The SIR and SEIR models are widely respected for modelling outbreaks of infectious



disease. However, most modern models are far more sophisticated, including different states and subpopulations. A simple SEIR model as used in this method might not simulate the real epidemic in a satisfactory way. The model does not take into account the variations in contact rates and disease intensity among different subpopulations. It is based on a hypothetical society where all inhabitants are average persons and mixes with everyone. The benefits by using a simple model is that in absence of too many assumptions, the model is more robust and easier to interpret.

As mentioned under Mathematical modelling,  $R_0$  is a theoretical value describing the pandemic potential in the beginning of the outbreak. The method used here, by building an SEIR model on constant values of  $\beta$  and  $\gamma$ , is a potential source of error.  $\beta$  in particular, but also  $\gamma$ , might in reality vary during the outbreak, giving another curve and possibly another  $R_0$ .

Finally, there was some trouble regarding the curve-fitting function in Berkley-Madonna. The program required limits and suggestions to the variables, to which the curve-fitting seemed quite sensitive. Experimenting with these limits led to the realization that if a SEIR model curve was to fit the data set, some of the variables had to take values far from what we would expect. The  $R_0$  values between 1,04 and 1,34 seems quite reasonable, according to literature (15). But the latency and infectious periods got generally too short, both less than 24 hours in our simulations. According to literature, the incubation or latency period is from 1 to 4 days (mean 2) and the infectious time from 3 to 5 days or even longer (18, 26, 31).

To conclude, there are many sources of error in this project. Especially the combination of uncertain data-gathering and processing, along with a too simplified model and method of  $R_0$ -calculation. This makes the results too uncertain to be conclusive, but still they could be of some use. For example: although supported by clinical observations, the commonly accepted values of latency and infectious periods is based on few solid sources. In a PubMed search for "influenza" and "incubation" I found an article (26) referring to another (31) which had no references for its stated values of incubation period. Further investigation and research in different fields is needed to learn more about influenza, as exemplified here by modelling of seasonal influenza outbreaks and estimation of its values of  $R_0$ , latency period, number of infected etc.

## **MODELLING AN OUTBREAK**

### **Method and discussion**

Each year, in the subject of pandemic influenza, tenfold of articles are published in internationally respected journals and magazines. Many of these use mathematical modelling as part of their discussion and theories. As already discussed briefly, simple models might be too simplified to represent reality. On the other hand, generalizations and assumptions have to be made even in the most advanced models, and the more complex a model is, the more difficult is the interpretation. Nevertheless, most studies use models with a complicated structure and apply a number of data from knowledge of the society and the pathogens (4, 5, 6, 7). Some of them apply SEIR-like models as part of the structure in their methods (4, 6). Examples of methods used is the construction of a small society based on census studies, with different sizes of households, schools, workplaces etc. Dependent on age and other characteristics, individuals have different contact patterns and probabilities to catch disease.

Other parameters, as for example the probability that an infected case is asymptomatic, or that an infected individual changes his contact pattern, are also taken into account. As a result, complex data programs are constructed and powerful computers are needed to run calculations (4). These studies often require months of work by many people from several departments.

I have chosen to present modelling with the SEIR model in its simplest form. Although far from methods applied in modern studies, it exemplifies mathematical modelling in an understandable way. I used the program Mathematica to construct a SEIR model as explained earlier. The program illustrates graphically different scenarios of an influenza pandemic, depending on the values of contact rate, infectious period and incubation period as well as total population and the initial numbers of infected and resistant. As already mentioned, the characteristics of a not yet emerged pandemic is of course not known. Based on observations, calculations and knowledge of the virus and the society we can have good guesses for different variables, but when preparing for a pandemic it is essential to do modelling of different scenarios. Through vaccination, medication and implementation of social measures one can change factors determining the course of the pandemic. Between writers of different scientific studies, there are substantial discussion about the probable sizes of all these factors. I have manipulated the factors  $R_0$ , contact rate, latency period, infectious period and the proportion of initially resistant, all according to numbers figuring in large studies. My modelling are meant to serve as examples of how mathematical modelling can be of great value in preparing for a pandemic. In all the following simulations, the total population is set to 1000 individuals, and the time unit is days.

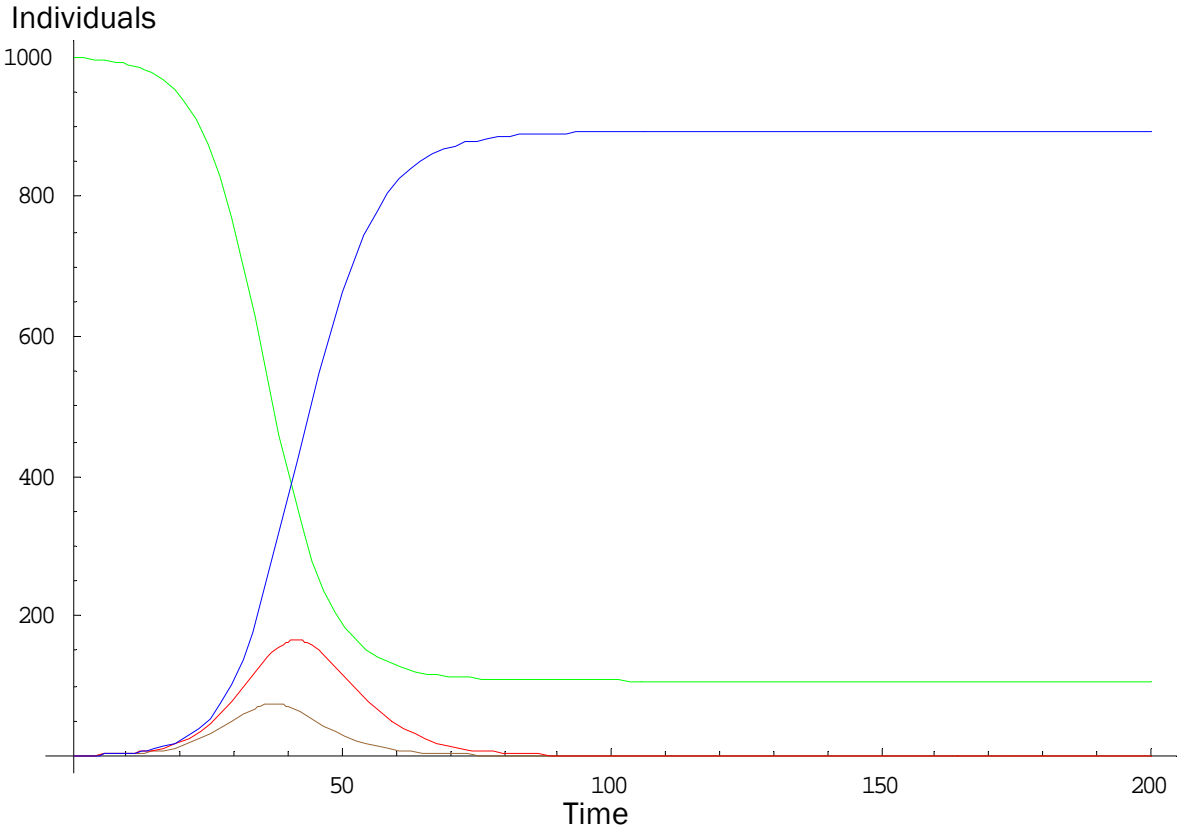


figure 2.1. SEIR model (green, brown, red, blue). The curves show the number of persons in each state each day. Latency period is set to 2 days, infectious period 5 days, contact rate 0.5,  $R_0 = 2.5$ .

In the scenario of figure 2.1., where  $R_0$  is 2.5, the peak of the outbreak would occur at approximately 42 days after the first cases with 16.5% of the population infected at the same time. A total of about 90% would go through infection, and the whole outbreak would be over after 80 days. Most studies estimate an  $R_0$  of less than 3 for the Spanish Flu, and even lower for later pandemics (5, 27). Figure 2.2. shows SEIR model simulations with  $R_0$  set to 1.75 and 1.25.

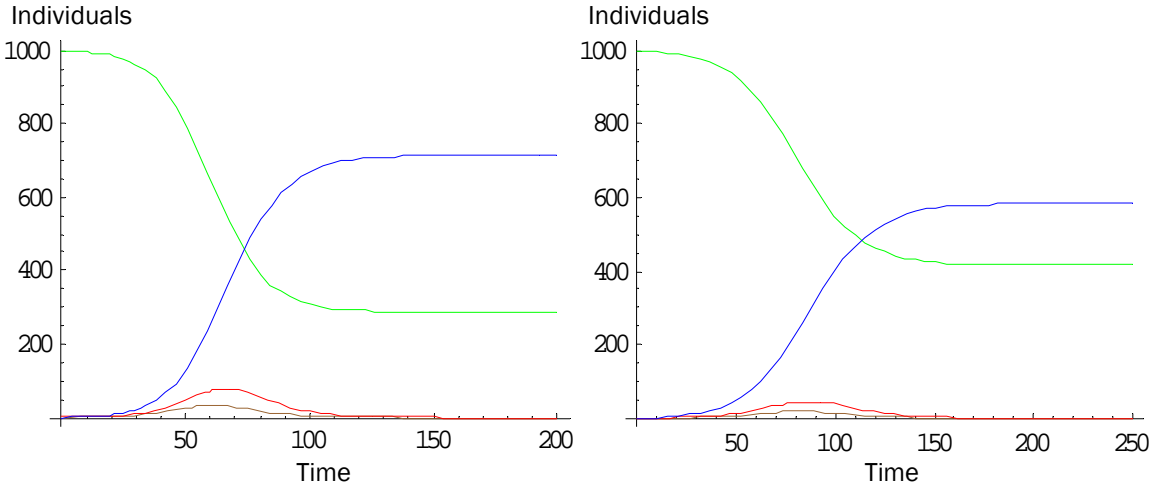


figure 2.2. SEIR models (green, brown, red, blue). The curves show the number of persons in each state each day. Latency period 2 days, infectious period 5 days. Left: contact rate 0.35,  $R_0 = 1.75$ . Right: contact rate 0.25,  $R_0 = 1.25$ .

To get a closer look at how these different values of  $R_0$  will influence the outbreak, figures 2.3 and 2.4 displays the Infected curves and the Recovered curves, respectively, from SEIR models with the three different values of  $R_0$ , namely 2.5, 1.75 and 1.25. As  $R_0$  drops, the peak of the outbreak is both delayed and reduced substantially, and the same holds for the number of cumulated infections. Such differences in  $R_0$  can result from the nature of the pandemic virus, the contact pattern in the population, and the effect of organized measures to contain or mitigate the pandemic.

These curves can help illustrating many aspects of a pandemic. Combined with the expected proportion of lethal cases among the infected, one can estimate the number of excess deaths. Similarly, one can estimate for example the size of workplace absenteeism or the increased burden expected to hit the health care system.

Figure 2.5 and 2.6. further illustrates how changes in the latency period and  $R_0$  may change the outbreak. The 25% reduction in the infectious period refers to the Norwegian Pandemic Preparedness plan where it is stated that Tamiflu reduces the infectious period by 1 to 2 days (26). Note that doubling the latency period postpones the peak of the outbreak but the number of cumulated infections is not reduced. A relatively small reduction in infectious period lowers both the peak and the number of cumulated infections dramatically.

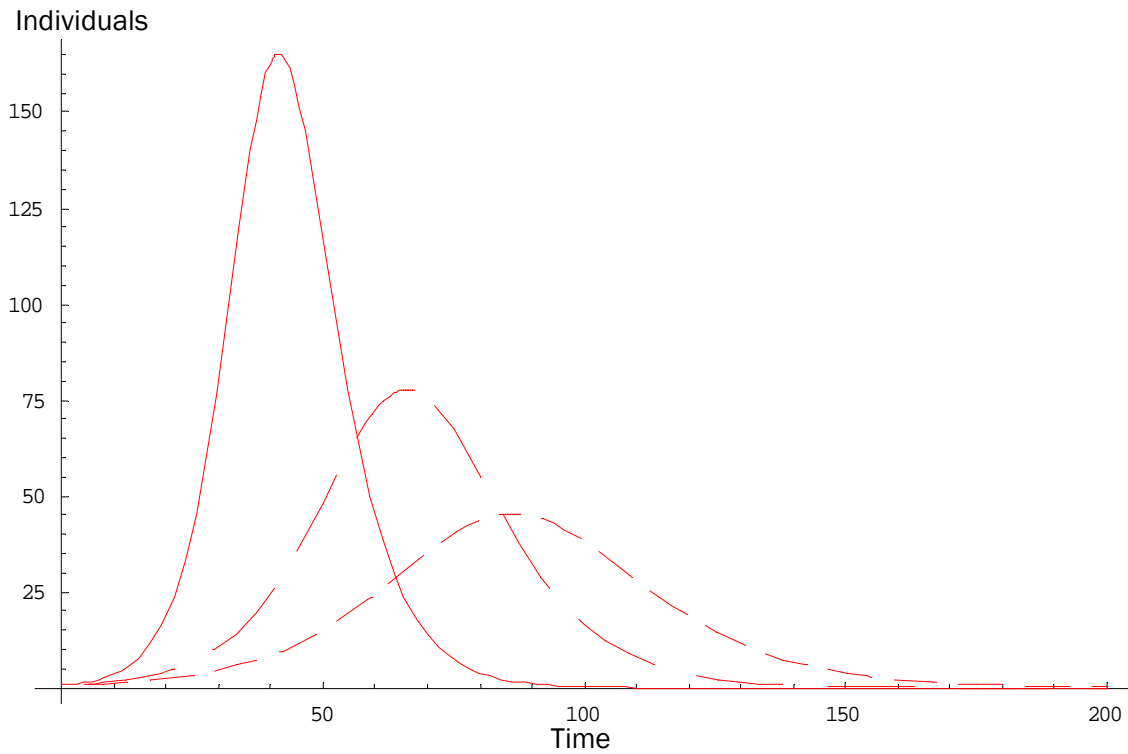


figure 2.3. Comparing infected-curves from three different SEIR simulations, each with a different value of  $R_0$ . Whole line:  $R_0$  2.5; Large dotted line:  $R_0$  1.75; Small dotted line:  $R_0$  1.25. Each curve shows the daily number of infected.

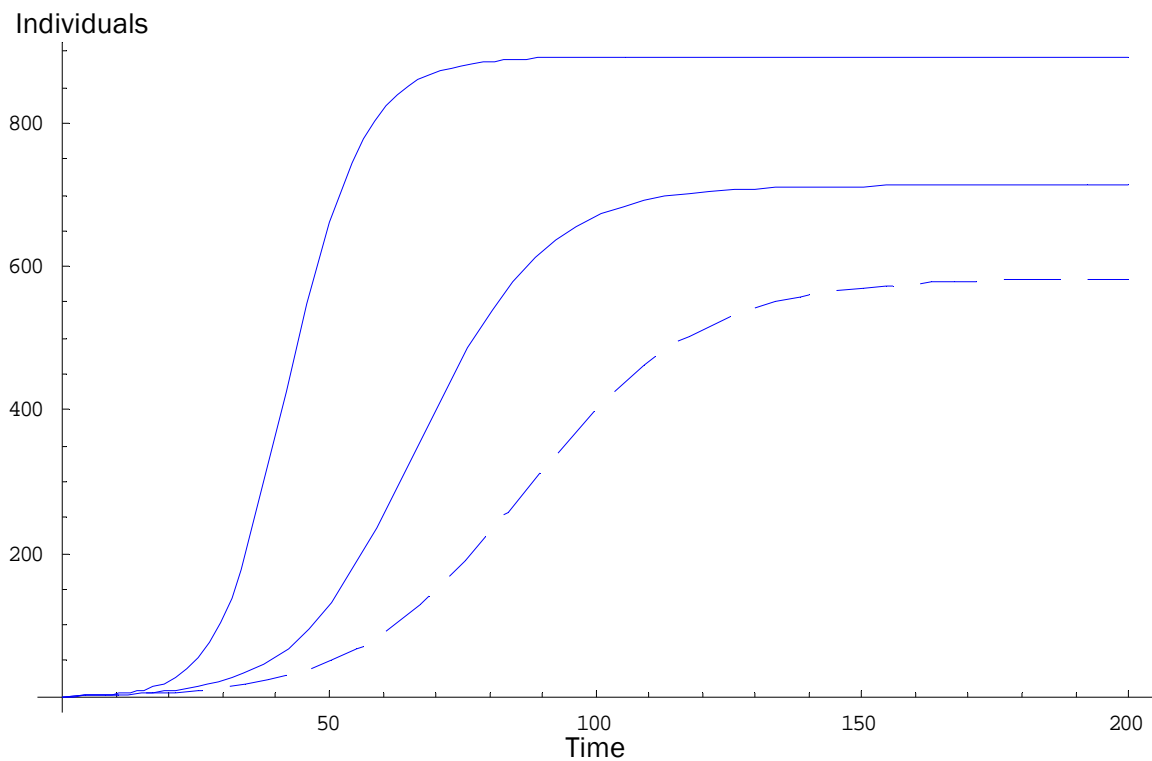


figure 2.4. Comparing recovered-curves from three different SEIR simulations, each with a different value of  $R_0$ . Whole line:  $R_0$  2.5; Large dotted line:  $R_0$  1.75; Small dotted line:  $R_0$  1.25. Each curve shows the daily number of recovered, corresponding to the number of cumulated infections.

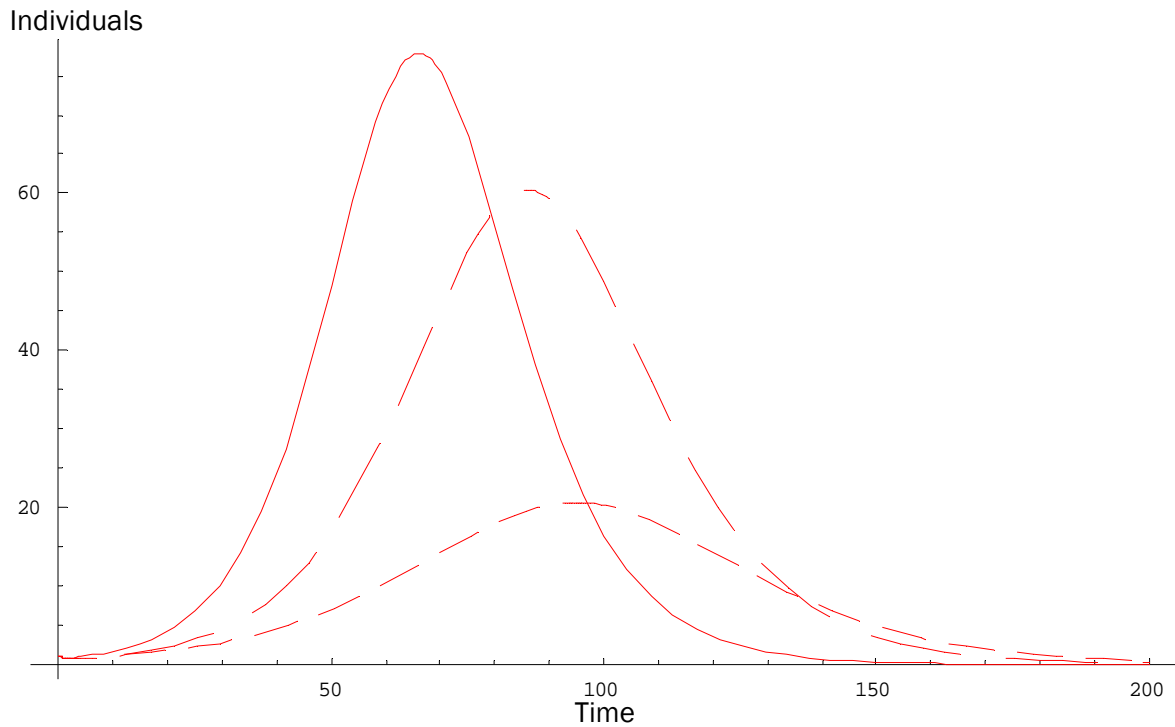


figure 2.5. Comparing infected-curves from three different SEIR simulations. Whole line:  $R_0$  1.75, latency period 2 days, infectious period 5 days, contact rate 0.35. Large dotted line: Doubling the latency period to 4 days,  $R_0$ , infectious period and contact rate unchanged. Small dotted line: Reducing the infectious period with 25%,  $R_0 \sim 1.31$ . Latency period 2 days, contact rate unchanged.

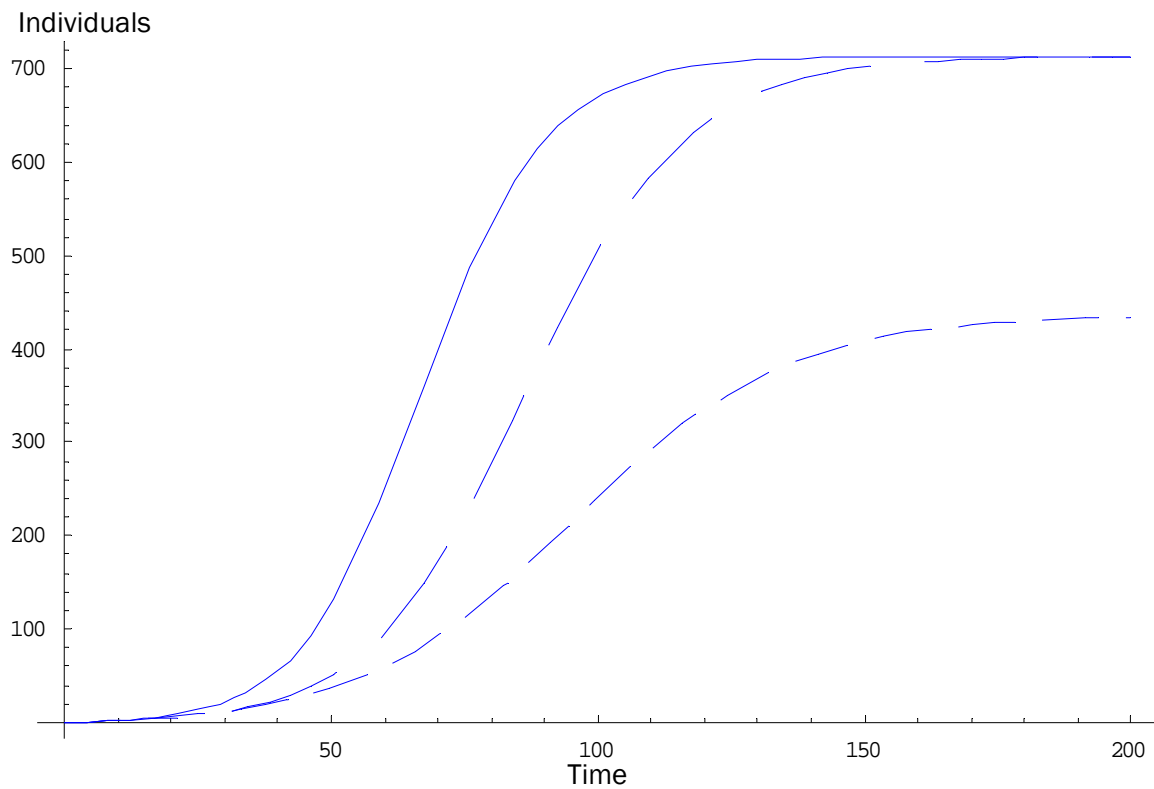


figure 2.6. Comparing curves of cumulated infected from three different SEIR simulations. Same conditions as figure 2.5.

Every season of epidemic influenza, some individuals are (partly) immune after having gone through infection with a similar virus. It is believed that this proportion will be negligible during a pandemic, but protective measures could result in corresponding conditions. One example is prophylaxis with antiviral drugs, another is vaccination of parts of the population (provided that time allows production and distribution of a vaccine before the pandemic hits). Figure 2.7. shows that increasing the proportion of initially resistant from 10% to 20% postpones and lowers the peak of the outbreak and reduces the cumulated infections with approximately 17%.

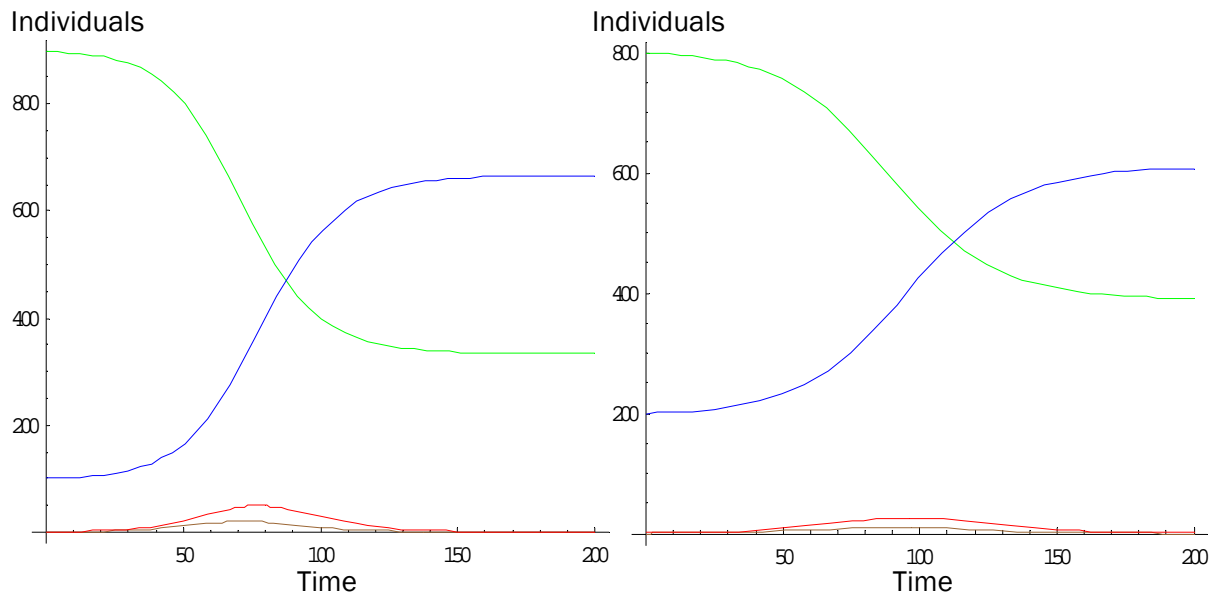


figure 2.7. SEIR models. Contact rate 0.35, infectious period 0.5,  $R_0$  1.75. Left: 10% of the population initially resistant. Right: 20% of the population initially resistant.

## FINAL DISCUSSION

The world must be prepared for the next influenza pandemic, although no one knows when, and how hard, it will hit. Massive outbreaks of avian influenza H5N1 in the poultry industry the last years as well as sporadic transmission to humans, might indicate that this subtype constitute the biggest pandemic threat in several decades. Much is already done, but future research, surveillance and planning must continue. The role of WHO and each country's national health authorities is crucial to coordinate these efforts.

In this paper, I have discussed mathematical modelling as an indispensable tool in epidemiology. Mathematical modelling form the backbone in many studies about pandemic influenza. Some studies conclude that a pandemic can be contained if measures including prophylactic use of antiviral medication are initiated swiftly. Others show that vaccines can be of great importance. I have talked about mathematically defined quantities, such as  $R_0$ , that make comparing different scenarios possible.

The results of  $R_0$  estimations from Norwegian numbers of seasonal influenza are too uncertain due to many possible sources of error in the method, but part of the results seems

reliable. Primarily, this work illustrates how mathematical methods are used in research and planning in the field of influenza epidemiology. The same holds for my last work, where I use SEIR models to demonstrate different scenarios for the course of a pandemic.

Pandemic Influenza Preparedness involves many occupational groups and statisticians and mathematicians are important contributors.

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