Global influenza dynamics and its consequences for containment strategies

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Abstract

Seasonal influenza is an easily transmittable disease which causes up to 500,000 deaths annually. There are three types of seasonal influenza, of which influenza A is the most common. The best protection against an influenza infection is vaccination. Due to the fast evolution of influenza, vaccines can become non-functional and therefore have to be updated regularly. Understanding the global circulation of seasonal influenza helps deciding which strains should be included in the vaccine. In contrast, for novel influenza strains that cause an influenza pandemic a vaccine will not always be immediately available. Other strategies are necessary to buy time for the development of a vaccine. For both seasonal and pandemic influenza, mathematical models are useful tools to simulate their global dynamics and methods to prevent their spreading. This thesis discusses the global dynamics of seasonal and pandemic influenza, obtained from experimental data and mathematical modeling, and the way in which this information can be used to reduce influenza infections.

1 Introduction

Worldwide, influenza epidemics are responsible for three to five million cases of severe illness and 250,000 to 500,000 deaths annually [WHO, 2009]. In temperate regions, influenza epidemics occur seasonally and peak in the winter and are almost absent in the summer. Three types of influenza circulate in humans (A, B and C), and of these three, influenza A is the most virulent. Influenza A is not only found in humans but also in a variety of animals, of which pigs and birds are the most noteworthy [Webster et al., 1992]; pigs for being the source of the swine influenza pandemic in 2009 and birds for being considered the most likely source of novel influenza pandemics prior to the pandemic of 2009. Distinct influenza A subtypes infect different species, although all influenza A subtypes appear in waterfowls [Webster et al., 1992].

Influenza A is subtyped according to two virus surface proteins, hemaegglutinin (HA) and neuraminidase (NA). Currently, 16 types of HA [Fouchier et al., 2005] and 9 types of NA have been identified [WHO, 1980]. HA binds to host cell receptors containing the appropriate saliac acid moieties and therefore is important in determining the virus tropism [Medina and Garca-Sastre, 2011]. NA is necessary for the proper budding and release of novel virions from the host cell surface as it cleaves the bond between HA and the host cell receptor [Medina and Garca-Sastre, 2011].

Of all influenza A subtypes, H1N1 and H3N2 are the strains currently circulating in humans and are the cause of seasonal influenza epidemics [WHO, 2009], although occasional infection of humans with other strains, e.g. highly pathogenic avian influenza (HPAI) A H5N1 strains, occurs. The H1N1 subtype already circulated in the human population prior to the influenza pandemic of 1957, when it was replaced by H2N2 [Hay et al., 2001, Medina and Garca-Sastre, 2011]. H2N2, subsequently, was replaced by H3N2 in the 1968 pandemic. H3N2 hereafter remained in the human population causing seasonal influenza epidemics, and H1N1 was reintroduced in the human population in 1977 [Hay et al., 2001, Medina and Garca-Sastre, 2011]. Since then, H1N1 and H3N2 co-occur in the human population [Hay et al., 2001]. Interesting to note is that pandemic influenza strains do not necessarily belong to a novel subtype, as illustrated by the influenza virus that was the cause of the 2009 pandemic which also was an influenza A H1N1 virus.

Being the virus' two major surface proteins, HA and NA are the main targets of the host's humoral immune system and therefore antigenic HA and NA data provide crucial information about vaccine strain selection. Because HA and NA are the main targets, changes in their antigenicity are considered to be a driving force in influenza evolution. Each season, changes in the amino acid composition of HA and NA are found which potentially change the antigenic properties of the influenza strain, a process known as antigenic drift. This causes influenza to partially evade immunity acquired in the human population and influenza therefore is able to keep causing epidemics. Antigenic drift also causes the need for the influenza vaccine to be updated frequently; over 20 updates of the H3N2 virus component of the influenza vaccine have been made since the virus' introduction in humans in 1968 [Fouchier and Smith, 2010].

Another, potentially more dramatic, process in influenza evolution is antigenic shift. In this process, viral genomes of different strains are reassorted and novel influenza subtypes are created which, due to a possible lack of immunity against these strains, can cause an influenza pandemic. This explains the major concern that, among the avian influenza strains that occasionally infect humans, eventually a variant emerges that is transmittable from human to human, as happened during the 1957 and the 1968 pandemics [Hsieh et al., 2006, Hay et al., 2001]. The 2009 influenza outbreak, originating in pigs, shows that species other than birds are also potential sources of human to human transmittable influenza strains. The 2009 pandemic strain went undetected for over a decade in pigs, where it was created by multiple reassortment events [Garten et al., 2009].

To ensure the availability of sufficient amounts of seasonal influenza vaccine, the composition of the vaccine has to be decided almost a year before the season in which the vaccine will be administered [Russell et al., 2008a]. This calls for reliable prediction methods for the influenza evolution but also for insight in the spread of seasonal influenza around the world. The latter is true as seasonal influenza epidemics are subject to global dynamics (discussed below), where the knowledge about the dynamics gives important insight in the development of epidemics. In contrast, novel potentially pandemic influenza strains call for immediate action to prevent spreading around the world, and different vaccination strategies are needed than in the case of seasonal influenza epidemics.

This thesis discusses views on the global dynamics and evolution of the seasonal influenza virus. Furthermore, this thesis illustrates the use of mathematical models to predict the dynamics of a pandemic influenza strain. With these models, the question of how to efficiently mitigate a pandemic, e.g. via vaccination or via travel bans to prevent spreading of the virus, is addressed. Based on these insights, this thesis suggests strategies for efficiently mitigating the impact of seasonal influenza epidemics as well as pandemic influenza.

2 Seasonal influenza is re-introduced annually

The exact factors that cause influenza epidemics to occur only in the winter season are unknown, however, it means that influenza has to bridge the summer season in which outbreaks do not occur. Knowing how influenza is capable of re-emerging each winter season aids in vaccine development by giving information about which influenza strains should be included in the vaccine. Two hypotheses have been proposed for the way in which influenza epidemics re-emerge annually: *a*) novel influenza strains are seeded from different regions annually and go locally extinct; and *b*) low levels of influenza virus persist locally over the summer season and seed the epidemic in the following winter season. These two possibilities are distinguishable in a phylogenetic analysis (see Figure 1). Virus samples from a certain region do not necessarily cluster together and are interspersed by samples from other regions if influenza is re-introduced annually (Figure 1A), because virus isolates from one region originate from another region. Virus samples from different seasons from the same region are expected to cluster together if influenza persists locally during the summer season (Figure 1B). Nowadays, a semi-annual meeting is held by the WHO to discuss the need for an update of the influenza vaccine [Russell et al., 2008a]. Hereto, genetic, antigenic, serological and epidemiological data are analyzed and the understanding for which of the two mechanisms underlies the seasonality of annual influenza epidemics helps the development of vaccines. Some of the analyses that lead to the hypothesis of the global circulation of influenza are briefly addressed in this section. The global circulation of influenza means that for the development of

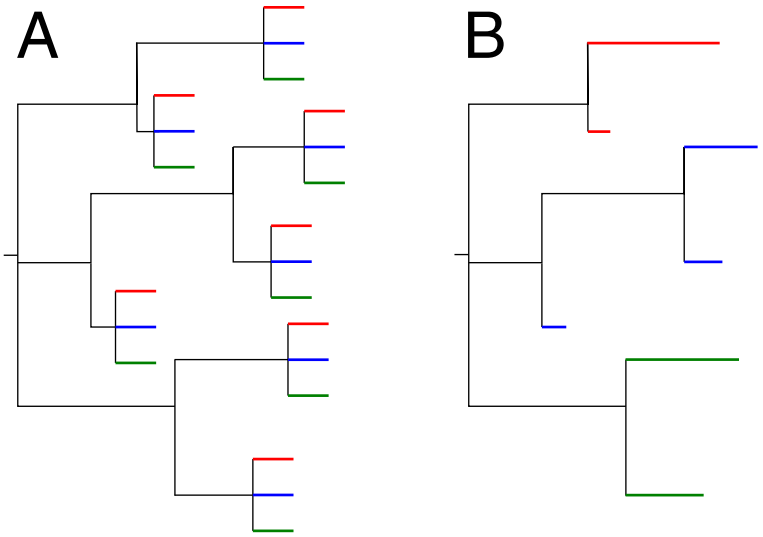

Figure 1: Phylogenetic trees for the two influenza seasonality hypotheses in temperate regions. (A) A hypothetical tree for virus samples from three different regions (red, blue and green) where the influenza virus is reintroduced annually, the influenza strains from the three different regions are more related to each other annually than to samples of the same region in another influenza season. (B) If the virus persists locally during the non-influenza season and seeds the next influenza epidemic in that region, virus samples from within a region cluster together. (Adapted from Nelson et al. [2007] and Russell et al. [2008b])

a vaccine global monitoring of influenza is requested to accurately predict which strains cause the next epidemic.

To distinguish between the local persistence and global circulation of influenza, H3N2 virus samples were taken in New York state and other localities. In a phylogenetic tree constructed for these samples, the strains sampled in New York state did not form a monophyletic group [Nelson et al., 2006, 2007]. The samples from New York state were interspersed by virus samples from other localities, which is in favour of the hypothesis of annual re-introduction of influenza (Figure 1A). Analyzing the time to the most recent common ancestor (MRCA) of the different influenza A genes of strains sampled in New York state revealed that, in many cases, the MRCA of the different genes dated back to several years before the season in which the strains were sampled [Rambaut et al., 2008]. The long time to the MRCA implies that genetic diversity in influenza is maintained over many years, something which is not expected if the virus would persist locally during the summer season.

Besides phylogenetic analyses, antigenic evolution analyses have also been used to elucidate whether influenza is re-introduced annually or persists locally. Where in phylogenetic methods viral sequences, e.g. viral RNA sequences, are used to reveal differences between the viruses, antigenic analyses use the difference in efficiency at which an immune system, primed on a specific influenza variant, targets another influenza variant. Such priming of the immune system is reached by vaccination with or being infected by this specific strain. Similar to the change in RNA sequence, the antigenicity of a virus changes during its evolution. These changes in the antigenicity over multiple influenza seasons are measurable, like the changes in RNA sequences, and are used to reconstruct the ancestry of strains (Box 1) [Smith et al., 2004]. The antigenic changes between influenza A H3N2 strains in subsequent seasons was monitored to reveal between-season and between-region differences. This was done for virus samples collected around the world from 2002 to 2007. The antigenic distances of these viruses to influenza A/Sydney/5/1997, a strain that dominated in 1998 and which was used as a reference strain because subsequent influenza strains were shown to evolve away from this strain [Russell et al., 2008b], were measured. These analyses showed that there is a lot of heterogeneity in antigenicity between regions in the same influenza season, but also in the same region between different influenza seasons [Russell et al., 2008b]. Despite the large heterogeneity within seasons and regions, a global trend of influenza evolving away from the reference strain was observed [Russell et al., 2008b]. Such a global trend is an indication for influenza to circulate

globally instead of persisting locally [Russell et al., 2008b].

Phylogenetic and antigenic analyses suggest that, in temperate regions, influenza strains causing seasonal influenza epidemics do not persist locally over summer [Russell et al., 2008b, Rambaut et al., 2008, Nelson et al., 2007, 2006]. Rather, influenza is annually re-introduced in temperate regions. Such an annual re-introduction implies that seasonal influenza circulates on a global scale.

3 Annual influenza epidemics do not originate from one specific region

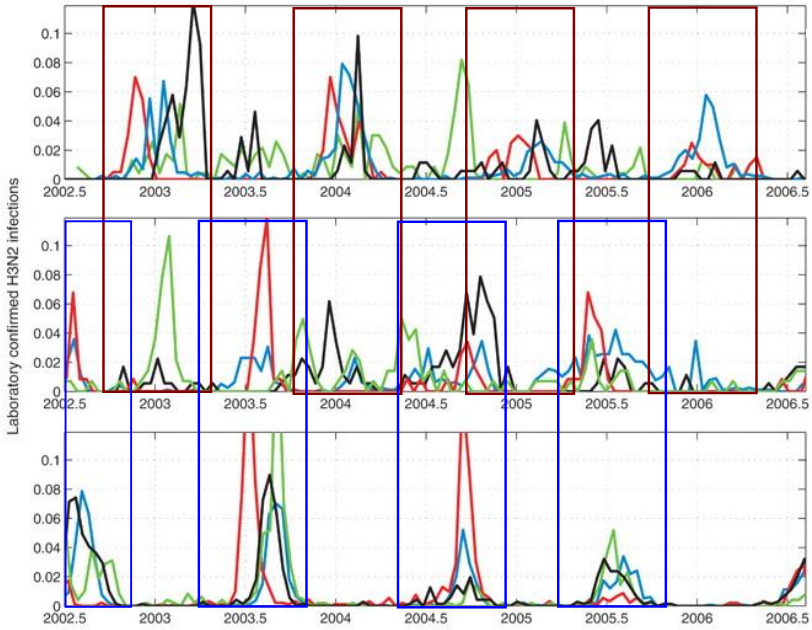

Figure 2: Timing of influenza epidemics in East (Northern Hemisphere, upper panel) and Southeast Asia (tropical region, middle panel) and Oceania (Southern Hemisphere, lower panel). Per two week intervals, the number of H3N2 infections, as a fraction of the total number of H3N2 infections at a specific location over the whole study period, are plotted. Peaks in the number of influenza infections in the Northern as well as the Southern Hemisphere coincide with peaks during the winter season on the Northern Hemisphere (red boxes) and on the Southern Hemisphere (blue boxes). Original picture from Russell et al. [2008b].

The observation that influenza circulates globally raises the question what the dynamics that govern this process are. By answering that question it is not only known that influenza circulates globally but also how it circulates globally. This knowledge helps in adequately predicting future epidemics but might also help in adequately intervening with the global circulation.

The relatively long time to the MRCA, as shown by Rambaut et al. [2008], suggests the presence of a source population where the virus circulates continuously and where the viral diversity is not limited by annual bottlenecks. If the latter would happen, strains would likely have an MRCA at the time of the most recent bottleneck; an MRCA multiple years ago would be highly unlikely. A source population may be fixed in one location, but can also consist of populations in different locations where the virus continuously circulates such that the source region consists of a network of locations. Non-source regions are referred to as sinks, meaning that they are seeded with influenza strains from elsewhere. A sink, on its turn, can seed other regions and thereby also act as a source. Antigenic and genetic analyses by Russell et al. [2008b] have suggested that strains causing the annual influenza epidemics originate in East-Southeast (E-SE) Asia, whereas Bedford et al. [2010] and Bahl et al. [2011] suggested that viral strains circulate globally and that every region acts both as a source and as a sink of seasonal influenza. Since knowing if the source is fixed or circulates among regions is important for vaccine development,

more reliable predictions of which strains will likely circulate in the next influenza season are possible if the spreading pattern of influenza is known.

Bahl et al. [2011] reasoned that if a single region were the source of seasonal influenza, a high genetic diversity of influenza would be expected in such a region. This was tested by measuring the genetic diversity of influenza samples collected in different regions. Temperate regions showed increases and decreases in their genetic influenza diversity over time which correlated with the season [Bahl et al., 2011]. Regions in E-SE Asia showed only little genetic diversity, which, according to Bahl et al. [2011], makes them unlikely to be the source of seasonal influenza. Because temperate regions also did not show a constant high level of genetic diversity, this supports the hypothesis that influenza circulates globally between regions with the appropriate influenza season.

Russell et al. [2008b], in contract, monitored the antigenicity of influenza strains to reveal the source of the annual influenza epidemics. By measuring the antigenic distance of strains collected around the world to a reference strain, a mean global antigenic distance was retrieved. By grouping strains by the region where they were sampled, the mean antigenic distance of strains from a specific region to the reference strain was calculated. The difference between the mean antigenic distance of a region and the mean global antigenic distance to the reference strain was used to indicate regions with a lower or a higher antigenic distance than the global mean [Russell et al., 2008b]. Regions that are antigenically above the global mean are antigenically advanced and thus a likely source, whereas regions that are antigenically below the global mean are antigenically lagging and thus likely sinks of seasonal influenza.

Making use of antigenic and genetic distances, Russell et al. [2008b] showed that strains collected in Southern American regions are antigenically below the global mean and that viral strains collected in eastern Asian regions, except for Japan, are above the global mean. Furthermore, due to the absence of a winter season, the seasonal influenza pattern as seen in temperate regions is absent in tropical regions in Asia [Viboud et al., 2006, Nelson and Holmes, 2007] and influenza may be expected to be endemic in eastern Asian regions. However, several studies showed a pattern of influenza epidemics in tropical regions occurring during periods of high rainfall [Dosseh et al., 2000, Chew et al., 1998, Rao and Banerjee, 1993] and the continuous circulation of influenza in one region is therefore unlikely. Russell et al. [2008b] therefore propose that influenza epidemics occur at different time points in different regions in east and Southeast Asia (E-SE) Asia (Figure 2, middle panel) and that E-SE Asian regions therewith act as the source of seasonal influenza epidemics.

There may also be another interpretation of the occurrence of epidemics at different time points in E-SE Asian regions. Peaks in the influenza incidence in Southeast Asia appear to coincide with peaks in the influenza incidence in regions located on the Northern Hemisphere (east Asia, Figure 2, upper panel) and regions located on the Southern Hemisphere (Oceania, Figure 2, lower panel). It is at least conceivable that such biannual fluctuations arise because of the spreading of influenza from temperate regions, via tropical regions, to temperate regions on the opposite hemisphere. Similar biannual fluctuations were also shown in the genetic diversity of influenza in Hong Kong [Bahl et al., 2011]. An increase in the influenza incidence and diversity is then observed when influenza crosses trough tropical regions. In contrast to the fixed source that Russell et al. [2008b] propose, this opens the possibility for many regions to occasionally be the source of the annual influenza epidemics.

The spreading pattern as discussed above is consistent with other models that do not consider an influenza source fixed in one location [Bedford et al., 2010, Bahl et al., 2011]. Moreover, the absence of a fixed source for seasonal influenza epidemics is also supported by the network of influenza spreading that Kenah et al. [2011] reveal. In this network, Hong Kong and Southeast Asia are located central between regions from the northern and southern hemisphere, serving as a bridge between those two [Kenah et al., 2011].

Further suggestions that not only regions in E-SE Asia act as the source of annual influenza epidemics comes, unintendedly, from Russell et al. [2008b] themselves. In their analysis of the antigenic distance of a region to the global mean they showed that regions in eastern Asia are antigenically above the global mean, however, regions in Southeast Asia are antigenically around the global mean. Different other regions, including the USA, are antigenically more above the global mean than Southeastern Asian regions. Therefore, Bedford et al. [2010] suggest that this shows that regions such as the USA could also act as the source of annual influenza epidemics, despite the fact that Southeast Asia is often mentioned as the source for annual influenza epidemics [Russell et al., 2008b, Chan et al., 2010, Russell et al.,

2008a].

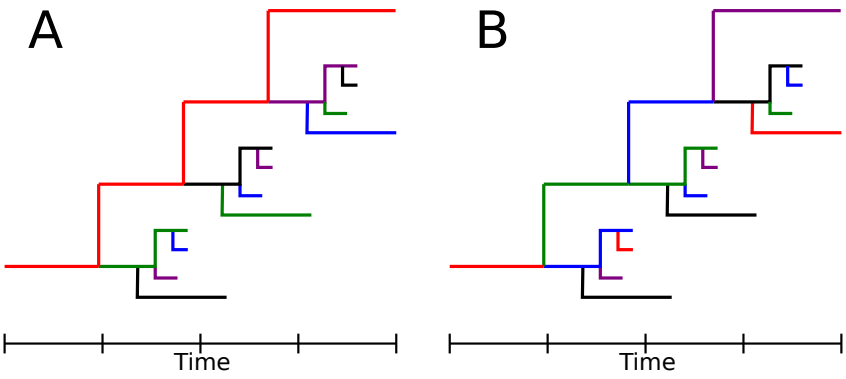

Figure 3: Genealogies which show the location of sampling. In two hypothetical genealogies that are constructed with the coalescence theory, timing of coalescence events and sampling locations are shown (different colours of the branches depict different localities). Coalescence events occur where, going backwards in time, two branches of the tree merge; the lineages share a common ancestor at this node. The location of the node also shows *a*) when this common ancestor was present and *b*) where this common ancestor was present. The trunk of the tree, from where each subtree originates, shows the source region, viral strains sampled world wide after all originate from this region. (A) If the annual influenza epidemics originate from a single source region (red), this region is most of the time found at the trunk of each subtree. (B) If different regions are the source of the annual epidemics, then the trunk of each subtree is occupied by different regions at different times.

In addition to the phylogenetic and antigenic analyses that have been discussed, the so-called coalescence method has been used to establish the genetic relationship between virus samples. In creating a phylogeny, one often considers genetic distances between sequences and orders the sequences in a tree according to the genetic differences. The branches of the tree are drawn such that the observed genetic differences are explained by the tree. Another way to construct a tree is by looking at the direct relatedness between strains. To explain this method, consider a population of N haploid individuals in which every individual has a specific allele a. In a sample of n individuals from the population, n copies of the allele a are present. Now, time is reversed, as one would do in constructing one's family tree, to reveal the ancestry of each of the n alleles. There is a chance that two of the alleles in the sample share the same parent (a common ancestor), which means that in the previous generation $n-1$ copies of the allele a were present (the chance that at a certain time point multiple alleles share a parental allele is assumed to be negligible [Otto and Day, 2007]). This event, where n alleles only have $n-1$ parent alleles, is known as a coalescence event [Otto and Day, 2007].

The n alleles are sampled in the present (t=0) and via simple statistic rules the chance of two alleles, from a sample $n = 2$, coalescing in the previous generation (t=1) is calculated. In the same way, the chance of these two alleles coalescing not in the previous generation but two generations ago (t=2) is calculated. Repeating this process gives a probability distribution for the coalescence of the two strains [Otto and Day, 2007]. Similarly, a distribution for a sample of n alleles to coalesce into $n-1$ alleles is found. This expression can be used iteratively to calculate the time to all coalescence events if a sample of size n is taken; $n \to n-1, \quad n-1 \to n-2 \ldots \to 1$. In a tree, a coalescence event is represented as two lineages coming together, revealing the common ancestor of these lineages. However, because of the probability distribution underlying a coalescence event, an immense amount of trees can be constructed using the basic idea described above.

The power of the coalescence method is that now a tree which shows the time, in terms of generations, to the ancestor of alleles is constructed; a genealogy instead of a phylogeny is constructed. The time can be used when mutations are taken into account; alleles that are very similar to each other share an ancestor (coalesce) very recently in the past and alleles that are not very similar to each other share an ancestor (coalesce) more distant in the past [Otto and Day, 2007]. The large number of possible trees that are constructed using the coalescence theory can thus be reduced, only the most likely trees are selected by using such information [Durbin et al., 2006, Fu and Li, 1999, Kuhner, 2009]. In such a tree, the distance between individuals gives the relatedness instead of the genetic distance between individuals

Box 1. Antigenic cartography

Influenza evolution may be better depicted by antigenic evolution than by genetic evolution, because antigenic changes have a direct effect on the recognition of an influenza strain by the immune system, whereas genetic changes do not necessarily change the recognition of the strain. For this, antigenic differences between viral strains are measured in a haemagglutination inhibition (HI) assay, which makes use of the ability of HA to agglutinate red blood cells. This agglutination is blocked by the presence of influenza antibodies. For different antibody-influenza strain combinations, different titers for which the agglutination is blocked are found and these give antigenic distances between the different influenza strains [Hirst, 1943].

Every HI titer is seen as a one dimensional representation of a vector of numbers (i.e. coordinates) that describes the binding between the HA and the antibody, where each entry of the vector describes a property, e.g. physic-chemical characteristics, of the binding between the HA and the antibody [Lapedes and Farber, 2001]. Differences in HI titer represent the distance between the coordinates, thus having sufficient HI data enables one to compute the relative coordinates for every HA and antibody [Lapedes and Farber, 2001]. All the coordinates are represented in an antigenic map, where the distances between any HA and antibody is visualized. Indeed, Smith et al. [2004] showed, with a model based on the idea described above, that vice-versa an HI titer can be predicted based on the distance between HA and an antibody on the antigenic map. Also, the antigenic distance is used to determine the necessity for the influenza vaccine to be updated. If the distance between the current vaccine strains and the strains expected to circulate is more than two units, the vaccine is updated.

To demonstrate the concept of antigenic cartography, the antigenic evolution of influenza A H3N2 is briefly discussed. Smith et al. [2004] developed a model based on the idea described above and used the model on influenza A H3N2 data from 1968, when it was introduced in humans, until 2003 to track its evolution. Over this period, several clusters of antigenically similar strains, instead of a gradual antigenic drift, were found (Figure 4). These clusters are chronologically ordered, with large antigenic distances between clusters and small antigenic distances within clusters.

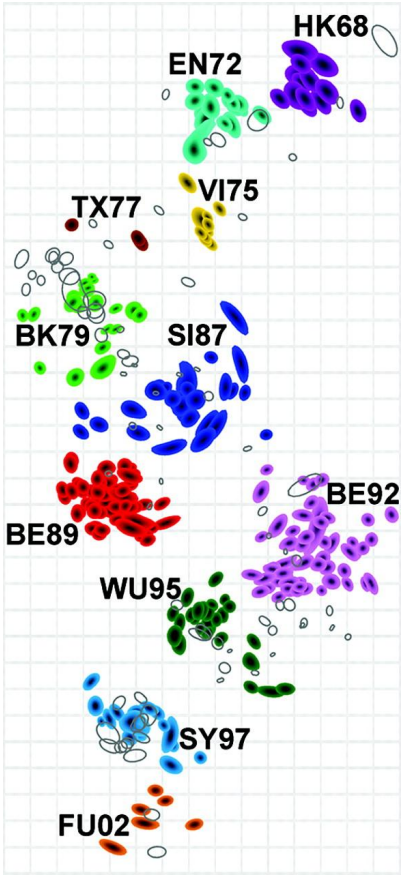

Figure 4: Antigenic evolution of influenza A H3N2 from 1968 to 2003. With the method developed by Smith et al. [2004], the relative positions of influenza strains (coloured surfaces) and antibodies (circles) are calculated and plotted. The distance between a strain and an antibody is representative of the HI titer between those two, where a distance of x units corresponds to a 2^x-fold lower titer. The colours represent different antigenic clusters and each cluster is named after the first strain in that cluster used in a vaccine. The location of isolation of the vaccine-strain (Hong Kong, England, Victoria, Texas, Bangkok, Sichuan, Beijing, Wuhan, Sydney and Fujian) is referred to by the two letters and the year of isolation is referred to by the two digits. Note that, as in an ordinary map, the x- and the y-axis represent distance and therefore the orientation of the map is free. Picture from Smith et al. [2004].

and therefore the time, in generations, to its ancestors.

Since the original formulation of the coalescence theory, the method has been expanded to include, among others, sampling region and sampling date in the construction of the genealogy. The tree then also shows the location where samples have been collected; locations that always appear at the trunk of the tree are likely source regions and regions that always appear at the tips of the tree are likely sink regions (Figure 3). Moreover, the genealogy constructed with the coalescence method is based on multiple trees that are concordant with the available data. Together, the genealogy created with this

method provides more information than the one based on phylogenetic methods; due to the incorporation of time and location in the genealogy, the spread of influenza around the globe can be inferred from such a genealogy. Therefore, the coalescence method is perfectly suitable to reveal the global dynamics of seasonal influenza (Figure 3).

The genealogy of the HA domain of influenza A H3N2 has been constructed using the coalescence method [Bedford et al., 2010]. In agreement with the hypothesis of annual reintroduction of influenza in a region, this analysis showed that locally influenza diversifies over the course of an epidemic and does not persist during the non-influenza season [Bedford et al., 2010]. However, opposed to a single influenza source region as suggested by Russell et al. [2008b], this analysis suggested that every region is able to act both as a sink and as a source in the global network (Figure 3B) [Bedford et al., 2010, Bahl et al., 2011]. In such a network where every region can act as a sink or as a source, influenza migrates between regions of different seasonality and thereby temperate regions, like the USA, are capable of seeding future epidemics worldwide. Note that, although every region may act both as a sink and as a source, not all regions need to contribute equally to the global network. Especially China, Southeast Asia and the USA are important regions where many epidemics originate [Bedford et al., 2010]. An explanation why earlier studies pointed to regions in E-SE Asia as being the sole source of the annual influenza epidemics is that these regions indeed are a major source of the annual influenza epidemics, although not the only one.

The dominant source-role of E-SE Asian and USA regions is an explanation for the long time to the MRCAs of influenza strains as found by Rambaut et al. [2008]. The virus does not experience severe bottlenecks because it continuously circulates through these regions. Therefore, a high viral diversity is maintained and lineages coalesce far back in time. Furthermore, a careful comparison of the time to the MRCA estimates of the HA segment based on a phylogenetic tree [Rambaut et al., 2008] and based on a genealogy constructed with the coalescence method [Bedford et al., 2010] shows high resemblance in terms of the time to the MRCA between those two. This shows that the large time to the MRCA estimates, at least for the HA segment, are not in conflict with the absence of a localized influenza source.

More evidence that not a single region is the source of the seasonal influenza comes from mathematical modeling. For this, the spreading of influenza was modeled using a Susceptible-Infectious-Recovered (SIR) model (Box 2). In this model, susceptible individuals can be infected by infectious individuals, thereby becoming infectious themselves. Infected individuals recover over time and then have immunity to the infection, which wanes over time, and recovered individuals become susceptible again. In such a SIR model, different regions can be included where each region consists of its own population, but individuals are allowed to travel between the regions. A simple model to simulate the global spreading of influenza includes the three major regions on the globe: the Northern Hemisphere, Tropical regions and the Southern Hemisphere [Bedford et al., 2010]. With this simple model, two scenarios were simulated. In the first scenario, influenza was only able to spread from the tropics to the two other regions but not between the temperate regions directly, therewith simulating the source-sink model. In the second scenario, the equal contact scenario, the contact rates between all three regions were equal and influenza was able to spread between all regions. Data was taken from these simulations to construct, with the coalescence theory, a genealogy which was compared with the genealogy from the experimental data.

The genealogy of the equal contact scenario matched the genealogy of the experimental data best, indicating that this scenario is more likely that the source-sink scenario [Bedford et al., 2010]. As seen in the experimental data, different regions source the annual influenza epidemics in the equal contact scenario (Figure 3B). Again, these analyses support the hypothesis that there is not a localized source for the annual influenza epidemics.

Box 2. The SIR model

Mathematical models are often used to describe disease dynamics. The Susceptible-Infectious-Recovered model is a simple mathematical model that assumes a closed population of size N. This population is subdivided in three compartments; individuals who are susceptible, S; individuals who are infected and are thereby infectious, I; and individuals who are recovered from the infection and are thereby no longer susceptible, R. In this model, all individuals are equal in terms of their susceptibility and infectiousness and are assumed to be well mixed. Infectious individuals infect susceptible individuals at rate β and are infectious for a period of $\frac{1}{\alpha}$ days. These assumptions translate into the following set of differential equations [Wu and Cowling, 2011]:

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI \\ \frac{dI}{dt} &= \beta SI - \alpha I \\ \frac{dR}{dt} &= \alpha I \end{aligned}$$

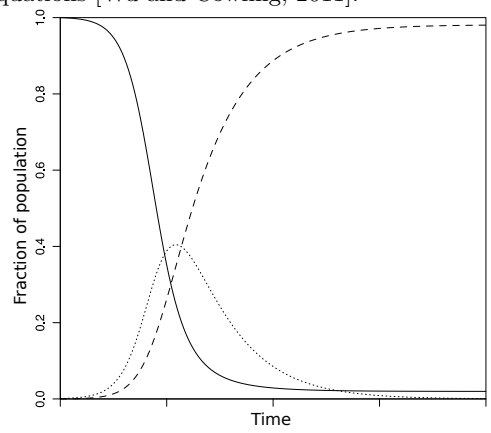

Figure 5: Dynamics of the SIR model. Initially, the number of susceptible individuals (solid line) decreases as the number of infectious individuals (dotted line) increases. Finally, infectious individuals recover and become immune (dashed line).

Although the model is simple, it shows the characteristics of an epidemic [Wu and Cowling, 2011]. The infectious population initially increases exponentially but reaches a peak as the number of susceptible individuals decreases (Figure 5).

The SIR model can easily be expanded by including other compartments [Wu and Cowling, 2011, Coburn et al., 2009]. Susceptible individuals can be vaccinated, thereby becoming less susceptible or immune to the infection. Infectious individuals can be treated and thereby decrease their time of infectiousness, or they can even be held in quarantine and are then unable to infect other individuals. Recovered individuals, on their turn, can become susceptible again. These are just a few examples to illustrate the flexibility of the model.

Besides adding other compartments to the SIR model, SIR models can be coupled [Coburn et al., 2009]. A single SIR model represents the population in a specific region and individuals can travel between the different regions. On top of that, seasonality can be added by e.g. oscillating the infectiousness α, where a high infectiousness represents the winter season and a low infectiousness represents the summer season. In this way, the global spreading of a disease can be modeled.

The basic SIR model is convenient to demonstrate the principle of the Basic Reproductive Number R_0, a measure for the severity of an epidemic. For an infection to spread in an entirely susceptible population, $S = N$, the initial growth rate of infectious individuals has to be larger than their recovery rate, $\beta NI - \alpha I > 0$. The latter gives the condition $R_0 = \frac{\beta N}{\alpha} > 1$ for an epidemic to occur. For $R_0 < 1$ the disease is unable to spread. Although the specific solution $R_0 = \frac{\beta N}{\alpha}$ is only true for the simple SIR model, the concept of R_0 is widely applicable and is an important parameter in estimating the severeness of the outbreak of a disease.

An important insight for vaccination is that only a fraction of the population has to be vaccinated to prevent the spreading of a disease. If in the SIR model V individuals are vaccinated, then $R_0 = \frac{\beta(N-V)}{\alpha}$. The fraction of the population that has to be vaccinated to prevent the spreading of a disease then is

$$\begin{aligned} \frac{\beta(N-V)}{\alpha} &< 1 \\ V &> N - \frac{\alpha}{\beta} \\ \frac{V}{N} &> 1 - \frac{1}{R_0} \end{aligned}$$

where $1 - \frac{1}{R_0}$ is known as the critical coverage [Wu and Cowling, 2011].

4 Pandemic influenza dynamics

In the last century, four influenza pandemics (in 1918, 1957, 1969 and 2009) have plagued the earth. The 1918 pandemic was the most devastating, with approximately 40 million deaths, while the 1957 and 1969 pandemics caused approximately two and one million deaths, respectively [WHO, 2005]. The 2009 pandemic was relatively mild, causing approximately 20,000 deaths [WHO, 2010]. These numbers, especially from the 20th century pandemics, show the need for an adequate response upon the outbreak of a potentially pandemic influenza strain. Mathematical models are useful to predict the circulation of such strains around the world and to help design methods to contain a pandemic.

Prior to the 2009 H1N1 pandemic, the focus was on the potential outbreak of the pandemic HPAI H5N1 virus. One of the mathematical models constructed to predict the spread of such a pandemic around the world is an extensive model based on the Susceptible-Infected-Recovered model [Colizza et al., 2007] (Box 2). In this model, 3100 airports were incorporated, thereby acounting for 99% of the worldwide air traffic. Each airport in the model represented the surrounding urban area and hence had its own set of equations. Seasonality was taken into account by changing the infectiousness of individuals according to the seasonality of the region where the airport was located. The spread of the pandemic strain was simulated by "introducing" the strain in one of the urban areas of the model [Colizza et al., 2007].

Not surprisingly, the potential of a novel strain to become pandemic turned out to depend on its R_0 (Box 2). R_0 gives the number of secondary cases that one infected individual generates in an entirely susceptible population and thus is a measure for the severeness of an epidemic. For a low R_0, influenza rarely spreads outside the region of origin of the novel influenza strain, and if so, only very few individuals are infected in those regions [Colizza et al., 2007]. For a moderate R_0, where influenza often does become pandemic, the pandemic potential also depends on the season and on the location of the region of origin of the novel influenza strain. The location of origin, the source, is important because an outbreak in a non-tropical region in its spring or summer season is unlikely to spread and become pandemic. Likewise, if the influenza strain arrives in a region, the sink, during the region's spring or summer season, the virus is unlikely to spread in that region [Colizza et al., 2007]. The latter case buys some time to develop a vaccine before the influenza season starts. Thus, the potential of an influenza strain to become pandemic does not only depend on the R_0, which is a trivial indicator, but also the season when and the location where the virus originates.

With the outbreak of the 2009 influenza H1N1 pandemic (H1N1pdm) virus, mathematical models were used to predict the spreading of the H1N1pdm virus and to predict the efficacy of containment strategies. Models that were first used to simulate the outbreak of a hypothetical pandemic influenza strain, e.g. the SIR model discussed above [Colizza et al., 2007], are suitable for this purpose. In the case of the 2009 outbreak, the location and time of origin of the pandemic virus were known, however, the R_0 was unknown. For a moderate $R_0 = 1.5$, the model predicted that a pandemic would occur in two phases [Flahault et al., 2009]. The H1N1pdm strain originated in the northern hemisphere (Mexico) when the influenza season of the northern hemisphere was at its end (April). This also meant that the influenza season in the southern hemisphere just commenced, and therefore a first disease wave would strike the southern hemisphere, followed by a large wave in the northern hemisphere in its subsequent influenza season. A small virus reservoir would remain in the tropics, seeding a second wave in the southern hemisphere in the following year [Flahault et al., 2009]. In agreement, such a two-wave pattern was also observed in other studies [Colizza et al., 2007, Kenah et al., 2011] and multiple waves have indeed been observed in past pandemics [Miller et al., 2009]. However, for a high R_0, $R_0 = 2.2$, the first wave would be much larger and, because little susceptible individuals would remain, a second wave would be absent. The difference between the spreading pattern of a pandemic for different R_0's demonstrates the importance of correctly estimating virological parameters.

Indeed, a first peak of H1N1pdm infections occurred in the 2009 winter season of the southern hemisphere [Kenah et al., 2011]. Already in November of 2009, regions in the northern hemisphere showed an H1N1pdm infection peak [Kenah et al., 2011]. A second wave in the southern hemisphere, as predicted for a moderate R_0, was not observed. For the R_0 of the H1N1pdm a wide range of values were estimated, $1.2 < R_0 < 2.1$, depending on the data and the method used [Kenah et al., 2011, Fraser et al., 2009, Yang et al., 2009, Balcan et al., 2009]. Mathematical modeling of the pandemic showed that

$R_0 = 1.85$ reflected the observed dynamics of the pandemic best [Kenah et al., 2011].

To model the spreading of a pandemic in even more detail, the models discussed above can be extended to include, among others, within-host influenza dynamics and subpopulations based on the host's age [Kenah et al., 2011]. The latter was done because in past pandemics children were at a higher risk of getting infected than adults [Miller et al., 2009]. Moreover, the age subpopulations were split in a low and a high risk group. With this model, in retrospective, the spread of the 2009 influenza H1N1 virus was modeled and this demonstrated the effectiveness of this model. Pandemic outbreaks in different regions, including Mexico, and at different time points, including the time of the suspected outbreak of the H1N1pdm (end March), were modeled to study the effect of the starting location and date of a pandemic on its global spread. In agreement with the results by Colizza et al. [2007], the starting date and location play a large role in the global dynamics of the pandemic. A pandemic starting early in the influenza season causes an immediate large peak, while a pandemic starting late in the influenza season may occur in two peaks, a small peak in the current influenza season and a large peak in the following influenza season [Kenah et al., 2011].

The pandemic virus is only capable of spreading to other regions if these regions are in their influenza season, as is the case with the seasonal influenza. Moreover, the region of origin is key in the capacity of the virus to become pandemic. A virus with pandemic potential originating in the tropics is more likely to cause a pandemic than virus originating in other regions [Colizza et al., 2007] because an influenza virus with pandemic potential originating in the tropics has the benefit of being close to both hemispheres which increases the chance of spreading to regions that are currently in their influenza season. If an influenza virus with pandemic potential originates in a temperate region then it will only spread if this region is in its influenza season. If the region is not in its influenza season, infectivity is low and the virus is unable to spread. The general spreading pattern that arises due to location and seasonal constraints is that in both hemispheres a wave of infections occurs in their respective influenza season, where the tropical regions serve as a bridge between the two hemispheres.

5 How to contain pandemic influenza

Not only the dynamics, but also strategies to mitigate the effects of or to contain pandemic influenza can be modeled. To this end, the models discussed above (Section 4) have been expanded with different vaccination strategies and the use of antiviral (AV) drugs. Other strategies to prevent the spreading of influenza are contact-reducing strategies (e.g. school or workplace closure or isolation of infected individuals) or travel restrictions [Ferguson et al., 2006, Hollingsworth et al., 2011].

Although it takes time to develop a vaccine that is antigenically close to the pandemic virus, vaccines that partially mismatch may still be beneficial. Indeed, a simple SIR model showed that a partially mismatching vaccine still leads to an epidemic that develops slower and has fewer cases [Hollingsworth et al., 2011]. Combining this strategy with contact-reducing strategies has been shown to be fairly effective in delaying the epidemic, which buys time for the development of an antigenically matching vaccine [Hollingsworth et al., 2011]. However, these results were obtained with a simple SIR model which did not take multiple regions nor seasonality into account and therefore the results obtained with this model merely indicate a trend of contact-reducing strategies.

Workplace closure is economically not a favourable contact-reducing strategy and a more elaborate model showed that by implementing other strategies the need to close workplaces, in order to prevent the spreading, would be reduced [Ferguson et al., 2006]. Other strategies include school closure or targeting households containing an infected individual. For the latter, Ferguson et al. [2006] investigated two options: prophylaxis using AV drugs and quarantine, in which the members of an infected household are requested to stay at home. Both strategies have their own (dis)advantages. Where both strategies are effective in controlling the pandemic, the former strategy requests a large stockpile of AV drugs and the latter strategy increases the risk of individuals in a household with one infected individual to become infected as well. Therefore, a combination of AV drug, vaccination and contact-reducing strategies is best in reducing the spread of a pandemic influenza strain [Ferguson et al., 2006].

The more elaborate models discussed above (Section 4) are able to predict the effect of different regions and seasonality on the efficacy of vaccines. Moreover, these models have the possibility to

investigate containment strategies, such as the distribution of AV drugs among regions. A strategy that immediately comes to mind is travel restriction from and to infected regions, however, modeling the effect of travel restriction on the containment of a pandemic showed that this effect is minimal [Colizza et al., 2007, Ferguson et al., 2006]. Colizza et al. [2007] reason that the chance of an infectious individual traveling, even though travel restrictions are implemented, are still high due to the large number of infectious individuals. Furthermore, an individual may be infected but is still latent. Such an individual can spread the disease to other regions unnoticed. Therefore, the main containment strategies should focus on the use of AV drugs or reducing the chance of contact with an infectious individual [Colizza et al., 2007, Kenah et al., 2011, Ferguson et al., 2006, Longini et al., 2004].

In the case of a severe influenza pandemic, where many individuals are infected, the global AV drug supply will likely be insufficient to treat everyone [Colizza et al., 2007]; only a few countries have an AV drug supply. Therefore, different scenarios are feasible in which the global AV drug supply that is available are distributed in different ways around the world. Modeling has shown that the most efficient way to contain a pandemic, and buy time until a vaccine is available, is that the countries who do have an AV drug supply donate a fraction of their supply to countries who do not have an AV drug supply [Colizza et al., 2007]. Sharing their supply is also beneficial for the countries who do have an AV drug supply due to an effect that is similar to herd immunity; the other countries experience a lower outbreak of the pandemic virus and hence fewer virus will spread to other countries, including those with an AV drug supply. Only focusing treatment on the region of origin of the pandemic strain, in an attempt to prevent spreading to other regions, is insufficient. As soon as the virus does reach another region the virus will spread uncontrolled [Colizza et al., 2007].

Besides the use of AV drugs, the effect of vaccination according to age and risk group with a vaccine that is available six months after the outbreak of an influenza pandemic has been modeled by Kenah et al. [2011]. The amount of vaccine that is available to a country is assumed to be related to the wealthiness of a country, measured as the gross domestic product, as it is likely that wealthy countries are able to buy more vaccine than poor countries [Kenah et al., 2011]. Similar to the administration of AV drugs, the most efficient vaccination strategy is to prioritize individuals in a high risk group [Kenah et al., 2011]. Also, the effect of vaccination is dependent on the location of a region. If a pandemic outbreak occurs at the beginning of the influenza season on the southern hemisphere, then a vaccine will arrive too late to offer protection on the southern hemisphere. However, the vaccine will then be available at the beginning of the influenza season on the northern hemisphere, which is just in time to have a substantial effect [Kenah et al., 2011].

It would be interesting to see the effect of AV drug administration, e.g. as studied by Colizza et al. [2007], in the more detailed model by Kenah et al. [2011] that was used to model the efficacy of vaccination. The effect of different age and risk groups then is apparent, which would lead to an even better policy for drug administration. Presumably, a pandemic virus would be better contained if risk groups were prioritized in AV drug administration. The effect of AV drug administration, to delay the spread of the pandemic, followed by the deployment of a vaccine would be an interesting scenario to model, since this is what intuitively is expected to happen. Likely, this will lead to less spread of the virus and fewer infected individuals than one of the two strategies alone.

6 Discussion

Understanding the dynamics of influenza spreading helps containing it. For seasonal influenza, a clear understanding of its dynamics aids in optimizing vaccines. After all, deciding which strains should be included in the vaccine is easier if the spread of influenza variants can be accurately predicted. Upon the outbreak of an influenza pandemic, designing strategies to efficiently control the pandemic is easier if the pattern of spreading of the pandemic is known.

Different studies showed that seasonal influenza strains are seeded into temperate region every season [Nelson et al., 2006, 2007], which prompted the investigation of the dynamics that underlie this global circulation of influenza. Tropical regions appeared to be perfect candidates to seed the temperate regions with influenza annually, especially those regions in E-SE Asia [Russell et al., 2008b]. However, more recent studies suggest that every region is a potential source for the annual influenza epidemics, although

regions in E-SE Asia and the USA are the main sources [Bedford et al., 2010, Bahl et al., 2011]. In these latter studies, techniques that include region and date of sampling are used to construct a genealogy. The trees thus constructed provide more information than a phylogeny based on genetic information alone and are better suited to reveal the global spreading pattern of the seasonal influenza virus.

The global circulation of influenza, where no single region is the source of the annual epidemics, toughens the prediction of which influenza variants will cause the next epidemic. Where the study by Bahl et al. [2011] only covers three years of influenza data, and therefore no trends in the global circulation of influenza are shown, the study by Bedford et al. [2010] covers over a decade of influenza data. Although no single source can be pinpointed, global trends in the circulation of influenza are apparent. Global trends in influenza evolution can be used to predict which influenza strains to incorporate in a vaccine [Russell et al., 2008a], since strains worldwide are expected to be antigenically similar enough for the vaccine to be effective. However, vaccination could be optimized be taking into account the strains circulating in likely sources of a specific region.

The development of a vaccine against pandemic influenza takes time as the vaccine can only be developed once the strain causing the pandemic is known. Several methods to reduce the spreading of the pandemic virus, e.g. AV drug administration or contact-reducing strategies, are available to buy time for the development of the vaccine. Important in the administration of vaccines is that a coverage of the entire population is not necessary, as herd immunity is achieved by vaccinating a part of the population (see also critical coverage, Box 2). Extensive models indeed show that only vaccinating a part of the population is already beneficial [Kenah et al., 2011]. The dynamics of pandemic influenza indicate which regions should receive the highest attention concerning vaccination, because vaccination in regions where the pandemic has not struck yet has the most effect [Kenah et al., 2011].

Important to note is that for all the studies that are discussed here no or only limited data from Africa and India, the latter having over 1.2 billion inhabitants (almost 20% of the world population) [United Nations, 2010], is available. The role of these regions in the global influenza network is unknown although these regions may be important in the global dynamics of influenza. To better understand the global influenza dynamics, these regions have to be taken into account and therefore more data is necessary from these regions. Also, only little data is available from seasonal influenza A H1N1, and its global dynamics are unknown, although it has been suggested that its dynamics are similar to those of H3N2 [Chan et al., 2010].

A factor not studied is the possibility of antigenic shift during an influenza strain's circulation. Such a shift could render a vaccine useless. Therefore, constant monitoring of the circulating viral strains, both the annual seasonal influenza and other influenza strains, which may harbor the potential to become pandemic, is vital to detect possible antigenic shifts and to immediately react, if necessary, to such changes. Yet, even simple mathematical models help in determining strategies to contain influenza and, as the 2009 influenza pandemic showed, help predicting how the pandemic will develop.

A lot of studies have looked into the global spreading of influenza. These suggest that there is no single source where seasonal influenza epidemics originate, rather, every region has the potential to seed the next seasonal epidemic. The recent outbreak of a pandemic influenza strain demonstrated that knowing the spreading pattern of influenza aids in adequately responding to such an outbreak. Where to deploy vaccines first and to which groups of a population vaccines should be administered can be determined better with such knowledge. The recent pandemic outbreak originating in pigs showed that the next influenza pandemic can come unexpected, but that by being well-prepared a pandemic outbreak can be contained.

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