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Daniel Bernoulli's epidemiological model revisited

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Abstract

The seminal paper by Daniel Bernoulli published in 1766 is put into a new perspective. After a short account of smallpox inoculation and of Bernoulli's life, the motivation for that paper and its impact are described. It determines the age-specific equilibrium prevalence of immune individuals in an endemic potentially lethal infectious disease. The gain in life expectancy after elimination of this cause of death can be explicitly expressed in terms of the case fatality and the endemic prevalence of susceptibles. D'Alembert developed in 1761 an alternative method for dealing with competing risks of death, which is also applicable to non-infectious diseases. Bernoulli's formula for the endemic prevalence of susceptibles has so far escaped attention. It involves the lifetime risk of the infection, the force of infection and the life expectancy at birth. A new formula for the basic reproduction number is derived which involves the average force of infection, the average case fatality and the life expectancy at the time of infection. One can use this estimate to assess the gain in life expectancy if only a fraction of the population is immunized.

Keywords: Daniel Bernoulli; Epidemiological models; Competing risks; Life table; Smallpox; Inoculation

1. Introduction

John Jacquez did not only write a major book on compartmental analysis which went to three editions [1], he also was very successful together with his co-authors Jim Koopman, Carl Simon and Ira Longini in applying this tool in infectious disease epidemiology, especially in the context of HIV [2]. Since he was also very much interested in the historical developments of a scientific

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field, the authors dedicate the following article as a personal tribute to the memory of this great scientist and charming person.

The seminal paper by Daniel Bernoulli [3] is put into a new perspective. Instead of restricting ourselves to the derivation of a life-table in the absence of a potentially lethal infection we first generalize Bernoulli's model by allowing both the force of infection and the case fatality to depend on age. Then we derive a new explicit formula, which links the gain in life expectancy to a weighted average of the case fatality and to the endemic prevalence of susceptibles. Bernoulli's formula for the endemic prevalence of susceptibles has so far escaped attention. It is expressed as a ratio of expected time spent in the susceptible state to the expectation of life at birth. Bernoulli's model is probably the first compartmental model. It describes the age-specific prevalence of immunes for an endemic infection which is potentially lethal. We compare Bernoulli's approach with d'Alembert's [4] alternative method for dealing with competing risks which is also applicable to non-infectious diseases. Since the inverse of the endemic prevalence of susceptibles equals the basic reproduction number of an infectious disease for homogeneously mixing populations, one can use Bernoulli's model to assess the gain in life expectancy at birth if only a fraction of the population is immunized. We calculate the life expectancy at birth of non-immunized individuals and of the total population as a function of the immunization coverage.

2. The method of smallpox inoculation

The natural mode of transmission of the smallpox virus is via the respiratory tract. The case fatality (i.e. the proportion of infected individuals who die as a result of the infection) appears to have increased over the centuries and peaked in the 18th century [5]. In China [6] and India [7] infectious material from smallpox cases was transferred into the skin of susceptibles with the intention to induce lifelong immunity by a mild infection with a low case fatality. In 1721 this method was introduced from Turkey into England by the wife of the English Ambassador to Constantinople, Lady Mary Wortley Montague. It is not widely known that inoculation was even attempted against measles, plague and several diseases of animals (rinderpest, sheep pox, contagious bovine pleuropneumonia) [8]. The practice of variolation (inoculation against smallpox) generated heated debates about the pros and cons of this procedure. Innumerable articles and books were written about this method. The (incomplete) bibliography of Klebs [9] contains 480 items! Right after the introduction of this method in England and later in France, the arguments were supported by statistical reasoning. Rusnock [10] provides an excellent introduction into the quantitative contributions to this debate in the 18th century prior to Bernoulli. It involves among others John Arbuthnot [11], Anton Deparcieux [12], James Jurin [13], and Charles-Marie de La Condamine [14].

3. Daniel Bernoulli's life

The following sketch of his life is based on the MacTutor History of Mathematics archive (http://www-history.mcs.st-andrews.ac.uk/history) where also a family tree of the Bernoullis can be found including eight famous mathematicians in three generations (see also [42]). Daniel

Bernoulli was born on 8 February (29 January, Julian Calendar) 1700 in Groningen, the Netherlands as the second son of Johann Bernoulli who was professor of mathematics there. In 1705 the family returned to Basel where Daniel's father took up the chair of his elder brother Jacob. Daniel also wanted to become a mathematician, but his father urged him to take up a commercial apprenticeship. After this failed, Daniel Bernoulli studied medicine in Heidelberg and Strasbourg and graduated in 1721 at the University of Basel with a dissertation entitled *De respiratione* on the mechanics of breathing. After some years in Venice where he studied practical medicine and published his *Mathematical exercises*, he got an offer together with his elder brother Nikolaus to take up positions at the St. Petersburg Academy in 1725. In 1727 began a very productive collaboration with Leonhard Euler. Daniel Bernoulli applied several times for a position in Basel but was unsuccessful because the drawing of lots went against him. Eventually he succeeded in 1733. He first became professor of anatomy and botany and in 1743 took on responsibility for teaching physiology instead of botany and in 1750 he became in addition professor of physics. He was never married and stayed in Basel until his death on 17 March 1782. His major achievements are associated with hydrodynamics and an anticipation of the kinetic theory of gases. He won the prize of the Paris Academy of Sciences ten times with contributions to a wide variety of topics, some of them dealing with marine technology. Sheynin [15] summarizes his work on probability: "... Bernoulli was the first to use systematically differential equations for deducing a number of formulae, one of the first to raise the problem of testing statistical hypotheses ...". On the occasion of his 300th birthday, the University of Basel organized a special exhibit. He is considered to be one of the greatest scientists of the 18th century.

4. Bernoulli's paper – its origins and impact

Bernoulli was stimulated to look into the inoculation controversy by Pierre Louis Moreau de Maupertius (1698–1759) and Charles Marie de la Condamine (1701–1774). The latter, especially, has written several memoranda favoring the introduction of inoculation into France [14]. In still unpublished letters he provided Bernoulli with data about the incidence and case fatality of smallpox and the safety of inoculation. De la Condamine acknowledges receipt of Bernoulli's paper and informs him that he started to read it to the Royal Academy of Sciences in Paris on 22 March 1760. According to the minutes of the Archives of the Academy and a marginal note of the printed version of Bernoulli's full contribution (including the mathematics), the reading was (re)started in a non-public session by de la Condamine on 30 April 1760. It had also been read in a public session of the Academy on 16 April 1760 by Joseph-Jérome Lefrançais de la Lande (1732–1807). Thus Bernoulli did not present the paper himself in Paris as it is sometimes claimed. There is an independent witness for the presence of Bernoulli in Basel: count Joseph Teleki, a student of mathematics from Hungary, writes in his diary for 16 April: "In the morning when I attended my course, I congratulated Mr. Daniel Bernoulli on his name day, which he greatly appreciated" [16].

A short version (without the mathematics) of Bernoulli's paper was published in the June issue of the Mercure de France [17]. The full paper finally appeared in print in 1766 which allowed Bernoulli to add in 1765 some responses to d'Alembert who had criticized his contribution in a public session on 12 November 1760. We shall come back to the controversy between Bernoulli

Fig. 1. Daniel Bernoulli (1700–1782). (Section from a painting by Nicolaus Grooth in 1760.)

and d'Alembert in the section about d'Alembert's approach. For a portrait of Bernoulli as he appeared in 1760, see Fig. 1.

As can be seen from Bernoulli's letter to Euler (see Section 7), the paper was well received by other readers apart from d'Alembert. This occasion was not the first time that Bernoulli and d'Alembert exchanged heated arguments. Earlier issues were concerned with the vibrating string [18] and the St. Petersburg game [19]. Soon after its publication, Bernoulli's paper was followed up by Lambert [20] who tried to generalize the method of Bernoulli taking into account age-dependent parameters. Trembley [21,22] and Duvillard [23] also pursued the same objective. Today Bernoulli's paper is still quoted frequently and is praised even for results which are not contained in it. For instance in [24] it is claimed that the first dynamic model of epidemics is due to Bernoulli and the authors then apply epidemic modeling to the spread of 'viruses' in computer networks. If they had read the paper carefully, they would have found out that the paper is only concerned with a static state, i.e. it is assumed that the force of infection stays constant throughout time.

The main objective of Bernoulli was to calculate the gain in life expectancy at birth if smallpox were to be eliminated as a cause of death. Because at the time annuities were being sold, his work on the prolongation of life expectancy at any age had immediate financial impact. Bernoulli's method to deal with competing risks has received considerable attention in the actuarial literature and is better known there than in the epidemiological literature. For an appreciation of Bernoulli's work in the context of competing risks, see the papers by Seal [25] and Daw [26]. The role of Bernoulli in the epidemiology of infectious diseases was probably first recognized in the survey

article by Brambilla [27] which is quoted by Dietz [28]. Since the latter article, however, concentrated on epidemic models, the endemic models or catalytic models according to Muench [29] were explicitly excluded from detailed description. In the second edition of Bailey's book [30] full tribute is given to Bernoulli's work and since then he is frequently quoted as originator of the first epidemiological model for an infectious disease.

5. Bernoulli's model

For the following presentation we use modern notation and consider the general case of age-dependent parameters such that the case of Bernoulli's model with constant parameters can be immediately obtained by specialization. Fig. 2 shows the structure of Bernoulli's model. The population is divided into susceptibles, i.e. those who have not yet been infected, and immunes, i.e. those who have been immunized for the rest of their life after one infection. The death rate due to all causes except due to the infection is denoted by $\mu(a)$. The force of infection $\lambda(a)$ is the rate according to which susceptibles are infected. Only a fraction $s(a)$ survives to become immune. The rest $c(a) = 1 - s(a)$ dies due to the infection. Traditionally, $c(a)$ is called the case fatality rate. Since it is not a rate (with dimension per unit of time) but a probability i.e. a dimensionless quantity we will refer to it as case fatality. Let $u(a)$ denote the probability for a newborn individual to be alive and susceptible at age a. Then $u(a)$ satisfies the differential equation

$$\frac{\mathrm{d}u}{\mathrm{d}a} = -[\lambda(a) + \mu(a)]u, \tag{1}$$

with the initial condition $u(0) = 1$.

The probability $w(a)$ to be immune and alive is given by

$$\frac{\mathrm{d}w}{\mathrm{d}a} = [1 - c(a)]\lambda(a)u(a) - \mu(a)w, \tag{2}$$

with the initial condition $w(0) = 0$.

The solutions of these equations are

$$u(a) = \exp\{-[\Lambda(a) + M(a)]\}, \tag{3}$$

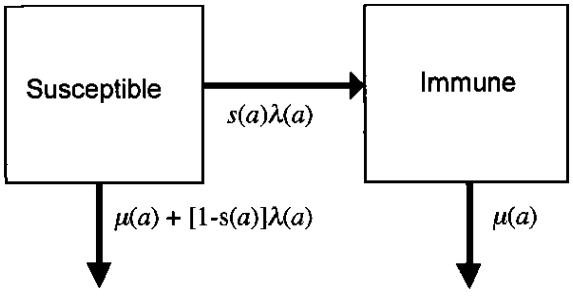

Fig. 2. States and transitions of Bernoulli's epidemiological model for an immunizing infection in a cohort which is in equilibrium with respect to time. $s(a)$ = probability of surviving the infection. $\lambda(a)$ = force of infection; $\mu(a)$ = death-rate due to other diseases.

$$w(a) = \mathrm{e}^{-M(a)} \int_0^a [1 - c(\tau)]\lambda(\tau)\mathrm{e}^{-\Lambda(\tau)}\,\mathrm{d}\tau, \tag{4}$$

where

$$\Lambda(a) = \int_0^a \lambda(\tau)\,\mathrm{d}\tau \tag{5}$$

and

$$M(a) = \int_0^a \mu(\tau)\,\mathrm{d}\tau. \tag{6}$$

Let $l(a)$ denote the probability to survive age a. Then,

$$l(a) = u(a) + w(a) \tag{7}$$

because the two states susceptible and immune are complementary to each other.

The survival function in the population without smallpox would be

$$l_0(a) = \mathrm{e}^{-M(a)}. \tag{8}$$

The survival function in the presence of smallpox can be written as a product of $l_0(a)$ and a factor which does not depend on the natural death rate and which is only determined by the force of infection and the case fatality. We get

$$l(a) = l_0(a)\left[\mathrm{e}^{-\Lambda(a)} + \int_0^a [1 - c(\tau)]\lambda(\tau)\mathrm{e}^{-\Lambda(\tau)}\,\mathrm{d}\tau\right]. \tag{9}$$

Let $x(a) = u(a)/l(a)$ denote the prevalence of susceptibles at age a and $z(a) = w(a)/l(a)$ the prevalence of immunes both at age a, then

$$z(a) = 1 - x(a). \tag{10}$$

(Since the duration of the infection is only a matter of weeks, this time period is negligible compared to the duration of the susceptible state and the immune state which can be years.)

By introducing the prevalence of susceptibles at age a, Bernoulli derived a differential equation which does not involve the general mortality $\mu(a)$. This has the form

$$\frac{\mathrm{d}x}{\mathrm{d}a} = -\lambda(a)x(a)[1 - c(a)x(a)] \tag{11}$$

with the initial condition $x(0) = 1$.

This equation shows that the decrease in the age-specific prevalence of susceptibles is reduced if the case fatality is greater than zero. Jacob Bernoulli (1657–1705), the oldest uncle of Daniel Bernoulli (also famous for his work on probability theory: *Ars Conjectandi* and the law of large numbers), had solved even more general equations (now called 'Bernoulli equation') involving arbitrary powers in 1696. This special Bernoulli equation has the solution

$$x(a) = \frac{\mathrm{e}^{-\Lambda(a)}}{\mathrm{e}^{-\Lambda(a)} + \int_0^a [1 - c(\tau)]\lambda(\tau)\mathrm{e}^{-\Lambda(\tau)}\,\mathrm{d}\tau}. \tag{12}$$

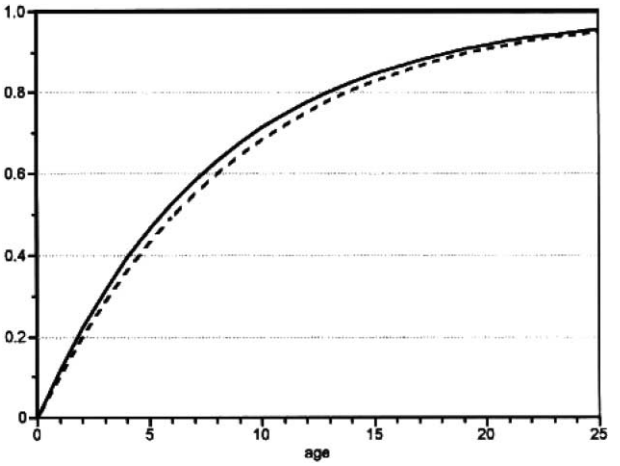

Fig. 3. The age-dependent prevalence of immune individuals with constant force of infection ($\lambda = 0.125$ per year) and $c = 0$ (continuous line) and $c = 0.125$ (broken line). For increasing case fatality the prevalence decreases.

For the case fatality Bernoulli had estimated $1/8 = 12.5\%$, and for the force of infection $1/8 = 0.125$ per year. Fig. 3 shows the age-specific prevalence of immune individuals for an infection without mortality ($c = 0$) and for an infection with a case fatality of 12.5%. The maximum difference is only about 3.3% at the age of six years. In view of large sampling errors due to small sample sizes of cross-sectional surveys, it would be impossible to detect a significant difference between the two curves, i.e. it seems unlikely that the case fatality may be estimated simultaneously with the force of infection from cross-sectional data alone. Age-prevalence curves (in the absence of infection-induced mortality) were introduced much later by Muench [31] in 1934, and are referred to as catalytic curves.

6. The gain in life expectancy at any age after elimination of one cause of death

In order to obtain the survival function in the absence of smallpox, one has to divide the observed survival function $l(a)$ by the denominator in Eq. (12). One gets

$$l_0(a) = \frac{l(a)}{e^{-\Lambda(a)} + \int_0^a [1 - c(\tau)]\lambda(\tau)e^{-\Lambda(\tau)}\,d\tau}. \tag{13}$$

Fig. 4 shows the life table used by Bernoulli together with the life table that would be expected if smallpox were eliminated as a cause of death. Bernoulli provides a table with the annual values for the two curves only up to age 25. The present curve uses the full table as given by Halley [32] on the basis of data from Breslau. (See Hald [33] for an excellent account on the construction of Halley's table which, strictly speaking, is not a life table because it gives the number of persons between age a and age $a + 1$ instead of the number of persons surviving to age a.)

Integrating the survival curves over all ages one can calculate the life expectancies at birth with and without smallpox. These numerical integrations can be replaced by analytical expressions,

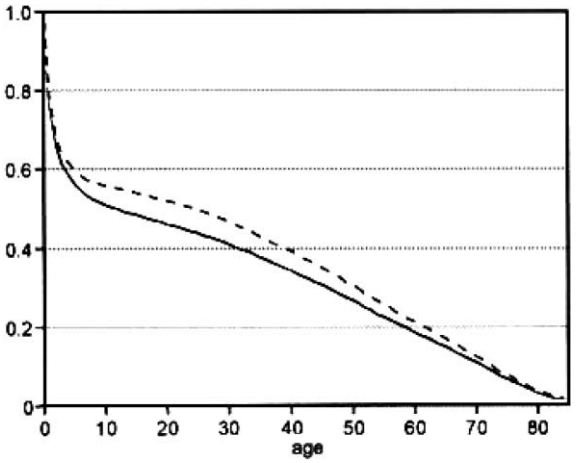

Fig. 4. The life table based on Halley in the state with smallpox (continuous line) and without smallpox (broken line). The median age would increase by 14 years from about 11.5 to 25.5 years!

which allow calculating the gain in life expectancy at birth directly from the parameters of the model as

$$L_0 = L(1 - \bar{c}\bar{x})/(1 - \bar{c}). \tag{14}$$

We will explain the four new symbols one by one.

L denotes the life expectancy at birth in the presence of smallpox. Then

$$L = \int_0^\infty l(a)\,\mathrm{d}a \tag{15}$$

and L_0 is the life expectancy at birth in the absence of smallpox,

$$L_0 = \int_0^\infty l_0(a)\,\mathrm{d}a. \tag{16}$$

The endemic prevalence of susceptibles $\bar{x}$ is the ratio of the expected time spent in the susceptible state

$$L_u = \int_0^\infty \mathrm{e}^{-\Lambda(a)-M(a)}\,\mathrm{d}a \tag{17}$$

and the life expectancy L at birth. Hence

$$\bar{x} = \frac{L_u}{L}. \tag{18}$$

The average case fatality $\bar{c}$ involves as weighting function not only the incidence of infections, but also the remaining life expectancy at the time of infection. We therefore get

$$\bar{c} = \frac{\int_0^\infty c(\tau)\lambda(\tau)\mathrm{e}^{-\Lambda(\tau)-M(\tau)}L_0(\tau)\,\mathrm{d}\tau}{\int_0^\infty \lambda(\tau)\mathrm{e}^{-\Lambda(\tau)-M(\tau)}L_0(\tau)\,\mathrm{d}\tau}. \tag{19}$$

Here $L_0(\tau)$ is the remaining life expectancy for an (immune) individual infected at age τ, which can be written as

$$L_0(\tau) = \int_\tau^\infty \mathrm{e}^{-[M(a)-M(\tau)]}\,\mathrm{d}a. \tag{20}$$

The denominator in (19) can be written as the product of the lifetime risk p_I and the life expectancy at infection L_w, two further important concepts which we now define.

$$p_I = \int_0^\infty \lambda(\tau)\mathrm{e}^{-\Lambda(\tau)-M(\tau)}\,\mathrm{d}\tau \tag{21}$$

is the proportion of a cohort which will ever be infected.

L_w denotes the conditional life expectancy at infection given that the individual did not die due to the infection. We get

$$L_w = \frac{\int_0^\infty L_0(\tau)\lambda(\tau)\mathrm{e}^{-\Lambda(\tau)-M(\tau)}\,\mathrm{d}\tau}{\int_0^\infty \lambda(\tau)\mathrm{e}^{-\Lambda(\tau)-M(\tau)}\,\mathrm{d}\tau}. \tag{22}$$

This expression can be simplified

$$L_w = \frac{\int_0^\infty \mathrm{e}^{-M(a)}\left(1-\mathrm{e}^{-\Lambda(a)}\right)\mathrm{d}a}{p_I} = \frac{L_0 - L_u}{p_I}.$$

The expression (14) can be derived starting from (9).

$$\begin{aligned} L &= L_u + \int_0^\infty \mathrm{e}^{-M(a)} \int_0^a [1-c(\tau)]\lambda(\tau)\mathrm{e}^{-\Lambda(\tau)}\,\mathrm{d}\tau\,\mathrm{d}a \\ &= L_u + \int_0^\infty (1-c(\tau))\lambda(\tau)\mathrm{e}^{-\Lambda(\tau)-M(\tau)} \int_\tau^\infty \mathrm{e}^{-[M(a)-M(\tau)]}\,\mathrm{d}a\,\mathrm{d}\tau = L_u + (1-\bar{c})L_w p_I \\ &= L_u + (1-\bar{c})(L_0 - L_u). \end{aligned} \tag{23}$$

The endemic prevalence of susceptibles can be expressed as a function of the lifetime risk p_I.

$$\bar{x} = \frac{p_I}{\bar{\lambda}L}. \tag{24}$$

In the denominator we have the average force of infection

$$\bar{\lambda} = \int_0^\infty \lambda(a)\mathrm{e}^{-\Lambda(a)-M(a)}\,\mathrm{d}a/L_u. \tag{25}$$

Thus, we can rewrite Eq. (14) in terms of these quantities.

$$L_0 = L(1-\bar{c}p_I/\bar{\lambda}L)/(1-\bar{c}). \tag{26}$$

From (23) we get for the lifetime risk p_I a simple expression in terms of the prevalence of immunes $\bar{z} = 1-\bar{x}$.

$$p_I = \frac{\bar{z}L}{(1-\bar{c})L_w}. \tag{27}$$

For non-fatal infections ($\bar{c} = 0$) the lifetime risk is smaller than the prevalence of immunes if the life expectancy at birth is smaller than the life expectancy at infection.

The lifetime risk of smallpox can be estimated from the observed proportion of deaths due to smallpox p_D.This quantity depends also on an average case fatality, but this time the weighting function is different

$$p_D = \int_0^\infty c(a)\lambda(a)e^{-\Lambda(a)-M(a)}\,da = \tilde{c}p_l. \tag{28}$$

Here $\tilde{c}$ denotes the average case fatality which links the proportion of deaths due to smallpox to the lifetime risk p_l.

$$\tilde{c} = \frac{\int_0^\infty c(a)\lambda(a)e^{-\Lambda(a)-M(a)}\,da}{\int_0^\infty \lambda(a)e^{-\Lambda(a)-M(a)}\,da}. \tag{29}$$

One can now replace the lifetime risk in Eq. (26) by the proportion of deaths due to smallpox p_D.

$$L_0 = \frac{L\left(1-\frac{\bar{c}}{\tilde{c}}\frac{p_D}{\bar{\lambda}L}\right)}{1-\bar{c}}. \tag{30}$$

This equation only contains quantities which in principle can be estimated from data. The estimates of Bernoulli are

$$L = 26.58\ [\text{years}], \quad c = 0.125, \quad p_D = 1/13 = 0.077, \quad \bar{\lambda} = 0.125\ [\text{per year}]. \tag{31}$$

If one enters these estimates into formula (30), one obtains a life expectancy at birth of 29 years and 8 months which only differs slightly from the value given by Bernoulli who used numerical integration. He comes up with a value of 29 years and 9 months.

The formula (14) can be generalized for all ages. Let $L(a)$ denote the life expectancy of an individual at age a in the situation of endemic smallpox. We denote by $\bar{c}(a)$ the average case fatality according to Eq. (19) where the lower integration boundary 0 is replaced by a and let $\bar{x}(a)$ denote the prevalence of susceptibles among individuals with minimum age a. Then

$$\bar{x}(a) = \frac{\int_a^\infty l(\tau)x(\tau)\,d\tau}{L(a)}.$$

This is to be distinguished from the quantity $x(a)$ which was defined earlier (Eq. (12)) which is the prevalence of susceptibles at age a. Following the same procedure for the derivation of Eq. (14), we get

$$L_0(a) = \frac{L(a)\left[1-\bar{c}(a)x(a)\bar{x}(a)\right]}{1-\bar{c}(a)x(a)}. \tag{32}$$

For $a = 0$ Eq. (32) reduces to Eq. (14) because it is assumed that at age 0 all individuals are susceptible.

Fig. 5 shows the two functions $x(a)$ and $\bar{x}(a)$ as a function of age for the estimates given by Bernoulli, and Fig. 6 shows the age-specific life expectancy in the population with and without smallpox. Due to the high childhood mortality children at age five have a 14.5 years higher life expectancy than newborns!

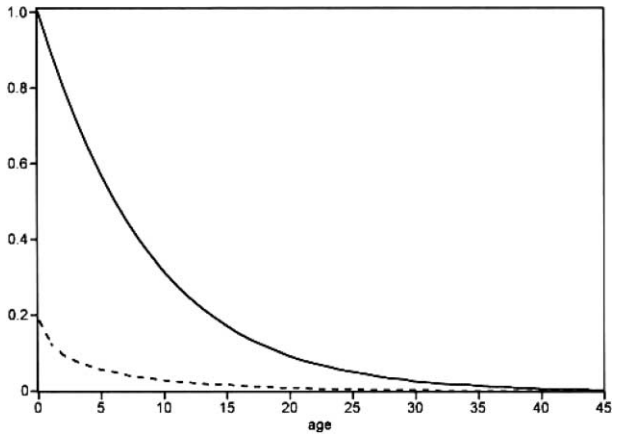

Fig. 5. The age-specific proportion of susceptibles (continuous line) and the average proportion of susceptibles (broken line) as a function of the minimum age. The proportion of susceptibles for the total population (minimum age zero) equals 19% for Halley's table.

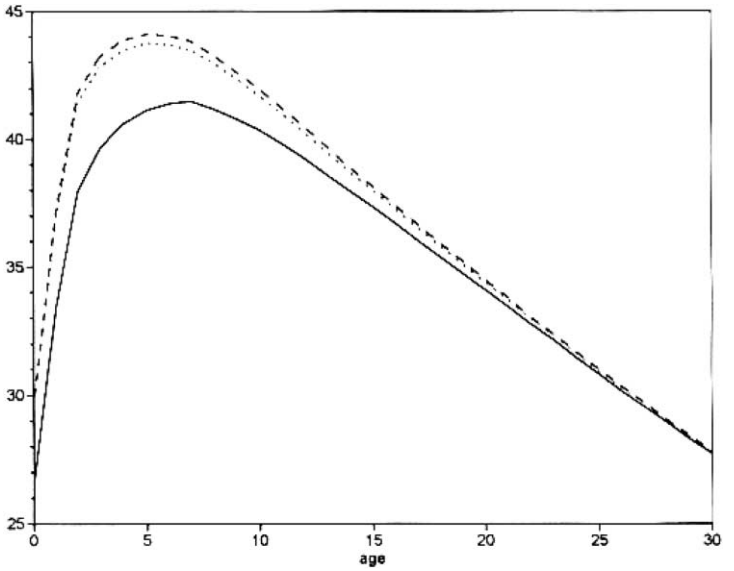

Fig. 6. The life expectancy of individuals who have survived a given age for Halley's table (with smallpox (continuous line) and without smallpox). The dotted line uses numerical integration (trapezoidal rule with yearly steps) and the broken line uses Eq. (32).

7. D'Alembert's approach

D'Alembert immediately wrote a criticism which he presented on 12 November 1760 to the Royal Academy of Sciences and which he published in the following year in his collected works.

This means that his critique of Daniel Bernoulli appeared five years before Bernoulli's contribution eventually was published by the Academy in 1766. Bernoulli was very annoyed about the critique of d'Alembert, which can be seen from his letter to Euler in April 1768:

Que dites vous des enormes platitudes du grand Dalembert sur les probabilités; comme je me trouve, trop souvent, injustement traité dans ses ouvrages, j'ai pris la resolution depuis assez longtemps de ne rien lire qui sorte de sa plume; j'ai pris cette resolution à l'occasion d'un memoire sur l'inoculation, que j'ai envoyé à l'Académie de Paris il y a 8 ans et qui par la nouveauté de l'analyse avait été recu avec un grand accueil; c'étoit, si j'ose le dire, comme une nouvelle province incorporée au corps des mathematiques; il semble que le succès de cette nouvelle analyse lui fit mal au coeur; il la critique de mille façons, toutes egalement ridicules et aprez l'avoir bien critiquée il se donne pour premier auteur d'une théorie qu'il n'avoit pas seulement entendu nommer. Il savoit cependant que mon memoire ne pouvoit paroitre que dans sept ou huit ans et il ne pouvoit en avoir connaissance qu'en qualité d'academicien et à cet egard mon memoire devoit etre sacré jusqu'à ce qu'il fut rendu public. *Dolus an virtus quis in hoste requirat*!

(The original of this letter is in the Archives of the Russian Academy of Sciences, St. Petersburg (Call No. f.1, op.3, Nr.51, l.150-151 R). We used a transcription of the Bernoulli Archive in Basel. The letter will be published in about three years by the Euler edition in the original French version and in a German translation.)

Translation: What do you say about the enormous platitudes of the great d'Alembert about the probabilities; as I find myself too frequently unjustly treated in his publications, I have decided already some time ago to read nothing anymore which comes from his pen; I have taken this decision on the occasion of a manuscript about inoculation which I sent to the Academy in Paris eight years ago and which was greatly appreciated because of the novelty of the analysis; it was, I dare say, like incorporating a new province into the body of mathematics; it seems that the success of this new analysis caused him pains of the heart; he has criticized it in a thousand ways all equally ridiculous, and after having it well criticized, he pretends to be the first author of a theory which he did not only hear mentioned. He, however, knew that my manuscript could only appear after some seven or eight years, and he could only have knowledge about it in his capacity as member of the Academy, and in this respect my manuscript should have stayed sacred until it was made public. Dolus an virtus quis in hoste requirat!

The Latin quote is from Vergil's Aeneid: 'What matters whether by valour or by stratagem we overcome the enemy?' In passing we mention that Euler knew the Aeneid by heart.

It is true that d'Alembert made many unreasonable criticisms of Bernoulli's paper, but if Bernoulli had taken the effort to read the paper by d'Alembert, he would have found that d'Alembert produced an alternative solution to this problem which nowadays one would call a non-parametric approach in contrast to the parametric model of Bernoulli. Fig. 7 shows d'Alembert's model. His approach is quite general and is not restricted to an immunizing disease. Let $\mu_d(a)$ denote the force of death due to some disease d. The force of death due to other causes is denoted again by $\mu(a)$. Let $\phi_d(a)$ denote the rate at which deaths due to the particular cause are recorded for individuals who die at age a. Then

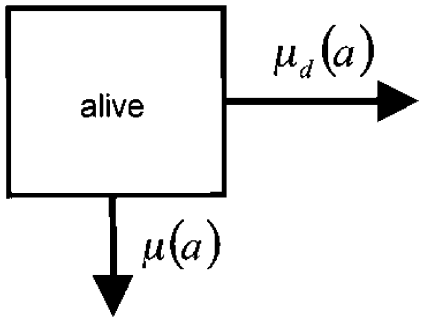

Fig. 7. D'Alembert's model. $\mu_d(a)$ denotes the death rate due to some disease d. The death rate due to other causes is denoted by $\mu(a)$. The two deaths rates are assumed to act independently.

$$\varphi_d(a) = \mu_d(a)l(a). \tag{33}$$

If one knows the survival function, one can calculate the force of mortality for that particular disease by dividing $\varphi_d(a)$ by $l(a)$. This allows us to find the survival function without the particular cause of death according to the following formula:

$$l_0(a) = \mathrm{e}^{-M(a)} = l(a)\exp\left(\int_0^a \mu_d(\tau)\,\mathrm{d}\tau\right). \tag{34}$$

Karn [34] used this method to calculate life tables after eliminating a wide variety of causes of death like cancer, tuberculosis and heart disease. If the only task is to calculate the survival function after eliminating a particular cause of death, then the method of d'Alembert is certainly more widely applicable than the method of Bernoulli being restricted to immunizing infections. The method of Bernoulli, on the other hand, provides much more insight for the interpretation of infectious disease data.

8. Estimation of age-dependence of the force of infection and the case fatality

It was already recognized by Bernoulli that his assumption of constant force of infection λ and case fatality c was not realistic but he had no data at hand to estimate these parameters as a function of age. In 1772, Lambert [20] tried to approach this problem by using data from The Hague which had been published for the years 1755–1769. In this period, 1455 smallpox deaths had been recorded and the age distribution is shown in Fig. 8. For the parameterization of Bernoulli, the age distribution of smallpox deaths is given by the equation

$$\varphi_d(a) = c(a)\lambda(a)\mathrm{e}^{-\Lambda(a)-M(a)}. \tag{35}$$

The age distribution of deaths due to other causes is given by

$$\varphi_g(a) = \mu(a)l(a). \tag{36}$$

Only data about deaths were available. One is therefore faced with the problem to estimate three age-dependent functions on the basis of two age-dependent functions, which is in principle

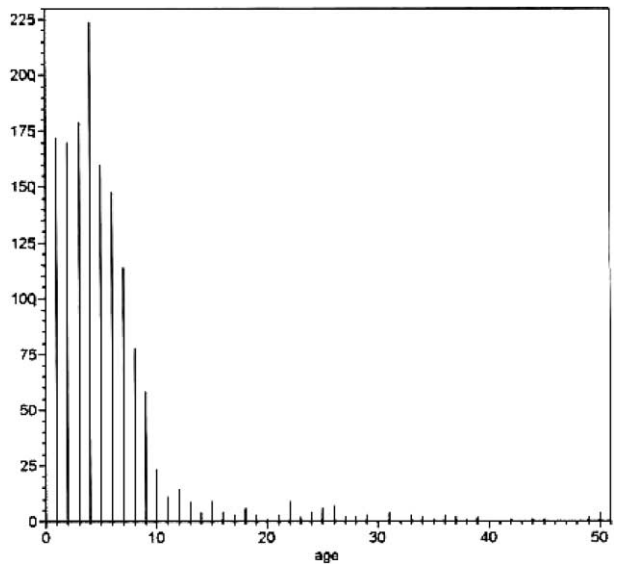

Fig. 8. Number of deaths due to smallpox in The Hague from 1755 to 1769 by age.

not possible without further assumptions. Lambert recognized this problem and made the arbitrary and unrealistic assumption that the shape of the force of infection equals the shape of the case fatality. Trembley [21] also used some iterative procedure for which he later excused himself: "... method is worth absolutely nothing and I owe some excuses to the public for having it presented to them" [22]. Duvillard [23] assumed that the force of infection is constant. Then he could estimate the case fatality and the general death rate. In order to estimate all three functions, one would need in addition to the age-distribution of smallpox deaths and general deaths also the age distribution of the infections, i.e.

$$\varphi_I(a) = \lambda(a)\mathrm{e}^{-\Lambda(a)-M(a)}. \tag{37}$$

Another possibility would be to observe directly the age specific case fatality by recording the probability of dying of all smallpox cases as a function of age. There were only scanty observations, some of which are quoted by Lambert. The following analysis is based on data from Verona. Rutten [35] gives a comprehensive survey of the available data about case fatality. He shows that there is great variability. Qualitatively the case fatality is U-shaped with a minimum around 15 years of age. Fig. 9 shows the observed and the fitted case fatality. The fit is obtained by a combination of exponential functions. If one takes this case fatality, one can estimate the force of infection for the smallpox data from The Hague, see Fig. 10. Here it becomes obvious that there is a strong age-dependence of the force of infection with a peak around 7 years. There is an inverse relationship between the mean case fatality and the prevalence of immunes for high age as has been explored by Rutten. He points out that two statements in the literature about smallpox in the 18th century are not consistent: on the one hand 'smallpox is a highly fatal infection', on the other hand 'sooner or later everybody gets the infection'. As Fig. 11 shows, either the infection has a low case fatality and a high maximum prevalence, or vice versa.

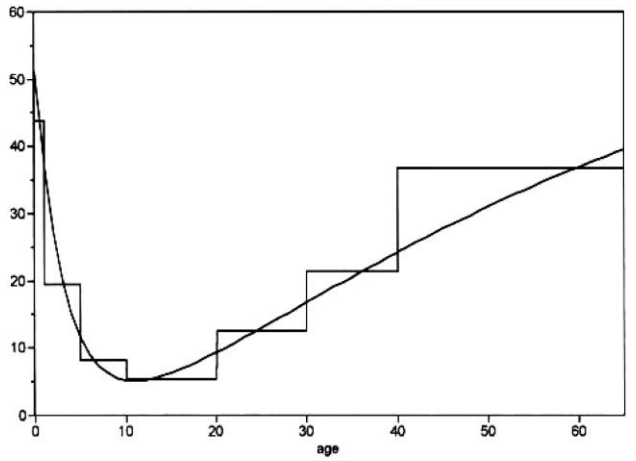

Fig. 9. Observed and fitted age-specific case fatality with respect to smallpox in Verona as quoted by Rutten [35]. The fitted function has the formula $0.51\exp(-0.31a) + 0.63(1 - \exp(-0.024a))^2$.

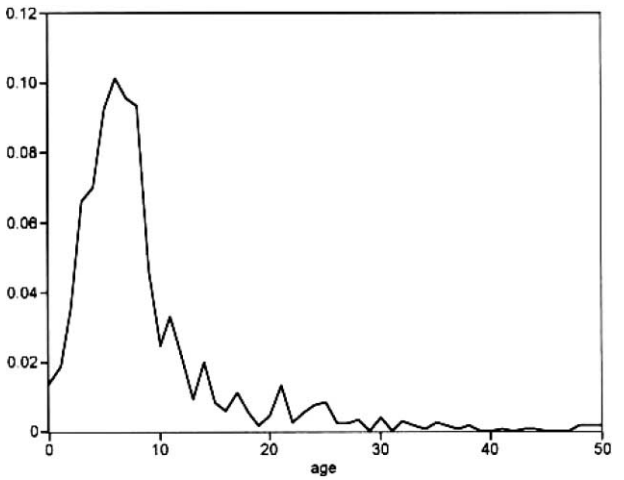

Fig. 10. Calculated age-specific force of infection for the smallpox data from The Hague.

9. The endemic prevalence of susceptibles

In April 1765, Bernoulli made some additions to his manuscript in which he responded to the criticism by d'Alembert. On p. 21, he adds the following paragraph:

"This Memoir having given a celebrated Academician the opportunity to formulate this question: 'Of all the people actually alive, how many are there who have not had smallpox?', his reasoning has led him to the following conclusion, that this number 'is at the very most a quarter of the total of living people'. Here is the solution of this question, according to my principles.

Let N be the total number of people alive, a the number who die each year, x the required number who have not had smallpox. Then $a/13 = x/64$, and $x = 64a/13$.

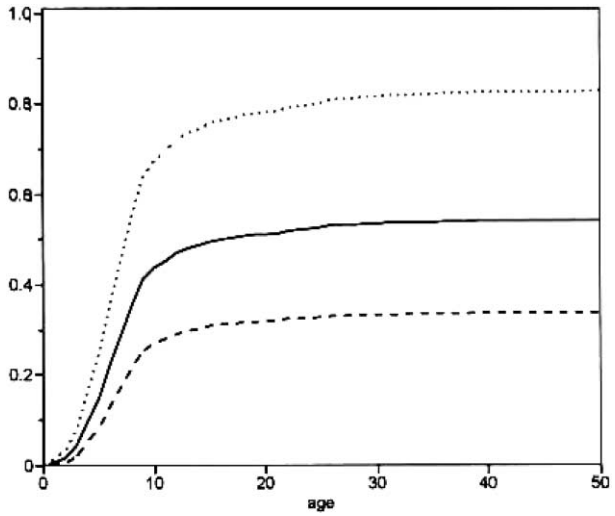

Fig. 11. Age-specific prevalence of immunes for the force of infection shown in Fig. 10 (continuous line) and a force of infection which is obtained when the case fatality is multiplied by a factor 1.5 (broken line) and by a factor 0.66 (dotted line).

If we write $N/a = g$, we have $x = (64/13)(N/g)$, and if we assume $g = 32$, this will be $2N/13$, and about 107,000 for Paris, assuming the number of inhabitants to be 700,000.''

If one replaces the numerical values in this paragraph by their symbols, one obtains Eq. (24) where p_I is replaced according to Eq. (28). Bernoulli's g is our L, the factor 64 is $1/(\bar{\lambda}\bar{c})$ and $1/13$ is p_D. This means that Bernoulli has already derived a very general formula for the endemic prevalence of susceptibles in an endemic situation, which is valid for arbitrary survival functions and for differential death. This formula involves the life expectancy at birth and the force of infection. This remarkable finding has been announced by us recently [36]. (See also the contribution to the discussion by Dietz to the stimulating paper by Farrington et al. [37].) In chronological order, Eq. (24) was derived by us independently of Bernoulli's paper. Only when this equation was known to us did we understand the cryptic wording of Bernoulli's insert.

In 1975, Dietz [38] had made the very special assumption that the general death rate μ is independent of age and that there is no differential mortality. Then Eq. (24) yields

$$\bar{x} = \frac{1}{\lambda}\frac{\lambda}{\lambda+\mu}\frac{1}{1/\mu} = \frac{\mu}{\lambda+\mu}. \tag{38}$$

The inverse of λ can be interpreted as the average age at infection in a cohort conditioned on survival. If A denotes the inverse of λ, then the inverse of the endemic prevalence of susceptibles is given by

$$\bar{x}^{-1} = 1 + L/A. \tag{39}$$

In a homogeneously mixing population, for which λ is constant, the inverse of the endemic prevalence of susceptibles equals the basic reproduction number R_0 of an infection, i.e. the number of secondary cases which one infectious case could generate in a completely susceptible population. It is very remarkable that Bernoulli already derived an expression for the endemic prevalence

of susceptibles, which basically involves the ratio of the time spent in the susceptible state and the duration of total life. He used Paris as an example for which he assumed a life expectancy at birth of 32 years. This is higher than the 26 years and 7 months for Breslau in the 17th century. On the basis of his other numerical estimates, he obtained an endemic prevalence of susceptibles of around 15% which corresponds to a basic reproduction number of 6.67. Recently Gani and Leach [39] quote our paper in the context of their attempts to estimate R_0 for smallpox if it would recur.

One can express the expected time spent in the susceptible state L_u in terms of the mean age at infection for those who get infected and the mean of those who die without getting the infection.

$$L_u = p_I \bar{A}_\lambda + (1 - p_I)\bar{A}_\mu, \tag{40}$$

where

$$\bar{A}_\lambda = \frac{\int_0^\infty a\lambda(a)\mathrm{e}^{-\Lambda(a)-M(a)}\,\mathrm{d}a}{\int_0^\infty \lambda(a)\mathrm{e}^{-\Lambda(a)-M(a)}\,\mathrm{d}a} \tag{41}$$

and

$$\bar{A}_\mu = \frac{\int_0^\infty a\mu(a)\mathrm{e}^{-\Lambda(a)-M(a)}\,\mathrm{d}a}{\int_0^\infty \mu(a)\mathrm{e}^{-\Lambda(a)-M(a)}\,\mathrm{d}a}. \tag{42}$$

For infections where the lifetime risk is nearly 100%, formula (24) reduces to

$$\bar{x} \approx \frac{\bar{A}_\lambda}{L}, \tag{43}$$

i.e. the endemic prevalence of susceptibles is approximately equal to the ratio of the average age at infection divided by the life expectancy at birth. The correct formula, however, involves the lifetime risk and the average age of those that die before acquiring the infection. For Halley's table and the case fatality of Verona we get $L_u = 5.34$ years. The lifetime risk p_I is 0.668. $\bar{A}_\lambda$ equals 6.86 years and $\bar{A}_\mu$ equals 2.28 years. According to formula (22) we get 38.8 years as the life expectancy at the age of infection.

Using (23), (25) and (40) one arrives at a very simple formula for the basic reproduction number for a homogeneously mixing population, which is given by

$$R_0 = 1 + \frac{(1-\bar{c})L_w}{\bar{A}_\lambda + \left(\frac{1}{p_I} - 1\right)\bar{A}_\mu} = 1 + \bar{\lambda}(1-\bar{c})L_w. \tag{44}$$

10. Implication for partial vaccination coverage

Bernoulli calculated the life expectancy at birth assuming that smallpox was completely eliminated. One motivation for his contribution was to convince the public about the benefit of this method if everybody would participate. We now know that partial coverage of protection has an influence on the force of infection for those who are not immunized. Assuming a constant force of infection and a case fatality as in Fig. 9, we study the life expectancy at birth for the unvaccinated and the life expectancy at birth for the total population as a function of those that are protected.

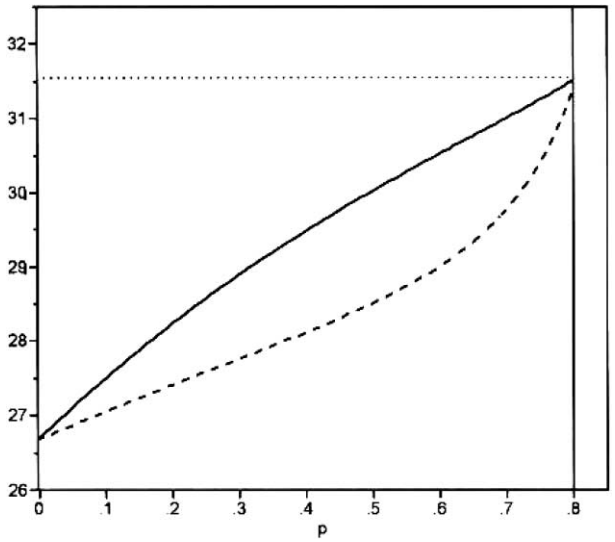

Fig. 12. Life expectancy at birth as a function of the proportion immunized p. The dotted line refers to those that are immunized, the broken line correponds to the non-immunized individuals and the continuous line represents the weighted average of the two values where the weight is given by p.

The model assumes that the inoculation is 100% effective and it neglects the risk of spreading the infection from those inoculated to susceptibles. Assuming that inoculation is given at birth, one obtains the life expectancies at birth as a function of coverage as shown in Fig. 12. When the coverage reaches about 80%, then the infection can no longer stay endemic.

11. Concluding remarks

The present paper puts the classical Bernoulli model for competing risks in a new perspective and shows that it provides insights, which so far have not yet been fully explored more than 200 years after its publication. (For a recent statistical book on competing risks see Crowder [40].) We consider it most important that most of the formulas for the equilibrium state involve the lifetime risk of the infection, i.e. involve a quantity which so far has been completely ignored in infectious disease epidemiology. The reason for this may be that in models without case fatality and constant general death rate, the equilibrium prevalence of immunes equals the lifetime risk. As this paper shows, however, that is not true in general. Depending on the life table and the case fatality, the lifetime risk can be greater or smaller than the prevalence of immunes. For the assessment of the public health importance of an infection it appears immediately obvious that one would need to know the proportion of a cohort which will get infected throughout life. Cross-sectional surveys for the prevalence of immunity can only give surrogate information. We find it remarkable that the Bernoulli model contains relationships between measurable quantities, which are still worthwhile to be explored and applied to present day infections.

The basic underlying assumption is stationarity. The sensitivity of the conclusions with respect to non-stationarity needs to be explored. This applies both to the demographic parameters and

the epidemiological parameters. With respect to demography, the model assumes a constant birth rate, which equals N/L, where N is the size of the population. It also assumes that the death rates due to other diseases stay constant over time. It is still debated to what extent the great reduction of smallpox as a cause of death in the 19th century contributed to population growth. The case fatality of smallpox always showed large variability with respect to time and age some of which may be due to the relative importance of variola major (high case fatality). The assumption of a time-independent force of infection is particularly problematic in view of the great seasonal variations, which have been observed in cities with endemic smallpox. In smaller populations below the critical community size the present model is obviously not applicable due to isolated outbreaks several years apart.

The present paper derives new estimating equations for Bernoulli's model, which facilitate sensitivity analyses with respect to the model parameters. The infection for which the model was constructed has been eradicated. This does not mean, however, that the model is no longer applicable. Many viruses, which cause potentially fatal infections and permanent immunity in survivors are still transmitted, especially in developing countries. Measles is among them.

Finally we would like to point out the key assumption in Bernoulli's model: the independence of the risk of dying due to the specific infection and the risk of dying due to other diseases. There is recent evidence that this assumption needs modification, and further studies are urgently needed [41].

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