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Outbreaks of the measles in the Dutch Bible Belt and in other places – New prospects for a 1000 year old virus

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ABSTRACT

In the Netherlands there has been nationwide vaccination against the measles since 1977. However, a tight-knit community of a few hundred thousand orthodox protestants in the "Dutch Bible Belt" refuses the vaccine. Within this community of orthodox protestants there has been an outbreak of the measles with roughly 2500 reported cases about every twelve years. Each outbreak has lasted about a year. The community of orthodox protestants is too small to permanently keep the virus in circulation and have the infection be endemic. The dynamics in orthodox-protestant schools has been widely recognized as the engine behind the epidemic outbreaks. It is shown how these dynamics are a kind of integrate-and-fire mechanism: new susceptibles enter the denominational schools until a critical mass is reached and an outbreak occurs.

From a public health perspective, periodic outbreaks of the measles are worse than an endemic situation. When the measles was endemic, almost every child would get infected at around the age of ten. This is also the age at which one is best able to cope with the disease. With the short periodic outbreaks, a significant fraction of the orthodox-protestant, schoolgoing population does not get infected during an outbreak. These "escapees," however, may then get infected during a next outbreak when they are adults and less well-equipped to handle the disease. The three subsequent outbreaks in the Dutch Bible Belt (1988, 1999, 2013) have indeed shown increasingly many adult cases and hospitalizations.

As vaccination rates in the developed world are decreasing, the situation in the Dutch Bible Belt is duplicated in other places. We point out how in some large European cities the relevant parameters resemble those in the Dutch Bible Belt.

We, furthermore, provide extensive background on the thousand year relation between humanity and the measles virus.

1. Introduction

Until about half a century ago, the measles was endemic in almost the entire world. Children were struck by it at around the age of ten and had lifelong immunity upon recovery. In the developed world immunization programs started in the 1960s and 1970s. Around 2000, many countries in the developing world followed. Preventing epidemic outbursts and possibly even eradicating the disease was a stated goal, but today that goal appears far from realized. Even though much has been achieved (deaths worldwide went from 2.6 million in 1980 (Strebel et al., 2011) to 89,780 in 2011 (Dabbagh et al., 2017)), outbreaks involving thousands of cases keep occurring in the United States and Europe. Meanwhile, antivaccination campaigns appear to get an ever larger and more receptive audience. Consequently, vaccination coverage is decreasing in a number of countries. In many European countries, less than 95% of children is currently getting vaccinated against the measles (van't Klooster and de Melker, 2017). As a result, the disease is resurging. In the European Union, the number of reported cases increased from 3767 cases in 2016 to 8786 cases in 2017. Most of these cases occurred in Romania and Italy.[1] In just the first six months of 2018, Europe as a whole had 41,000 measles cases and at least 37 measles-caused deaths.[2] With over 23,000 cases, it is Ukraine that has been hit hardest.

The 95% threshold for measles vaccination is considered critical. In ordinary social traffic, the *basic reproduction number* for the measles is between 12 and 18 (Laksono et al., 2016). This means that in an

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[1] https://ecdc.europa.eu/en/measles/surveillance-and-disease-data/monthly-measles-rubella-monitoring-reports.
[2] http://www.euro.who.int/en/media-centre/sections/press-releases/2018/measles-cases-hit-record-high-in-the-european-region.

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entirely susceptible population, one person with the measles infects on average between twelve and eighteen susceptibles. The number of infections produced by one infected individual when part of the population is already infected or immune is what we will call the *effective reproduction number*. It is obvious that by immunizing 95% of the population, the effective reproduction number is brought down to below one. With an effective reproduction number that is less than one, no epidemic outbreak can occur.

Though most people endure the infection without sustaining permanent damage, the measles is far from an innocent ailment (Moss, 2017). In the early 1900s it was still fatal in about 1% of cases. The introduction of antibiotics after World War 2 helped bring down fatalities in the developed world to about 0.1%. Antibiotics are, of course, ineffective against the virus that causes the measles. However, a measles infection triggers immunosuppression (Carp et al., 1996) and bacterial infections that "hitchhike" along with the measles virus *can* be treated with antibiotics. Ear infections and pneumonia are the most common complications to accompany the measles.[3]

In the Netherlands, nationwide vaccination started in 1976. But from the beginning of the vaccination program, a number of orthodox protestants have refused the vaccine. Overall, more than 95% of Dutch children is still immunized and if the orthodox-protestant community were homogeneously distributed within the general population, it would benefit from herd immunity. However, the orthodox protestants are geographically and socially clustered. What has happened as a result is periodic outbreaks within the orthodox-protestant community. The outbreaks have had similar duration (about a year), similar size (about 2500 reported cases), and have come at twelve year intervals. In 2013 and 2014, the third outbreak since the start of nationwide vaccination occurred. Fig. 1 shows the number of measles cases in the Netherlands between 1976 and 2016.

Below we will analyze the mechanism behind the periodic outbreaks. We will see that simple kinetics, as in a chemical reaction, can account for the periodicity. The Dutch example may be instructive, because as vaccination rates are falling throughout the developed world, more such periodic outbreaks will be inevitable.

2. The past, present, and future of the measles virus

Antivaccination advocates commonly claim that the measles is "natural" and "part of the way life is supposed to be." However, with some common-sense arguments it can be understood that the measles must be a recent phenomenon. For the measles, the time between the first exposure and the end of being infectious is about 20 days. This means that in order to stay in circulation, the virus needs at least about 20 new susceptibles per year. The general population has to supply these susceptibles through births. With a birth rate of 2%, this implies that only a community of more than 1000 people can permanently "host" the virus. In the days of hunting and gathering, humans lived in communities of no more than a few tens (Nolan and Lenski, 2015). With more sophisticated calculations it can be shown that a community of more than 100,000 people is necessary to be reasonably sure that the virus will be sustained for centuries (Bartlett, 1957). In other words, the measles was impossible before the invention of agriculture and the emergence of cities.

Many reviews about the measles mention that there is "linguistic evidence" for the disease to have first emerged between the 5th and 7th century. The references by McNeill (1976) and Griffin (2007) are commonly cited to accompany this statement even though no such linguistic evidence is presented in either of these two sources. It is, however, fairly straightforward to put together such evidence from historical knowledge and with the help of Google Translate. The word "evidence," though, may suggest too much rigor here. Deriving the genesis of an ailment from vocabulary is mostly conjecture and surmise. We should, furthermore, realize that naming and classifying ailments is very much a modern and scientific preoccupation. The pre-Linnaean, medieval mind may have been less concerned about such categorization.

First of all, there are indications that the measles did not exist during the Roman Empire. Neo-Latin languages, like French, Italian, and Spanish, developed as offshoots of Latin. In many words in French, Italian, and Spanish, the common Latin root is still recognizable. For instance, the words for fever are *fièvre*, *febbre*, and *fiebre*, respectively. This is, of course, because the Romans knew what fever was and had a word for it: *febris*. The words for measles in French, Italian, and Spanish are *rougeole*, *morbillo*, and *sarampión*, respectively. That there is no apparent common root may demonstrate that the words were established when, after the fall of the Roman Empire, the Neo-Latin languages had started to evolve independently. This may imply that the measles did not exist during the Roman Empire or, at least, was not recognized as a distinct ailment.

Further pursuing the linguistic angle, the facts suggest that the measles and recognition of the measles emerged in the early Middle Ages. Shortly after the fall of the Roman Empire, Germanic migrations took place: Germanic tribes populated Britain and, later, also Iceland. That all Germanic languages have similar words for the measles may lead one to infer that the Germanic migrants took an awareness of the measles with them. Finally, in Eastern Europe the Hungarians came from the east to current-day Hungary in the course of the 9th century. They displaced and separated a population that spoke a Proto-Slavic language. That the Slavic populations around Hungary have similar words for the measles (*osýpky*, *ošpice*, and *ospice* in Slovak, Slovenian, and Croatian, respectively) and that the Hungarians brought their own word (*kanyaró*) is indicative of existence and cognizance of the ailment before the 9th century.

The first solid evidence for presence and awareness of the measles stems from 910 AD. In that year the Persian physician known in the West as Rhazes wrote a book titled *On Smallpox and Measles*. Discriminating between measles and smallpox has historically been problematic as these ailments are characterized by similar rashes.

Today it is also possible to trace origins through the sequencing of genomes. Through such analysis it was found in 2010 that the measles virus split off from the rinderpest virus around 1100 AD (Furuse et al., 2010). Known in English as the cattle plague, rinderpest affects cows and other even-toed hoofed animals and was actually still killing cattle by the thousands in the 1980s. Ironically, it is mostly through vaccination programs that the rinderpest is completely eradicated today.

The 1100 AD date appears to be at odds with the linguistics and with the written account of Rhazes. Confronted with this anomaly, the authors of reference by Furuse et al. (2010) point out that the early Middle Ages may be within the margin of error of the 1100 AD estimate. However, it is also possible that the rinderpest virus jumped several times and that all currently active strains derive from one transmission event of around 1100 AD. The agent of the rinderpest and the measles is an RNA virus and these viruses mutate and evolve fast (Holland et al., 1982). Currently, there are competing strains of the measles virus and it appears that all currently active strains descend from one 1943 ancestor (Furuse et al., 2010). The fast evolution also means that the history from before 910 AD may be nebulous. It is possible that the rinderpest virus was transmitted to humans during the Roman Empire or even before. But the resulting symptoms for a human may have been different from what they are today.

Nevertheless, a medieval, European origin of the measles is not unlikely. During the early Middle Ages, the population of Central and Western Europe was increasing and densities developed in which the measles virus could be sustained. Milk, butter, and cheese, furthermore, became popular low-class foods at the time and dairy farming came to be correspondingly common and widespread (Adamson, 2004). Dairy farming implies spending much time in the close proximity of cows.

[3] https://www.cdc.gov/measles/about/complications.html.

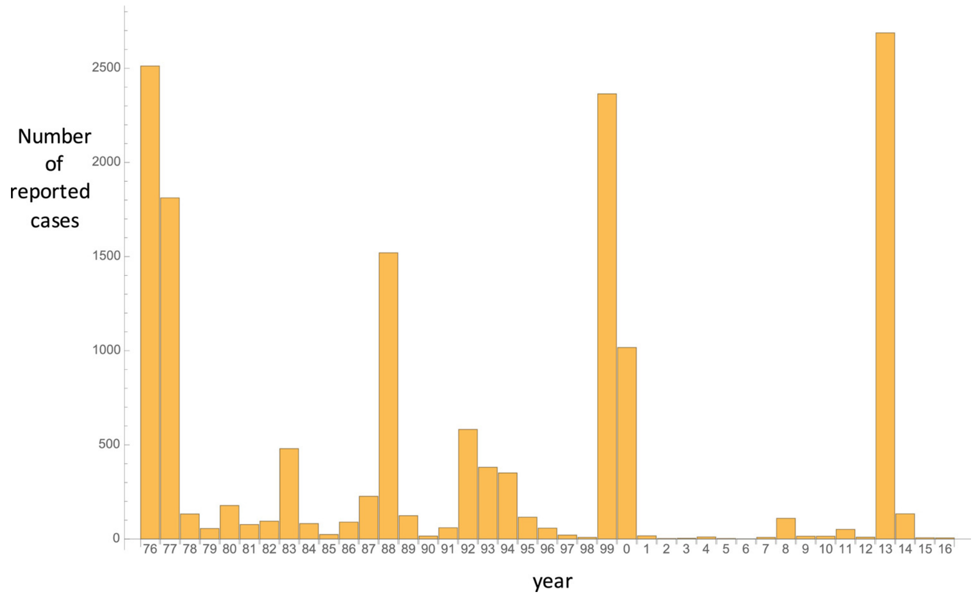

Fig. 1. The annual number of reported cases of the measles in the Netherlands in the period 1976–2016. Data are from the Dutch National Institute for Public Health and the Environment (see https://www.rivm.nl/dsresource?objectid=6ce81bc5-d296-4215-b744-8321a7ad9139).

Moreover, it was and still is common in Europe to have so-called "housebarns," i.e. living quarters and stables being under one roof. Obviously, such setups make for easy zoonosis.

The measure for success in the competition between different strains of a virus is the strain's effective reproduction number, i.e., the number of newly infected hosts that is produced by a single infected host. In trying to maximize this number, a virus has to find a compromise. A virus that aggressively seizes a host's resources and quickly excretes a lot of copies of itself into the environment will rapidly incapacitate or even kill a host. Such a high-virulence strategy thus reduces the time during which new hosts can be infected. With a host that transmits at a smaller rate, but remains relatively vigorous for a long time, a high effective reproduction number can be achieved as well. Eventually, the optimal virulence is also determined by factors like how long the virus can survive outside the host and whether the virus is transmitted directly or via a so-called "vector," i.e. an insect or other animal (Cresler et al., 2016).

The environment for the measles virus has changed during the last millennium and it is unfortunate that there is no reliable record about how virulence and other characteristics have evolved in response.

Until the 1980s the "conventional wisdom" was that it is not in a parasite's interest to do much damage to a host (Lenski and May, 1994). In this view a virus is at its most harmful shortly after invading a new host species, but ultimately evolves towards a form of peaceful coexistence with its host. A decreasing virulence has indeed been observed in some cases. The most prominent example is the myxoma virus that, in 1950, was introduced to European rabbits in Australia and was initially lethal for more than 99% of infected rabbits. In the years following, the mortality indeed dropped. However, in the late 1950s the percentage appeared to stabilize at between 70 and 95% (Bull, 1994). What happened since is not a further evolution towards harmlessness, but a subtle arms race between the virus and its host (Kerr et al., 2017).

Between 1800 and 1950, populations in Europe, India, and China roughly doubled. At the same time, populations urbanized and fast travel between urban centers became more common. In a large dense population with a lot of person-to-person contacts, a greater virulence will be favored. This can be readily understood: hosts become "less valuable" if they are more easily available. Rapid exploitation of the host and quickly realizing the effective reproduction number is also a good strategy in the competition with other strains and with other parasites (Lenski and May, 1994).

The large scale vaccination of the last half century has created a new situation for the measles virus. In most of the world the virus is again facing susceptible populations that are small and low density. A likely adaptation will be a longer latency time (the time between first exposure and infectiousness). Such longer latency time increases the chance that the host has traveled before becoming infectious. For the virus such travel means a new population with, possibly, new susceptibles. A longer lasting infectiousness before the occurrence of the first symptoms is a further likely adjustment. These adaptations can be viewed as "the virus' attempt" to become endemic again and they will lead to bigger, less clustered, and longer lasting outbreaks.

3. A quantitative accounting for measles outbreaks in the Dutch Bible Belt

Though the Netherlands has a reputation for very liberal attitudes, there is actually a Dutch Bible Belt. The area has a length of about two hundred kilometers and a width of several tens of kilometers. It runs across the country roughly from Middelburg in the south-west to Zwolle in the east. In this strip the about 250,000 orthodox protestants are for the most part clustered in about 30 midsize towns. The post-WW2 secularization in the Netherlands occurred to a lesser extent in the Bible Belt and the orthodox-protestant community in the area has since come to stand out even more. The orthodox protestants adhere to a strict interpretation of Calvinism and many view matters as insurance and vaccination as a form of interference with divine providence. But as with many protestant churches, there is a degree of decentralization in matters of doctrine and recommendations of local clergy actually vary. As a result, a majority of orthodox protestants *does* vaccinate today (Ruijs et al., 2012).

The Dutch educational policy is fairly unique. In its current form it has been in place for more than a century and it is an established feature of Dutch society. However, this policy ultimately makes matters worse for epidemic control. Religious communities in the Netherlands can organize their own schools and, provided some minimum requirements are satisfied, such schools will be publicly funded. Religious denominations have made ample use of this opportunity. In the Netherlands there are 180 orthodox-protestant primary schools and seven orthodox-protestant secondary schools. These secondary schools do sometimes operate in more than one location. Orthodox-protestant parents commonly make their children commute long distances in order for them to attend orthodox-protestant schools. This system scrambles geographic boundaries and allows infected students to freely mix with others from a larger range of the Dutch Bible Belt. What results is a region that behaves homogeneously – what chemists refer to as a "continuously stirred tank reactor." Measles outbreaks show almost no geographic separation across the entire Dutch Bible Belt and the mathematics can be simplified to depend only on time.

Fig. 1 shows how there have been three measles outbreaks in the Dutch Bible Belt since vaccination began in 1976. The outbreaks each last roughly a year, consist of 2000–3000 reported cases, and occur about twelve years apart. Below we will quantitatively account for the apparent oscillatory behavior.

The process of infection can be thought of as a chemical reaction: when a susceptible individual and an infective individual come into contact, there is a probability that the susceptible will also become infected, i.e.,

$$\mathrm{S} + \mathrm{I} \xrightarrow{\alpha} \mathrm{I} + \mathrm{I}. \tag{1}$$

As a rule, chemistry considers substrate concentrations. The rate α is then called the reaction rate. In epidemiology it is customary to work with the *number* of susceptibles, S, and the *number* of infected, I. The rate α is then called the contact rate and it represents the fraction of the susceptibles that is infected by one infected person in the course of one unit of time. Below we will use one day as our unit of time. With Eq. (1), we have

$$\frac{\mathrm{dI}}{\mathrm{dt}} = \alpha S\, I \tag{2}$$

for the number of newly infected per day.

The parameter α is not just a characteristic of the disease. It also depends on factors like population density, moving patterns, social customs, hygiene, and even the weather (Postnikov, 2016). For one and the same ailment, the contact rate can be different in different settings and at different times. Furthermore, Eq. (2) is a mass-action law. In a chemical reaction involving $N \approx 10^6$ molecules, the standard deviation is of the order $\sqrt{N}$ and less than one percent of N. The system can then legitimately be treated as deterministic. When, on the other hand, we consider a few thousand infections, the standard deviation can become considerable. A single infection event (cf. Eq. (1)) is a stochastic process and, especially in the beginning of an outbreak when there are few infected individuals, the stochasticity cannot be neglected.

For the reasons listed in the previous paragraph, there is no model that will lead to a quantitatively-accurate explanation for the 12-year period, the one-year outbreak duration, and the 2500 cases. We are not looking at a clockwork where we know and/or control all the variables. However, we can show how and why the oscillatory dynamics arises and we can derive how the 12-year period is consistent with acceptable estimates of the contact rate α and of the size of the unvaccinated population (Kurtz, 1970, 1971).

3.1. The pre-1976 endemicity

Before 1976, the orthodox protestants were part of the general population in the geographic area and, as such, part of an endemic measles dynamics of the total Dutch Bible Belt population. We will set the total population of the Dutch Bible Belt at one million.

Even in the endemic situation, the number of measles cases tends to oscillate. The origin of these oscillations is easily understood. A small happenstance increase in the infected population increases the likelihood of infections and can thus increase the infected population even further. In the same way a small decrease can develop into a further decrease. These positive feedbacks make the steady state of the process in Eq. (1) unstable and lead to significant fluctuations around the steady state. In this way, small seasonal fluctuations and the timing of school holidays can lead to large peaks and deep valleys in the number of measles cases per week. Ultimately, the variations in the number of measles cases synchronizes with these external triggers and periodic dynamics emerges. Biennial peaks appeared to be particularly common (Bartlett, 1957; Yorke and London, 1973a,b; Conlan and Grenfell, 2007).

In spite of the fluctuations, the measles virus was continuously present in the Dutch Bible Belt before 1976. A short derivation shows that a steady state exists. At steady state, the number of new infections per day is at all times equal to the number of births per day. With the 2% birth rate of 1960 and a population of one million people, we have $dI/dt \approx 50$ births per day. The duration of infectiousness has actually been hard to establish (Moss, 2017). Infectiousness, moreover, is not an on/off phenomenon; it varies from one individual to another and it also varies in the course of the disease. Following authoritative models (Olsen and Schaffer, 1990; Keeling and Grenfell, 1997; Stone et al., 2007), we set the duration of infectiousness at 5 days. This means that at any time we have $I \approx 250$ infected individuals in the community. We will consider a person susceptible after he or she enters the school population. This is at about the age of five. Children would get the measles on average at the age of about ten. We will take this age as applying to everyone and we will consider the five-to-ten age group as the susceptibles. With 20,000 births per year this leads to $S \approx 100{,}000$ for the steady-state-number of susceptibles. Next applying Eq. (2), we derive $\alpha \approx 2 \times 10^{-6}$ as an estimate for the contact rate. This estimate for α is very reasonable. Similar rates were, for instance, derived for New York City and for Baltimore (Yorke and London, 1973a).

As already mentioned, for the measles the basic reproduction number is generally given as between 12 and 18. The basic reproduction number, R_0, is related to the contact rate through $R_0 = \alpha N \tau$, where N represents the total size of the population and τ is the duration of infectiousness. With $N = 10^6$ and $\tau = 5$ days, we find $R_0 = 10$. This is again a reasonable estimate. As the Dutch Bible Belt extends over a large area and has smaller population densities than more urban settings like New York City and Baltimore, smaller values for α and R_0 are expected.

3.2. The post-1976 periodic outbreaks

For a quantitative analysis of the situation in the Dutch Bible Belt after nationwide vaccination started, we need to know the number of unvaccinated individuals in the population throughout the years. It is not trivial to come to a responsible estimate of this number. The number of orthodox-protestant households in the Bible Belt depends strongly on the way of counting (self-identification in a survey, church attendance, church membership). In a previous study it was suggested to take the orthodox-protestant schools as the basis for the estimate (Bier and Brak, 2015). The assumption with this choice is that parents that are sufficiently serious about orthodox protestantism to not vaccinate their children will also send their children to an orthodox-protestant school rather than to a possibly more nearby nondenominational school. Some of the orthodox-protestant schools admit children from outside the orthodox-protestant community. But those that do so, generally limit the percentage of "dissidents" to about five or ten.

As was mentioned before, a large fraction of orthodox-protestant parents *does* actually get their children vaccinated. The Dutch health authorities campaign heavily to make parents vaccinate and they have arranged for quick and easy access to vaccination. The record keeping has suffered under the easy access, but is estimated that more than 60% of children from orthodox protestant households ultimately gets vaccinated (Ruijs et al., 2012).

The Dutch Ministry of Education maintains a website with a spreadsheet that lists all the publicly funded schools and the religious affiliation of these schools, if there is one.[4] For each school the number

[4] https://www.duo.nl/open_onderwijsdata/databestanden/.

of students is also listed. It is in orthodox-protestant schools where large numbers of susceptibles gather daily and can be most easily infected. The dynamics in primary and secondary schools has long been recognized as the engine behind epidemic outbreaks (Yorke and London, 1973a) and centering a quantitative analysis around the schools is sensible.

All of the orthodox-protestant primary schools together comprise about 40,000 students. Without outbreaks for more than a decade, we estimate that about 30% of this population is susceptible. This implies around 12,000 unvaccinated children distributed over eight grades (Dutch children go to primary school from age 4 to age 12). There are then 1500 unvaccinated students per grade. This also means that every year 1500 new unvaccinated children enter the school system.

With children getting the measles at the age of ten, we find that right after vaccination was completed in 1976, there were $S \approx 7500$ schoolchildren left susceptible to the measles. Applying Eq. (2) again and taking the previously derived $\alpha \approx 2 \times 10^{-6}$, we see that one infected individual (i.e. $I = 1$) leads to $dI/dt \approx 0.015$ infections per day. In the course five days of infectiousness, the number of newly caused infectives, i.e. the effective reproduction number, will then be about 0.075. This is more than an order of magnitude too small for the virus to survive.

However, after 1976 there is a steady influx of 1500 susceptibles annually into the school system. In 1988 there were $S \approx 7500 + (12 \times 1500) = 25{,}000$ susceptibles in the age group 5–22. Apparently, this is more than the critical mass that is necessary to initiate an outbreak. We apply Eq. (2) again with the realization that dI/dt must be larger than 0.2 for the effective reproduction number to be larger than one and an outbreak to ensue. This leads to $\alpha > 8 \times 10^{-6}$ for the contact rate.

This $\alpha > 8 \times 10^{-6}$ is significantly larger than the $\alpha \approx 2 \times 10^{-6}$ that we derived earlier for the general Dutch Bible Belt population before vaccination. However, we bring to mind again that the contact rate α is the fraction of the susceptible population that is infected by one infectious person in one day. It is to be expected that that fraction will be significantly higher when the infected and susceptibles are concentrated in just a handful of schools. Because of the clustering of the orthodox protestants, the contact rate for the measles in the Dutch Bible Belt rose after 1976. On the basis of the data of post-1976 Dutch outbreaks, the authors of the reference by Wallinga et al. (2003) derive a basic reproduction number of 23.

Measles outbreaks in the Dutch Bible Belt occurred again in 1999/2000 and in 2013. These outbreaks were of similar duration and similar size compared to the 1988 outbreak. It is reasonable to assume that these outbreaks also started when the number of susceptibles again reached about 25,000. The twelve years between 1988 and 2000 supplied 18,000 new susceptibles. The remaining 7000 susceptibles must originate from before 1988 and must never have been infected during the 1988 outbreak. The same arithmetic applies to the 2000–2013 period and the 2013 outbreak.

There is a consensus that the number of reported cases is much lower than the actual number of cases. Not all parents take their measles-afflicted child to a medical professional and not all medical professionals report all cases they see to the authorities (van Isterdael et al., 2004). But there is disagreement about what the real number of cases is.

3.3. When does an outbreak start and what is the true number of cases?

An outbreak can only occur when the effective reproduction number is larger than one. An infected person can then come from the outside and ignite the outbreak. We will call the effective reproduction number Z_0 and set $Z_0 = 1 + \varepsilon$. The variable ε indicates by what percentage the susceptible population exceeds the threshold at which an outbreak can occur.

The simplest and most well-known model for an epidemic outbreak is the Kermack–McKendrick model (Murray, 2002). With this model a straightforward relation can be derived between ε and the fraction p of susceptibles that never gets infected during the outbreak. The Kermack–McKendrick model is as follows:

$$\dot{S} = -\alpha S\,I, \quad \dot{I} = \alpha S\,I - \beta I, \quad \text{and} \quad \dot{R} = \beta I. \tag{3}$$

Here the dot denotes a derivative with respect to time ($\dot{} \equiv d/dt$), S represents the number of susceptible individuals, and I represents the number of infected individuals, as in Eq. (2). The parameter α is again the contact rate and the parameter β is the recovery rate. With the aforementioned $\tau = 5$ days we have $\beta = 0.2$, i.e., 20% of the infected leaving the infecting population per day. Leaving the infecting population means joining the "removed" group R. At the beginning of the outbreak, we have $S(0)$ for the number of susceptible individuals and $R(0) = 0$. This is the initial condition. Dividing the first equation by the third equation in (3), we obtain $dS/dR = -(\alpha/\beta)S$. With the initial condition we then derive $S(t) = S(0)\exp[-\alpha R(t)/\beta]$ as an integral of Eq. (3). This equation is valid at all times. For the aforementioned fraction p, we have $p = S(t \to \infty)/S(0)$. Likewise, we have at the end of the outbreak $I(t \to \infty) = 0$ and thus $(1 - p) = R(t \to \infty)/S(0)$. Putting all this together and using $Z_0 = (1 + \varepsilon) = \alpha S(0)/\beta$, we arrive at the equation that connects p and ε: $p = \exp[(p - 1)(1 + \varepsilon)]$. This leads to $p(\varepsilon) = -W[-e^{-(1+\varepsilon)}(1 + \varepsilon)]/(1 + \varepsilon)$, where $W[.]$ is the Lambert W function. The Lambert W function is also known as the "product logarithm" and is available in *Mathematica* and *MATLAB*.

Generally, estimates for ε at the onset of measles outbreaks in the Dutch Bible Belt have been of an order smaller than 10^{-2} (Wallinga et al., 2003). For ε close to zero, a first order Taylor expansion around $\varepsilon = 0$ becomes valid in the derivation of the previous paragraph. Such expansion gives $p(\varepsilon) \approx 1 - 2\varepsilon$. This means that with $\varepsilon = 0.1$, eighty percent of susceptibles would never get infected during the outbreak.

It has often been assumed that almost all susceptibles get infected during an outbreak. However, for this to be the case, the effective reproduction number at $t = 0$ would have to be high. The value of ε at the beginning of the outbreak needs to be larger than two for more than 94% percent of the susceptible population to get infected during the outbreak. With such a large ε, the question arises why a smaller outbreak did not happen earlier while ε was smaller, but Z_0 still larger than one. After all, the virus should "visit" frequently as the Netherlands and its Bible Belt have relatively dense populations, good infrastructure, and are common starting points, transit points, and destinations for travel.

In England and Wales vaccination started in 1968. Since then there have been irregular and geograpically-independent small outbreaks in these areas that have been the subject of much research (Fine and Clarkson, 1982; Bolker and Grenfell, 1996). As was mentioned before, the Dutch Bible Belt consists of about 30 midsize towns. Contacts between these towns are apparently sufficiently intense for the entire susceptible orthodox-protestant population to be legitimately treated as one unit where mass-action applies. Fig. 1 shows small outbreaks in 1983, in 1992–1994, and in 2008. The latter two small outbreaks occurred in the anthroposophic community. The anthroposophists are a "spiritual" minority; they also refuse the measles vaccine, but, compared to the orthodox protestants, they are less numerous and less geographically clustered. A phenomenon like the three similar big outbreaks at twelve year intervals that Fig. 1 shows, has not been seen in the British case.

The 12-year period and the similarity in size and duration of the three outbreaks in the Dutch Bible Belt indicate that the process and its onset are not stochastic. Our assessment in the previous subsection suggests that about one fourth to one third of all susceptibles never becomes infected during an outbreak. According to the Kermack–McKendrick model, for 30% of susceptibles to *not* be infected during an outbreak, i.e. $p(\varepsilon) = 0.3$, it would require that $\varepsilon = 0.7$. This implies that only one-in-ten to one-in-six cases are reported. This may be a reasonable estimate that is consistent with the reference by van

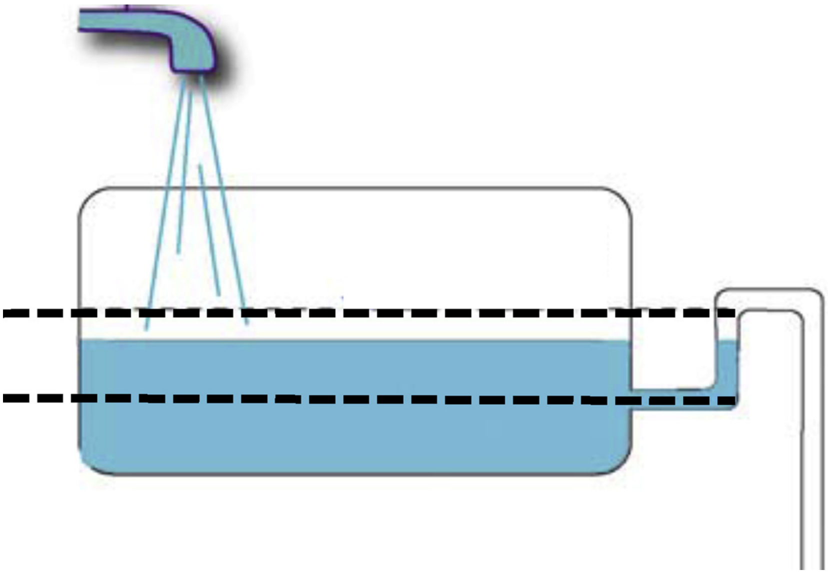

Fig. 2. An archetypal example of a relaxation oscillation or integrate-and-fire system. A reservoir slowly fills up with water. Once the indicated critical level is reached, siphoning starts and the water level in the tank is rapidly brought down to the indicated minimum. After that the slow filling-up starts again. A similar dynamics occurs with the periodic outbreaks of an infectious disease. Outbreaks occur when an apparent critical mass of susceptibles is exceeded.

Isterdael et al. (2004). Our conclusion that a relevant fraction of susceptibles does not get infected during an outbreak is supported by the fact that with every subsequent outbreak there has been an increasing number of adult patients (Bier and Brak, 2015).

Though there remain questions about the details of the underlying mechanism, we can classify the periodic-outbreak dynamics as a relaxation oscillation (see Fig. 2). Such systems are also known as integrate-and-fire. Systems with a slow build up followed by a rapid “reset” are commonly found in nature and technology. The well-known “dippy bird” is a more lighthearted example (Güémez et al., 2003; Lorenz, 2006).

4. Outbreaks in settings similar to the Dutch Bible Belt

Several cities in the developed world have had measles outbreaks in the last few decades in spite of a well-functioning public health system and good overall vaccination coverage. Many urban areas are like the Dutch Bible Belt in that they have a total population of a few million and about 200 schools over which susceptible children are distributed. In previous sections of this article we observed how geographic separation is not a significant variable in the Dutch Bible Belt and how the outbreak kinetics are adequately described with the aforementioned continuously-stirred-tank-reactor approach. Such an approach should be even more legitimate in case of densely populated cities. Urban settings, however, are different from the Dutch Bible Belt in that they are hubs for travel and migration and that relevant epidemiological parameters may change rapidly. In cities, fashions and fads come and go while the countryside remains as it is. Opposition to vaccines based on the belief that they are harmful to one's health is mostly an urban and suburban upper-middle-class phenomenon of the last two decades (Leib et al., 2011; Carrel and Bitterman, 2015). It is unlikely that outbreaks in a city will exhibit a periodicity as in the Dutch Bible Belt. However, thresholds similar to those that we found for the Dutch Bible Belt should apply. With these thresholds we can predict where and when outbreaks can occur.

In 2015 there was a measles outbreak in Berlin, the German capital. The outbreak involved 1243 reported cases.[5] The susceptibles that provided the “fuel” for the outbreak came from two major sources: (i) children of parents who oppose vaccination in the belief that it is harmful and (ii) unvaccinated and undervaccinated immigrants and refugees from areas like Syria and the former Yugoslavia where civil war had led to a collapse of public health systems. There are other major cities in Europe where vaccination coverage has been on the decline through similar developments and where critical levels for an outbreak may be close.

Poland's capital, Warsaw, currently has a population of about 2 million. This is about 5% of the total population of Poland. In the city of Warsaw there are 251 public primary schools and around 100 private primary schools that are generally small.[6] So in terms of the number of inhabitants and the number of schools, Warsaw resembles the Dutch Bible Belt and a similar outbreak threshold should apply.

The anti-vaccination movement is rapidly gaining ground in Poland. Vaccination coverage is falling at increasing speed and has recently dropped below the critical 95%.[7]

Though Warsaw is less multicultural than Berlin or other West European capitals, it does have a significant number of foreign residents. Ukrainians are by far the largest group. In 2017 in the city of Warsaw, 64,000 declarations of intention to employ a foreigner were submitted.[8] We assume that most of these applications resulted in a foreigner being hired to work in the city for at least a couple of months. In the Mazowiecki Voivodship (the district in which Warsaw is located) as a whole, Ukrainians received 380,000 work permits in 2017. This was 93% of the total number of issued permits in the voivodship.[9] Many Ukrainians may also be living and working in Poland undocumented and, all in all, it is estimated that there are between 900,000 up to well over a million Ukrainians residing in Poland.[10] With economic collapse,

[5] http://trace.tennessee.edu/cgi/viewcontent.cgi?article=3020&context=utk_chanhonoproj and https://www.washingtonpost.com/news/worldviews/wp/2015/02/07/germany-is-battling-a-measles-outbreak-that-is-10-times-worse-than-the-one-in-the-u-s and https://www.theguardian.com/world/2015/feb/13/measles-berlin-traced-unvaccinated-refugees-two-cases-linked-

(footnote continued)
us.

[6] http://edukacja.warszawa.pl/placowki/szkoly-podstawowe and http://www.ourkids.net/pl/prywatne-szkoly-podstawowe-w-warszawie.php#maincontent.

[7] http://szczepienia.pzh.gov.pl/en/stories/increasing-vaccine-hesitancy/ and http://www.euro.who.int/en/media-centre/sections/press-releases/2017/measles-outbreaks-across-europe-threaten-progress-towards-elimination.

[8] https://www.up.warszawa.pl/statystyka/analiza/raport2017.pdf, pp. 87–88.

[9] http://wupwarszawa.praca.gov.pl/documents/47726/7464762/Raport%20roczny%202017%20tekst/0d04307d-e38a-48b0-aa3b-475761e3ee72?t=1531394573531.

[10] https://www.nbp.pl/aktualnosci/wiadomosci_2018/obywatele-Ukrainy-

the proliferation of conspiracy theories, and armed conflict, vaccination coverage in Ukraine has dropped sharply over the last two decades and has currently reached an average of about 50%.[11] Frequent outbreaks of the measles have occurred as a result. In the first half of 2018 there were 23,000 reported measles cases in Ukraine and in a recent WHO report it is stated that "Since September 2017, over 621,000 un- or undervaccinated children have been identified."[12] Areas of Western Ukraine that border Poland were also impacted by the 2018 outbreaks.[13] According to data of the Polish National Bank, 900,000 Ukrainians traveled to Poland in 2017 and 85% of these were from Western Ukraine.[14] It is hard to estimate the total number of immigrants (not only from Ukraine) in the Warsaw area. Firm data are only available on registered students and on documented workers via work permits. The number of susceptible children, attending public or private primary schools, homeschooled or just in contact with schoolgoing peers is uncertain and the susceptible fraction of the immigrant population is even more uncertain.

As a rough estimate we take there to be 15,000 children in Warsaw for every age between 5 and 15.[15] If 5% of these children are unvaccinated (as was mentioned earlier, immunization coverage is currently below 95%), then we have a total of 7500 schoolgoing susceptibles. As was mentioned already, it is hard to guess the number of susceptible immigrants. If we conservatively estimate that 20% of one million Ukrainians in Poland is living in the Warsaw area and that 5% of these are susceptible, then we arrive at a number of about 10,000 additional susceptibles. The total number of susceptibles thus comes to about 18,000. This number is already close to the about 25,000 susceptibles that appeared to be sufficient to trigger an outbreak in the Dutch Bible Belt. It is again hard to make an exact prediction, but if current trends continue, then Warsaw will likely see a large outbreak within the next decade.

Measles susceptibility of Ukrainians and of other foreign-born residents in Poland is generally not a consequence of a conscious objection against the vaccine. In Ukraine, basic government services were disrupted and lives were upended. Many of those that migrated to Poland may subsequently have forgotten about the infectious diseases that they can still contract. There is an obvious course of action for Warsaw and for other Polish cities if they want to ward off outbreaks of the measles. It is imperative that they organize a large scale effort, involving primary care physicians and public health offices, to reach out and administer vaccines to documented and undocumented immigrants alike. Recently, a government agency organized the vaccination of more than 200 immigrant workers in a company in the Mazowiecki Voivodship.[16] More such initiatives are necessary.

5. Discussion

Our analysis of the previous section leads to the spectrum depicted in Fig. 3. The best situation for a community is the herd immunity that ensues when more than 95% is vaccinated against the measles and when the unvaccinated are homogeneously distributed among the general population. In that case no outbreak will ever get started. On the other end of the spectrum is the endemic situation. This is when the virus is continuously present in the population and at all times able to continue the chain of transmission. In between is the zone where the relaxation oscillations, i.e. periodic outbreaks, occur. Before 1976 the unvaccinated orthodox-protestant population of the Dutch Bible Belt was part of an endemic dynamics. After 1976 the number of vaccinated individuals is sufficiently high that endemicity is no longer maintained and an outbreak occurs whenever the unvaccinated population exceeds a critical level.

In his well-known 1976 book *Plagues and Peoples*, the historian William McNeill argues that the effect of infectious disease on the course of history has been underestimated (McNeill, 1976). It is indeed true that many more people died of infectious disease before hygiene, vaccines, and antibiotics became common in the course of the 20th century. McNeill extensively discusses the historical significance of what is illustrated in Fig. 3. He points out that in the course of the Middle Ages, population densities in continental Europe and Asia increased and with respect to many diseases (smallpox, diphtheria, measles, etc.) the situation effectively moved from the "periodic outbreaks" to the "endemic" part of the bar in Fig. 3. McNeill writes … *diseases that on their initial appearance in Europe had been highly lethal, settled toward endemicity, at least in those places where sufficiently dense populations existed to sustain a chain of infection indefinitely*. He next points out that the periodic outbreaks are socially more costly than the steady-state endemicity: … *infectious disease that affects only the young has a much lighter demographic impact on exposed communities than is the case when a disease strikes a virgin community, so that old and young die indiscriminately. This process of epidemiological adjustment was energetically under way in Europe as a whole during the so-called Dark Ages. As a result, the crippling demographic consequences of exposure to unfamiliar diseases disappeared within a few centuries*. As an example McNeill next points out how, in the early Middle Ages, population densities in Japan and Great Britain were smaller than those on the nearby continents: … *records show that the Japanese islands pretty well came abreast of the disease patterns of China (and the rest of the civilized world) during the thirteenth century. For more than six hundred years prior to that time, however, Japan probably suffered more from epidemics than other, more populous, and less remote parts of the civilized world. As long as the island populations were not sufficient to enable such formidable killers as smallpox and measles to become endemic childhood diseases, epidemics of these (and other similar) infections coming approximately a generation apart must have cut repeatedly and heavily into Japanese population, and held back the economic and cultural development of the islands in drastic fashion. Precisely the same considerations apply also to the British Isles. The surprisingly low level of British population in medieval times as compared to that of France, Italy, or Germany, may owe far more to the vulnerability of an islanded population to epidemic attrition than to any other factors*. It is only in the late Middle Ages that Japan and Great Britain reached population densities at which infectious diseases like measles and smallpox became endemic. After that a steady growth of the population followed and made it possible for these island nations to become military and economic world powers.

Ever more children in the developed world remain unvaccinated. Parents that refuse for religious reasons are actually only responsible for a minority of nonvaccinated children. Many children remain unvaccinated because families fall between the cracks of the system. This can happen, for instance, when parents migrate and do not have ongoing medical care. Strongly rising is the number of parents that refuse to let their children be vaccinated in the mistaken belief that vaccinations are unnecessary and/or negatively affect a child's health. Falling vaccination rates will not immediately bring the developed world back to the endemicities of the 19th century. What will first happen is ever

(*footnote continued*)
pracujacy-w-Polsce-raport.pdf.

[11] https://data.unicef.org/wp-content/uploads/country_profiles/Ukraine/immunization_country_profiles/immunization_ukr.pdf and https://data.worldbank.org/indicator/SH.IMM.MEAS?locations=PL-UA.

[12] http://www.euro.who.int/en/health-topics/communicable-diseases/measles-and-rubella/news/news/2018/5/ukraine-restores-immunization-coverage-in-momentous-effort-to-stop-measles-outbreak-that-has-affected-more-than-12-000-this-year.

[13] https://112.international/society/measles-outbreak-in-ukraine-254-cases-reported-in-lviv-region-25139.html.

[14] https://www.nbp.pl/aktualnosci/wiadomosci_2018/obywatele-Ukrainy-pracujacy-w-Polsce-raport.pdf.

[15] http://edukacja.warszawa.pl/edukacja-warszawska/oswiata-w-liczbach/20153-warszawska-oswiata-w-liczbach-3-wrzesnia-2018-r.

[16] https://www.mp.pl/szczepienia/aktualnosci/195845,gis-sytuacja-epidemiologiczna-odry-w-polsce-jest-niepokojaca.

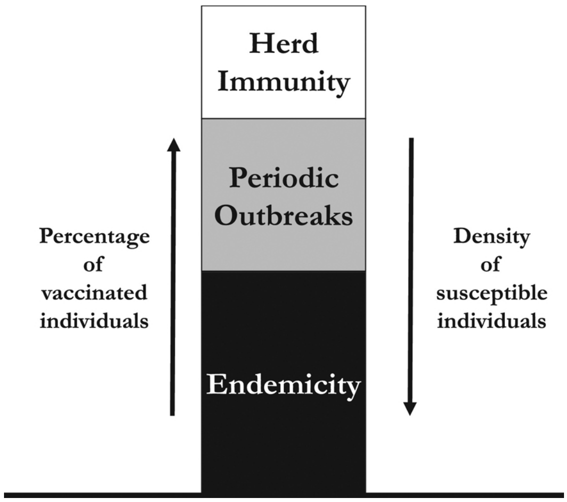

Fig. 3. The dependence of the infectious disease dynamics on the fraction of the population that is vaccinated. Endemicity ensues with a large density of susceptible individuals. When vaccination brings the density below a certain threshold, herd immunity occurs. In between is the range where periodic outbreaks happen.

more local outbreaks. Viruses will most likely evolve to make these outbreaks larger and longer lasting. Among the infectious diseases, the measles is the one that is most easily communicated and measles outbreaks will therefore be most prominent. But with falling vaccination rates, also outbreaks of other infectious diseases will occur and become more common. As McNeill points out, the periodic outbreaks come with a higher social cost than the endemic situation. The case of the measles in the Dutch Bible Belt is instructive here. The measles is best handled when the patient is between five and fifteen years old. At that age the immune system generally copes well with the measles and with other infectious diseases. With older patients the probability that complications occur is higher and hospitalization is more often necessary. As was pointed out before, in the Dutch Bible Belt with every subsequent measles outbreak since 1988 there have been more adult patients and concurrently more hospitalizations. This is a worrisome trend and it may be what is to come on a wider scale if vaccination rates keep dropping and the developed world takes a small step back towards the Dark Ages.

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