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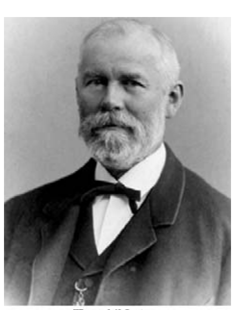
Letter to the Editor

The earliest notes on the reproduction number in relation to herd immunity: Theophil Lotz and smallpox vaccination

1. Introduction

During the late 19th century, the earliest epidemiologic evaluations of vaccination were performed on smallpox, the first disease against which a vaccine was developed (Fenner et al., 1988), and some of the results even raised the hope to eradicate the disease supported by an original theory (Lotz, 1880).

As the introduction of compulsory mass vaccination intensified technical and political debates (Edwardes, 1892), epidemiologic investigations, based on firm statistical evidence, were needed to convince the public of the benefits of vaccination especially after the mid-19th century (Simon, 1887). Whereas the oldest statistical evidence ignored several important aspects of immunization and exaggerated its effectiveness, some health officers and researchers insisted on the harmful effects of vaccination (Edwardes, 1892; Simon, 1887). Theophil Lotz, a Swiss physician, decided to put the arguments of both sides to the test by rigorously analysing available statistical data and by developing a simple mathematical model to clarify the impact of vaccination on the spread of disease (Lotz, 1880). Lotz, thereby, foresaw two of the most important theoretical concepts in modern infectious disease epidemiology, nearly a century ahead of time: the basic reproduction number, R_0, i.e. the average number of secondary cases arising from the introduction of an index case (Anderson and May, 1991; Diekmann and Heesterbeek, 2000), and its application to herd immunity.



Theophil Lotz

Theophil Lotz was born in Rümlingen, Basel, on October 28, 1842. After graduating in medicine in 1861, he underwent early training in Göttingen, Leipzig and other German cities, where his interest was attracted to hygiene and infectious diseases (Leichenrede, 1908). Thereafter, he settled in Basel as a regional physician where he also devoted himself to sanitary practices. He contributed to the local hygiene and public health, e.g. by helping to improve the water supply, until his death on October 25, 1908. The 'protectiveness of smallpox vaccination' was intensely discussed after Germany had introduced compulsory revaccinations (Hennock, 1998). Inspired by the discussion and confronted with the necessity to take up a well-defined decision, he wrote a book entitled "Pocken und Vaccination" (Smallpox and Vaccination), compiling the most impressive epidemiologic and statistical analyses of his time (Lotz, 1880). However, in part because Lotz wrote more for a local than an international audience, and in part because of the controversial and political nature of the subject, his work was very rarely cited and has thus been effectively ignored for more than a century.

2. Lotz's theory on the spread of smallpox

The earliest evidence of the effectiveness of smallpox vaccination, based on national statistics in Sweden, showed a dramatic decline in the annual number of smallpox-related deaths after the introduction of vaccination (Fig. 1) (Lotz, 1880; Edwardes, 1892). Whereas evidence of this type satisfied vaccination enthusiasts, their opponents found reason to criticise the validity of their conclusions. Adolf Vogt, a major opponent of vaccination, claimed the time series comparisons were technically flawed due to (a) gradual sanitary improvements, (b) possible natural decline, (c) the effect of inoculation among elderly, and so on (Vogt, 1879). Lotz considered it essential to pursue the discussions logically and to base all arguments on sound evaluation of the available data, and developed an idea of a geometric progression in the number of smallpox cases during an epidemic. He assumed that each primary case generated on average a given number of secondary cases:

> Supposing that each case carries the contagion only to two others who are capable of developing smallpox, the number of cases will grow from generation to generation, starting with one case and growing to 2, 4, 8, 16, 32, 64, etc. Generally speaking, if we denote the initial number of cases by a, the infection ratio (the average

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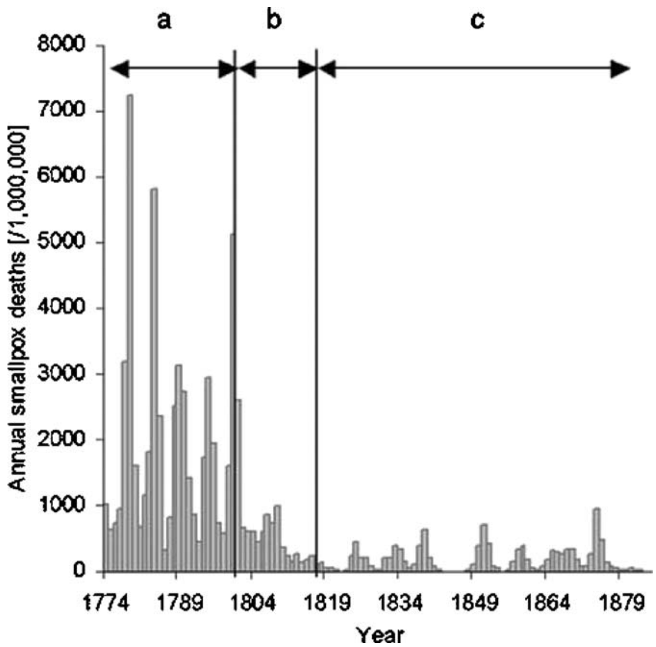

Fig. 1. Annual reported number of smallpox deaths per million inhabitants in Sweden from the late 18th to 19th century. (a) Before introduction of vaccination, (b) after introduction of vaccination, (c) after introduction of compulsory vaccination (see Lotz, 1880).

> number infected by one case) by q and the generation number by n, the number of cases increases according to the series
> $a, aq, aq^2, aq^3, \ldots, aq^n$.
> Starting with a single index case, the number of cases in the nth generation is equal to the infection ratio to the power of n (authors' translation).

Lotz's 'infection ratio' q is the earliest expression of the basic reproduction number, R_0, which had not been formally introduced until his time. To further describe the dynamics in the generation of new cases, Lotz suggested an average time of 15 days for what now would be called the 'generation interval' or the 'serial interval', the mean time interval between onset of index case and onset of the secondary cases (Bailey, 1975; Diekmann and Heesterbeek, 2000; Fine, 2003):

> If we assume an average of 15 days per generation of smallpox (i.e. the time from onset of disease to the consecutive ones), the sixth generation would be infected three months and the eighth generation four months after onset of the initial cases. With $a = 1$ (the initial number of cases), the infection ratio 2 and $n = 6$ (the number of generations), we get $1 \times 2^6 = 64$ cases, and $1 \times 2^8 = 256$ cases in the eighth generation.

In other words, Lotz reasonably applied demographic (or ecological) ideas to explain the generation of cases of directly transmitted diseases. In the same year, William Farr implicitly introduced the same concept, the net reproduction ratio, in demography (Farr, 1880; Lewes, 1984).

3. Impact of vaccination on Lotz's net growth

Following the theory given above, Lotz discussed the effect of vaccination in protecting a community against introduction of smallpox:

> If only a fraction of those who were otherwise susceptible against the infection were rendered resistant against the poison, the infection ratio would be reduced by the same fraction. If we call the reduction ε, the series above becomes the following series:
> $a, aq\varepsilon, aq^2\varepsilon^2, aq^3\varepsilon^3, \ldots, aq^n\varepsilon^n$.
> The reduction in the number of cases which occurs in the nth generation is, and this is of critical importance, equal to the reduction in the first generation to the power of n.

The reduction factor ε can be interpreted as the relative risk of vaccinated compared to unvaccinated individuals, and $1-\varepsilon$ provides an estimate of direct effectiveness of vaccination in case of mass vaccination (Haber, 1999). Using a 20% reduction ($\varepsilon = 0.8$), Lotz convincingly demonstrated the potential impact of vaccination, assuming small effectiveness, targeted at susceptible individuals: instead of 64 cases, we expect only 17 cases in the 6th generation, and instead of 256 cases, we expect only 43 in the 8th generation, from which he concluded:

> A moderate reduction in the infection ratio, thereby, exerts a huge influence on the development of the epidemic, as it is multiplied from generation to generation; it is also evident, that it is much easier to localize such a slowed-down epidemic.

Lotz appropriately understood the way of expecting the number of secondary transmissions under vaccination. The term $q\varepsilon$ denotes nowadays the effective reproduction number (Bailey, 1975; Diekmann and Heesterbeek, 2000). Applying his theory, Lotz refuted Vogt's argument: Whereas Vogt concluded the effectiveness of smallpox vaccination as small, based on a comparison between vaccination coverage and the number of cases in different groups (i.e., 'groups with 87 and 94% of vaccination coverage showing quite different numbers of cases implied almost no influence of vaccination'), Lotz accentuated the importance of the unvaccinated fraction in relation to the number of cases and clarified a flaw in Vogt's logic (i.e., in the above example, 13% and 6% should be compared with the number of cases). The discussion following his theory came very close to determining the required vaccination coverage for eradication in a randomly mixing population (Anderson and May, 1982; Diekmann and Heesterbeek, 2000).

4. Community benefit of vaccination

Immediately after introducing his original theory, Lotz emphasized the community benefit of vaccination and considered it an important goal of a community to achieve a high degree of herd immunity:

> Everyone who is protected by vaccination, does not only have an individual benefit, but the benefit extends to those who would have been infected by the vaccinee, had he developed the disease. This very issue is the crucial point of vaccination, that vaccinees are not only protected to their own benefit, but to the benefit of the community, and that unvaccinated individuals are susceptible not only to their own adversity, but to the adversity of the community.

Moreover, comparing the spatial spread of disease to a fire, Lotz accentuated its importance:

> Keeping other circumstances constant, a conflagration within a settlement (which can be well compared to an epidemic) proceeds much quicker and causes more damage if the number of poorly built and straw-thatched buildings (i.e. the ones susceptible to fire) is more numerous. If solid buildings (i.e. such that are less susceptible to fire) are built among the easily inflammable ones, a solid house is not only inflamed less easily, but also protects the house (or maybe even a whole row of houses) next to it.

5. The earliest history of theoretical epidemiology

Lotz's 'infection ratio' was the earliest explicit and appropriate description of R_0. Even though Farr and Böckh reasonably estimated marital or age-specific fertility rates in the same or following years (Farr, 1880; Böckh, 1886; Lewes, 1984; Dietz, 1993), their arguments and uses of the net reproduction ratio were rather implicitly defined compared to that of Lotz (Lewes, 1984). Theoretical explanations on the spread of infectious diseases were rare at his time except for the work by Daniel Bernoulli (Dietz and Heesterbeek, 2002). The geometric progression of an epidemic was also discussed shortly after and probably independently from Lotz in Berlin by the epidemiologist Adolf Gottstein (1857–1941) (Dietz & Heesterbeek, "Epidemics: the discovery of their dynamics", in preparation). Later, documentations on the implicit growth of cases have been recognized (En'ko, 1889; Dietz, 1988), followed in the mid-20th century by the formal definition by Macdonald who elaborated the efforts of Ross (Ross, 1911; Macdonald, 1952). Thus, Lotz was far ahead of his time in theoretical epidemiology (Heesterbeek, 2002), and his theory and discussion on smallpox vaccination fully corresponds to what was widely discussed in the late 20th century: i.e. on the control of directly transmitted disease by vaccination (Anderson and May, 1982, 1990; Diekmann and Heesterbeek, 2000). The impact of herd immunity had implicitly been discussed by Farr (1839–40, also see Fine, 1993), but, except from the work of Lotz, does not seem to have been theoretically documented until Fox et al. in the late 20th century (1971, also see Fine, 1993). Although threshold vaccination coverage for eradication was biased by several factors, i.e. non-homogenous distribution of population and contacts, contact tracing, and ring vaccination (Fine, 1993), evidence of herd immunity was finally suggested after smallpox eradication, based on surveillance data on vaccination coverage and population density (Arita et al., 1986).

Despite the global eradication of smallpox, one of the biggest success stories of public health, the possibility of bioterrorist attacks using variola virus has recently been raised, and we have entered yet another round of discussing the pros and cons of smallpox vaccination. The current debates of preparedness issues are far more complex than those on compulsory mass vaccination. Newer vaccination schemes considerably complicate the balance of individual and community benefits (Bauch et al., 2003), and other public health measures have been and will be combined with vaccination in case of the return of smallpox (Eichner, 2003).

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