Rev. Med. Virol. 2004; 14: 275–288.
Published online in Wiley InterScience (www.interscience.wiley.com).
Reviews in Medical Virology
DOI: 10.1002/rmv.443

CLASSIC PAPER

An attempt at a new analysis of the mortality caused by smallpox and of the advantages of inoculation to prevent it†

Daniel Bernoulli

Reviewed by Sally Blower*
AIDS Institute and Department of Biomathematics, David Geffen School of Medicine at UCLA, 1100 Glendon Avenue, PH2, Los Angeles, CA 90024, USA

Accepted: 15 May 2004

'I simply wish that, in a matter which so closely concerns the wellbeing of the human race, no decision shall be made without all the knowledge which a little analysis and calculation can provide'
Daniel Bernoulli 1760.

INTRODUCTION

Should the general population be vaccinated against smallpox (*Variola Major*)? Would the benefits of mass vaccination outweigh the risks? How many deaths would occur as the result of a mass vaccination campaign against smallpox? Can mathematical models of smallpox vaccination be used to determine health policy? Although smallpox was declared eradicated by the World Health Organization in 1979, these questions have all been recently debated based upon the premise that smallpox may be used as a weapon of bioterrorism. Hence, a series of analyses has recently been published that use mathematical models to try to determine the most effective public health response in the event of such an attack [1–4]. However, these same controversial public health questions were debated in the 18th century when smallpox was endemic and *Reviews in Medical Virology* has published two classic papers describing the natural history of smallpox in 1902 and 1913 to help inform these discussions [5,6]. We now publish an even earlier paper.

In 1760 Daniel Bernoulli (1700–1782), one of the greatest scientists of the 18th century, wrote a mathematical analysis of the problem in order to try to influence public health policy by encouraging the universal inoculation against smallpox; his analysis was first presented at the Royal Academy of Sciences in Paris in 1760 and later published in 1766 [7]. Here, we republish and discuss both the historical and the current significance of Bernoulli's classic paper. A detailed discussion of the mathematics of Bernoulli's analysis has previously been presented by Dietz and Heesterbeck [8].

According to Creighton [9] smallpox first appeared in England in the 16th century. Smallpox was known in Western Europe in medieval times, but a particularly virulent strain emerged in the early 17th century and gradually the case fatality rate increased [10]. By the 18th century smallpox was endemic. Bernoulli calculated that approximately three quarters of all living people (in the 18th century) had been infected with smallpox [7]. One-tenth of all mortality at that time was due to smallpox, although there was considerable annual variation in smallpox mortality due to epidemic outbreaks overlaying the endemic smallpox mortality rate. For example, in London during the period 1761–1796 the annual number of deaths due to smallpox varied from 3000 to 15 000. Where smallpox was endemic it was almost wholly a disease of childhood, with a case-fatality rate of 20%–30%; the mean age of death due to smallpox has been estimated as 2.6 years [10] or 4.5 years [11].

*Corresponding author: Dr S. Blower, AIDS Institute and Department of Biomathematics, David Geffen School of Medicine at UCLA, 1100 Glendon Avenue, PH2, Los Angeles, CA 90024, USA. E-mail: sblower@mednet.ucla.edu

†Reproduced from a translation of Mem Math Phy Acad Roy Sci Paris 1766, published by Adult Education Department, Nottingham, 1971.

Almost all adults were immune to smallpox as they had been infected as children and had either died or survived and developed immunity. China and India began the practice of transferring infectious material from a smallpox pustule to an uninfected individual in order to induce a mild infection (sometimes called 'artificial smallpox') that would then be followed by lifelong immunity; this practice was called variolation. In 1721 variolation was introduced into England. The practice of variolation generated heated debates as 'artificial smallpox' was sometimes fatal; Bernoulli decided that the best way to evaluate the public health consequences of variolation was to use mathematical reasoning [7]. Over time the controversy was resolved and inoculation became widespread in England; by the end of the 19th century smallpox was no longer endemic in England.

The main purpose of Bernoulli's analyses was to encourage universal inoculation against smallpox. He argued his case by calculating the gain in life expectancy that would be achieved if smallpox were eradicated. To calculate this gain he assumed that: (i) the risk of catching smallpox (given that the individual has never had smallpox) was the same at any age (and was 1 in 8), and (ii) the case fatality rate of smallpox was independent of age (and was 12.5%). He derived an equation (for any year of age) for calculating the number of people who had never had smallpox as a fraction of the people currently alive. He then used a second equation to calculate how many lives would be saved if smallpox were completely eliminated. The central part of Bernoulli's analysis is summarised in the form of two tables that show the number of individuals that survive each year (up to the age of 25), beginning with a cohort of 1300 newborns, with and without smallpox mortality [7]. Bernoulli used a Life Table drawn up by Edmund Halley (the astronomer who named the famous comet) as the basis for expected survivorship (i.e. the expected survival curve including smallpox mortality), and he then used these numbers in conjunction with his equations to derive the expected number of infections and deaths due to smallpox each year (Table 1). Thus, he was able to calculate (see Table 2) the expected number of individuals surviving each year if smallpox was eradicated. The benefits in eliminating smallpox could be viewed either as the increase in the number of survivors per year or as the increase in average life expectancy. Only 565 out of 1300 newborns reached the age of 25 in the 18th century when smallpox was endemic (Table 1); Bernoulli's calculations revealed that 644 individuals (out of 1300) would survive to age 25 if smallpox was eliminated (Table 2). His calculations also showed that universal inoculation against smallpox would increase expectation of life at birth from 26 years 7 months to 29 years 9 months. As Bernoulli said 'Here are two ways of looking at the same thing, but the first will interest many more people than the second, because in the first we bestow the advantage directly and entirely on those who are saved, whilst in the other we distribute the same benefit over the whole generation' [7].

D. BERNOULLI

Originally printed in *Mem Math Phy Acad Roy Sci Paris* 1766. Translated as 'An attempt at a new analysis of the mortality caused by smallpox and of the advantages of inoculation to prevent it.' In *Smallpox Inoculation: An Eighteenth Century Mathematical Controversy*, Bradley L. Adult Education Department, Nottingham, 1971, 21.

Reprinted

In the interests of brevity, paragraphs 8–10 and 15–21 have not been reprinted here.

*Paragraph 1**

It is established by a long serious of observations that smallpox carries off a thirteenth or a fourteenth part of every generation. I have seen lists which show a fourteenth; I have seen others, from Breslau, which extend to a thirteenth; some go a little further than that. Moreover, we know that this disease carries off about an eighth or a seventh of those whom it attacks, provided that we take the ratio over a large number of epidemics. These epidemics differ so much that some carry off over a third of those attacked, whilst others impose this fatal tribute on only 1 in 20, 30, 40 or even more. Hence it appears to me entirely natural to say that smallpox mortality depends less on the constitution of those whom it attacks than on the more or less malignant nature of the cause which produces it, and which is common to a whole region. We may presume that smallpox would rarely be fatal if the epidemic cause had not made it so. This simple consideration itself creates a presumption which is

*This appears to be the beginning of the original Memoir. In the margin at the right hand side of the page are the words 'Commence de lire le 30 Avril 1760'.—L.B.

Table 1

Age in years	Survivors according to M. Halley	Not having had smallpox	Having had smallpox	Catching smallpox each year	Dying of smallpox each year	Total smallpox deaths	Deaths from other diseases each year
0	1,300	1,300	0				
1	1,000	896	104	137	17.1	17.1	283
2	855	685	170	99	12.4	29.5	133
3	798	571	227	78	9.7	39.2	47
4	760	485	275	66	8.3	47.5	30
5	732	416	316	56	7.0	54.5	21
6	710	359	351	48	6.0	60.5	16
7	692	311	381	42	5.2	65.7	12.8
8	680	272	408	36	4.5	70.2	7.5
9	670	237	433	32	4.0	74.2	6
10	661	208	453	28	3.5	77.7	5.5
11	653	182	471	24.4	3.0	80.7	5
12	646	160	486	21.4	2.7	83.4	4.3
13	640	140	500	18.7	2.3	85.7	3.7
14	634	123	511	16.6	2.1	87.8	3.9
15	628	108	520	14.4	1.8	89.6	4.2
16	622	94	528	12.6	1.6	91.2	4.4
17	616	83	533	11.0	1.4	92.6	4.6
18	610	72	538	9.7	1.2	93.8	4.8
19	604	63	541	8.4	1.0	94.8	5
20	598	56	542	7.4	0.9	95.7	5.1
21	592	48.5	543	6.5	0.8	96.5	5.2
22	586	42.5	543	5.6	0.7	97.2	5.3
23	579	37	542	5.0	0.6	97.8	6.4
24	572	32.4	540	4.4	0.5	98.3	6.5

very favourable to inoculation, since, in carrying this out, we are in a position to choose the time of a very mild epidemic, and, to my mind, the mildest epidemic is that which shows no activity at all. I consider that to be the whole interval between two obvious epidemics. Moreover it has been noticed that, on the one hand, the more natural smallpox spreads, the more dangerous it is; and, on the other, that inoculation carried out at the height of an epidemic is not by any means as reliable as if it were done quite outside any epidemic. I do not deny, for all that, that some small part of the danger of smallpox may originate in a certain disposition on the part of the patient, but the fact must be that by inoculation we avert this remaining danger, provided that we take all the measures which long experience has dictated, since, with these measures, all those inoculated recover, or nearly all. This is a phenomenon which I have no intention of explaining, but, for the wellbeing of mankind, it is sad that its truth is still contested. In this Memoir, my intention is simply to make a comparison between the condition of mankind as it is without inoculation and what it would be if this salutory operation were either generally admitted or simply followed with certain rules. It is still true that we lack adequat information to answer this question precisely, but it seemed to me that we have enough information to throw some new light on a subject whose great importance we are beginning to realise.

Paragraph 2

I said to begin with that natural smallpox carries off an eighth or a seventh of those who contract it. In England, the latter ratio is fairly commonly adopted. In other countries it would not

Table 2

Ages by years	Natural state with smallpox	State without smallpox	Difference or gain
0	1,300	1.300	0
1	1,000	1,017.1	17.1
2	855	881.8	26.8
3	798	833.3	35.3
4	760	802.0	42.0
5	732	779.8	47.8
6	710	762.8	52.8
7	692	749.1	57.2
8	680	740.9	60.9
9	670	734.4	64.4
10	661	728.4	67.4
11	653	722.9	69.9
12	646	718.2	72.2
13	640	741.1*	74.1
14	634	709.7	75.7
15	628	705.0	77.0
16	622	700.1	78.1
17	616	695.0	79.0
18	610	689.6	79.6
19	604	684.0	80.0
20	598	678.2	80.2
21	592	672.3	80.3
22	586	666.3	80.3
23	579	659.0	80.0
24	572	651.7	79.7
25	565	644.3	79.3

This Table enables us to see at a glance how many out of 1,300 children; supposed born at the same time, would remain alive from year to year up to the age of twentyfive, supposing them liable to smallpox; and how many would remain if they were all free from this disease; with the comparison and the difference of the two states.
*This figure should be 714.1—L.B.

appear that the mortality of the disease is so great. Actually, here at Bâle, it has been epidemic for nine months, and the doctors tell me that it is very widespread and pretty malignant. However, if I can rely on the evidence of one of our most reputable doctors, scarcely one in twenty has died of it. I notice that whatever method we use to determine the average ratio, we can always advance wellfounded arguments for slightly reducing the mortality out of the total number who are attacked. As for the ratio between smallpox mortality and the total mortality of mankind, in England it is generally assumed to be one in fourteen. There are lists reported by M. Susmilch which show that, in London, 19 745 died of smallpox out of 260 875, which gives a ratio of 1 to $13\frac{1}{5}$; in Vienna this disease carried off 1083 out of 13 521, that is 1 in $12\frac{1}{2}$; in Berlin, 586 out of 6771, that is 1 in $11\frac{1}{2}$. in Breslau, 431 out of 4578 that is 1 in $10\frac{1}{2}$. But these last ratios have only been taken for two or three years, during which there may have been a rather serious epidemic. Besides these specific instances we have several others, but they are more vague and less definite. If we knew exactly all the average ratios, which could have been determined from a large number of carefully considered and well thought out observations, we could give a complete theory of the risks of smallpox. Such a theory would dictate the rules which every reasonable man should follow. Here, then, are two elements which we still only know very superficially, and which it would be important to know very precisely.

Paragraph 3

The first of these elements is the risk which one runs every year of catching smallpox, if one has not already had it. The second is the risk, for the various ages, of dying of it when one has caught it. Using our knowledge of these two, we would be in a position to make a pretty exact comparison between the two above-mentioned conditions of mankind, the one natural and the other free from the destruction caused by smallpox. The second of the two elements would be quite easy to determine if doctors would keep a register of their smallpox patients in which they noted the age of each patient and those who died of it. From a large number of such registers, the results of which would be communicated to the Dean of the Faculty, we would deduce exactly, for each age at which smallpox was contracted, the risk of dying of it. An expert would draw several other useful consequences from them, even about our first element, which is not so easy to determine. In this uncertainty, only one method remains, that is to make the most probable hypotheses about these two elements. Here are the ones which I have chosen.

(1) I shall assume that, independent of age, in a large number of persons who have not had smallpox, the disease annually attacks one person out of as many persons as there are units in the number n. According to this hypothesis, the danger of catching the disease would remain the same at every age of one's life, provided that one had not already had it. If, for example, we put $n = 10$, it would be the fate of every person to be decimated every year of his life in order to know whether he would have smallpox this year or not, right up to the moment when that fate actually befell him. This hypothesis seems to me to be very probable for all young people up to the age of sixteen to twenty years. If we see few people over that age who catch smallpox, it is because the great majority have already been infected by it. What follows will enable us to see what degree of probability this hypothesis merits.

(2) In the second place, I shall assume that, at whatever age one catches smallpox, the danger of dying of it is always the same and that out of a number of patients expressed by the number m, one dies of it. With regard to this assumption, I note that no doctor would take it into his head to suppose that, other things being equal, smallpox is more or less dangerous merely on account of the age at which it is caught, provided that this age does not exceed twenty. It is only above this age that we usually suppose that smallpox becomes a little more dangerous. We shall later have occasion to examine this hypothesis more closely.

Paragraph 4

As our intention is, above all, to disentangle smallpox mortality from the total mortality for each age, at least up to twenty, it is necessary first of all to know the total average mortality. We have no lack of mortality lists for different countries, in which it is indicated how many out of a given number of persons die at each year of age, right up to the death of the last of them; we regard this total number of persons as having been born at the same time. These lists usually have obvious inequalities, unless the numbers have been taken from a very large number of annual lists. They are shaped like a rough road which has to be levelled and smoothed; we add to some and subtract as much from others until we arrive at a uniform law within the variations. M. Susmilch quotes such a Table, constructed by M. Halley, in which no abrupt or formless variation can be seen. The Table which I shall set out later starts with 1000 children all at the same age of one complete year, but M. Halley does not state what number of new-born children the table assumes, 1 000 of whom are still alive at the end of a year. M. Susmilch takes it to be 1238, saying that this would be the average number of children born annually in Breslau, but all the other lists show that the mortality in the first year is greater than 238 out of 1238. See, for example, the Table inserted in the second volume of M.de Buffon's excellent *Histoire Naturelle*, page 590. There you will find that 6454 out of 23 994 new-born children died before the end of their first year, and according to this ratio we would have to start M. Halley's Table with 1368 instead of 1238. It would appear that M. Halley wished to start with a round number, simply observing the right proportions for each age. I shall choose somewhere between 1368 and 1238, and I shall assume that out of 1300 newborn children there are 1000 who reach the age of one complete year, after which I shall adopt M. Halley's Table just as it stands.

Paragraph 5

Let the present age, expressed in years, $= x$, the number of survivors at this age $= \xi$, the number of those who have not had smallpox at this age $= s$; and let us retain the meaning given above (Par. 3) to the letters n and m. Here is the reasoning which can be followed to find a general expression for s, which should be the main aim of these researches. I say, then, that the element $-\mathrm{d}s$ is equal to the number who catch smallpox in the period $\mathrm{d}x$, and according to our hypotheses this number is $\frac{s\mathrm{d}x}{n}$; for if, in the space of a year, 1 out of n catches smallpox, it follows that in a period $\mathrm{d}x$ there would be $\frac{s\mathrm{d}x}{n}$ who would catch the disease out of s persons. In this number $\frac{s\mathrm{d}x}{n}$ those who die of it would be included, but we must add those who die of other diseases in the same period dx and out of the same number s. The number who die of smallpox in the period dx is $\frac{s\mathrm{d}x}{mn}$, and consequently the total number who die of other diseases is $-\mathrm{d} - \frac{s\mathrm{d}x}{mn}$. But this last number should be decreased in the ratio ξ to s, since we are only concerned with the decrease in those who have not yet had smallpox, whose number is s. We thus have the equation

$$-\mathrm{d}s = \frac{s\mathrm{d}x}{n} - \frac{s\mathrm{d}\xi}{\xi} - \frac{ss\mathrm{d}x}{mn\xi}$$

In this equation, the elements ds and dξ are intrinsically negative, since the numbers s and ξ are decreasing, which is why we have to add the negative sign, but the sign of the last term is negative because a real subtraction has had to be made. It will be seen that by $1/n$ and $1/m$ I really mean the degree of the risk of catching smallpox, for those who have not yet had it, and of dying of it when attacked, assuming that those who have once had it are in no danger of catching it again. If there are some cases of people catching the disease on two separate occasions, they are so rare as not to merit attention. It is very remarkable that our differential equation admits of integration, though indefinite terms are involved, and there are three of them, a situation which is rare in problems which investigate the state of Nature and which differ so greatly from abstract problems. Here are the steps which lead to the integration.

We have

$$\frac{s\mathrm{d}\xi}{\xi} - \mathrm{d}s = \frac{s\mathrm{d}x}{n} - \frac{ss\mathrm{d}x}{mn\xi}$$

This, multiplied by $\frac{\xi}{ss}$, gives

$$\frac{s\mathrm{d}\xi - \xi\mathrm{d}s}{ss} = \frac{\xi\mathrm{d}x}{ns} - \frac{\mathrm{d}x}{mn}$$

If we put $\frac{\xi}{s} = q$, we have

$$\mathrm{d}q = \frac{q\mathrm{d}x}{n} - \frac{\mathrm{d}x}{mn}$$

or $mn\mathrm{d}q = mq\mathrm{d}x - \mathrm{d}x$, which gives

$$\frac{mn\mathrm{d}g}{mq-1} = \mathrm{d}x$$

whose integral is n log $(mq-1) = x + C$, where C is the required constant. If we replace q by ξ/s we have n log $(\frac{m\xi}{s} - 1) = x + C$. If we denote by e the number whose hyperbolic logarithm is unity (that is, 2718) we have, from the last equation,

$$\left(\frac{m\xi}{s} - 1\right)^n = e^{x+C}$$

and hence finally

$$s = \frac{m}{e^{\frac{x+C}{n}} + 1}\xi$$

Paragraph 6

Here, then, is the value of s, determined by quantities all of which I treat as known. But before dealing with the application of this equation, I shall make some comments on the constant C as well as on the choice of the values of m and n. As for the constant C, the most natural way to determine it is to say that at the beginning of each generation, when $x=0$, we should have $s = \xi$, each letter then expressing the number of newborn children involved. This consideration gives $e^{\frac{C}{n}} = m - 1$ and consequently

$$s = \frac{m}{(m-1)e^{\frac{x}{n}} + 1}\xi$$

I shall adhere to this equation, though it may be possible, according to the majority of doctors, that some children may have smallpox before birth. If we wished to have regard to this consideration, it would be necessary to make a small change in the constant and our theory could only be improved thereby, a point which I wished to have noted in advance. Such children would have to be thought of as born with a disposition never to catch smallpox, and it would appear that those who have submitted to inoculation without thereby catching the disease should, for the most part, be placed in this class.

As for the values of the numbers n and m, I am content to assume that they remain constant, at any rate up to the age of about twenty; but we are still free to choose their absolute values, which is why we must try to choose such as best fit the information which we have about the nature of smallpox, relative to each climate. It is easily seen that the more we increase the number n, the less we load childhood and youth, and vice versa. If we took a very large number for n, almost everyone would die before catching smallpox for, taking n to be infinitely large, we have $s = \xi$. If, on the contrary, we assume n to be a very small number, all children, or almost all, would be affected in their infancy. It seems that in Paris there are more people well on in years who are subject to the disease than there are in Bâle, where smallpox, in eight or nine months, has attacked more than 600 persons, of whom the oldest whom I have heard named would not have completed 23 years. If this conjecture is justified, we would have to take n bigger for Paris than for Bâle. After some thought, I have decided to calculate the number who would probably not have had smallpox, for each age, by taking $n=8$. Finally, I shall similarly assume $m=8$, that is to say, that smallpox carries off one in eight of those whom it attacks. These assumptions finally give the equation

$$s = \frac{8}{7e^{\frac{x}{8}} + 1}\xi$$

Paragraph 7

This last equation, which is simply numerical, puts us in a position to calculate the value of s for each age, which has led me to construct the Table at the end of this Memoir. Here is the explanation of it:

> The *first* column shows the ages by completed years, which I have denoted by x, starting with 0 which corresponds to the day of birth.
>
> The *second* column shows the number still alive at each age out of the total of 1300, whom I take as all born on the same day. This column is based on M. Halley's Table. These numbers are denoted by the variable ξ.
>
> The *third* column is based on the final equation of the previous paragraph, so that it gives, for each age, the number who, according to my hypothesis, have not yet had smallpox.
>
> The *fourth* column, on the other hand, gives the number who have already had smallpox and have recovered from it, and have not died of any other diseases. They are expressed by $\xi - s$.
>
> The *fifth* column shows the number who will probably have caught smallpox during the previous year. This is, according to my hypothesis, one eighth of all those who have not yet had it, or $s/8$; but, for greater exactitude, I shall here take for s not the value which we have found for the beginning of each year, but for the middle of the preceding year; that is to say, I shall take the arithmetic mean between the two numbers of the third column which follow each other. Thus the first number of this fifth column shows how many new-born children will have caught smallpox during their first year of life.
>
> The *sixth* column shows the number who die of smallpox during the year which we have described. Thus, according to my hypothesis, all these numbers are one eighth of the corresponding numbers of the fifth column.
>
> The *seventh* column shows the sum of all who have died of smallpox from birth up to each completed year of life.
>
> The *eighth* column shows the number whom all other diseases, apart from smallpox, carry off during each current year. Thus, each number of this column is the difference between the total deaths of the past year, which we know from the second column, and those who have died of smallpox during the same past year.

When these numbers are too small for fractions to be neglected, I shall add a decimal figure. For the rest, I shall not extend this Table beyond 24 years, since the effect of smallpox cannot be considerable after this age, relative to the whole of mankind. Moreover, the principles which we have employed will thus be more certain. I shall content myself, then, with indicating the small remaining mortality which smallpox could probably still cause.

Paragraph 11

A great deal of trouble has been taken to evaluate the gain which could be hoped for from inoculation if it were generally introduced, and the advantage to each individual who was inoculated. It is, in general, clear that this profit and this advantage could not fail to be considerable and infinitely precious, but what sort of units could we use to measure it? By the average life which could be expected after inoculation? Are all the years of life equally valuable? However that may be, I maintain that the matter is indeterminate so long as we are ignorant of the effect of smallpox on each year throughout the whole duration of a generation and its ratio to the effect of all the other diseases. If this knowledge is lacking, recourse is had to estimates, most often deceptive, and to several kinds of quantities, called averages, which can often be badly applied. I have decided, therefore, that the only course to take is to determine, for the same generation of 1300 newborn children, what would be the number of survivors at the end of each year if the whole of this generation were rid of smallpox or, which comes to the same thing, if nobody died of it. Given such a determination, it will be sufficient to compare the results with the second column of our Table in order to see at a glance the relation between these two modes of life. It will then be easy to go further and to reply to several other very interesting questions which can be asked about this subject. Here, then, is the way in which we can procede to prepare this new list, contenting ourselves with examining the situation year by year; as, indeed, we are obliged to do, since we have no six-monthly mortality lists which we could use with greater accuracy. The sixth column shows that smallpox carried off 17 children during the first year of life; so that, without the disease, there would be 1017 instead of 1000 (Col. 2) who would reach the age of one year. Then we must consider that if 133 (Col. 8) die during the second year out of 1000 alive at the beginning of it, 135.3 will die out of 1017, so that 881.7 will remain alive and will reach the third year. In general, we will continue the list of the numbers which we are determining if we reduce the last number determined by $\frac{p}{q}r$, taking for q the successive numbers of the second column of the first Table, for r those of the eighth column and for p the preceding term of the new list, since the number who die each year of all diseases except smallpox is undoubtedly proportional to the number who live to this age, whatever be the proportion between those who have already had smallpox and those who have not yet had it. So we see in the Table which follows that there are 855 who reach the third year in the natural state, in which smallpox does occur, and that there would be 881.7 in the state in which there was no smallpox. The preceding Table shows, too, that during the course of the third year all diseases except smallpox carry off 47. We have to say, then, if 47 die out of 855, how many will die out of 881.7; we find that it is 48.4 which we have to subtract from 881.7 to find the next number, which is therefore 833.3. In this way, I have constructed the second Table at the end of this Memoir, in which the first two columns are the same as in the first Table, though I have given the second column another name, 'natural state with smallpox', in contradistinction to the third column, which shows the 'state without smallpox' and which gives the number of survivors each year assuming that nobody must die of smallpox. I add a column which shows the difference between the two states.

Paragraph 12

The Table which I have just explained throws, at a glance, a great light on the problems which we usually pose in order to determine the havoc which smallpox inflicts on the human race, its terrible effect on the propagation and conservation of the species and the gain which mankind would achieve if it could be rid of this source of destruction. Although I shall use expressions like this, I hope that I shall not irritate those who declare themselves against inoculation. Here, then, are the corollories which I deduce from the second Table which seem to me to be of the greatest importance.

(a) The *absolute* gain, shown in the fourth column, increases perceptibly at first, but the increments in the gain diminish. The biggest absolute gain corresponds to the age of twenty to twentytwo. At this age, the number of survivors for the state supposed exempt from smallpox exceeds the number of survivors for the natural state with smallpox by 80.3, the total number of births being taken to be 1300. After this age, the numbers expressing the gain diminish; it would be easy to foresee that this would happen, since in extreme old age the number of survivors must be extremely small for both states.

(b) The true estimate of the gain should be made by the ratio of the gain to the corresponding number of survivors in the natural state. We can, in this sense, call it the *relative* gain. At the age of five complete years, the natural state provides only 732 living persons, and the other provides 47.8 more, which is about a fifteenth. At the age of ten, there are 661 alive in the natural state and 67.4 more in the state without smallpox, that is more than a tenth of the number who remain alive naturally at the age of ten complete years. At the age of fifteen, the relative gain is 77 to 628 which this age shows as living in the natural state. This ratio of 77 to 628 is approximately 1 to 8, so that the relative gain at the age of fifteen is approximately one eighth.

(c) We see, too, that the relative gain should increase right up to the death of the last survivor of the 1300 children supposed born on the same day, assuming that one remains exposed to catching smallpox for so long as one has not had it; since, for a large even number, there will always be more who die amongst those who have not had smallpox than amongst those who have already had it, all other ratios being kept the same. This, too, our Table shows, for although the absolute gain begins to diminish at the age of twenty-two the relative gains do not cease to increase. We have seen that the relative gain at the age of fifteen is about one eighth. At the age of twenty it is 80.2 against 598, which is about 1 to $7\frac{1}{2}$. Finally, at the age of twenty-five, the gain is 79.3 against 565, giving a relative gain of about one seventh. We see, then, that it continually increases, but it will never go beyond one seventh, which is the ratio of those who die of smallpox, when attacked, to those who recover from it. Here is a pretty theorem which I shall subsequently demonstate, that the asymptotic ratio of the gain to the number living is, in general, 1 to $m-1$, and the ratio of those left alive in the natural state to those left alive in the state exempt from smallpox is $m-1$ to m. I have given m the value 8 because it seemed to me that this value corresponds best to the phenomena of smallpox. Others take $m=7$, and with this assumption the gain becomes greater, namely one sixth.

(d) As the ratio between the two states no longer changes appreciably for fully grown men, who are the only ones useful to the State, this ratio will be approximately 7 to 8. If Paris were to provide annually 7000 persons aged twenty, this capital would provide 8000 of them if there were no smallpox. Moreover, we see from the Table that, at the age of sixteen, the ratio between the two states is already 622 to 700. But this is the age at which one is beginning to be useful to the State, as much by the services which one can render to society as by propagating the human race. So we see that 'civil birth' would, without the destruction wrought by smallpox, increase in the ratio of 622 to 700. We can call the entry of a person into his seventeenth year 'civil birth'. I estimate that this 'civil birth' is 175 000 for the whole of France, and I say that, without the mortality caused by smallpox, it would be 200 000, so that France would gain 25 000 persons every year, all useful to the State and to society. This gain would even go much further after the first few years had elapsed. The absolute gain at the age of sixteen complete years is 78, which is almost one eighth of the civil birth, given in our Table as 622.

(e) In the natural state, or at any rate that which, according to M. Halley, is appropriate for the town of Breslau, a whole generation is diminished by one half at the age of 11 years 5 months, and in the other state this only happens at the age of 24 years 3 months. At $6\frac{1}{2}$ years there are no more alive in the first state than there are in the second at the age of sixteen. Similarly, the age of 9 years on the one hand and 21 on the other are equally fertile in the two states. Anyone who wishes to continue our Table can deduce other corollaries of the same kind, and the continuation of the Table can be done quite easily, without appreciable error. It is simply a matter of continuing the second column just as M. Halley has given it and then multiplying each number by 8/7 in order to get the corresponding numbers of the third column after the age of twenty-five.

(f) We can use the term 'total quantity of life' of the whole generation, for each of the two states, for the sum of all the numbers of the second column and of the third column respectively, assuming the two columns to be continued until the generation of 1300 children is completely extinguished. This rule will be more accurate if we take only half of the first number, namely 1300, since it is appropriate to assume that those who die in a certain year all die in the middle of it. If, then, we divide the 'total quantity of life' by the total number of newborn children, that is by 1300, we will have the 'quantity of life', or simply the average life of each newborn child. Using this correction, the sum of the numbers of the second column, including the age of twenty-five, is 17 353, and the sum of the other numbers of the second column from twenty-five years (exclusive) to the age of eightyfour (inclusive) is 17 187 according to M. Halley's Table. At this age of 84 complete years there would still be 20 living, whose quantity of life should be about 65 years more, so that the previous sum of 17 187 should be increased by 65, giving 17 252. Hence the total quantity of life in the natural state is $17\,353 + 17\,252$ or 34 605. Then, dividing by 1300, we have 26 years 7 months as the average life for each newborn child in the natural state. In the same way, we find the natural average life for children one year old to be 33 years 5 months, and for those two years old to be 38 years. These last two cases agree pretty well with M. de Buffon's Table at the end of his excellent *Histoire Naturelle*, Volume 2, though this Table was constructed from an entirely different mortality table; but the first average life, for newborn children, which I have found to be 26 years 7 or 8 months, differs enormously from that of 8 years given by this illustrious author. There must be a printing error; perhaps, instead of 8 years, it ought to be 26 years 8 months or 28 years.

If, in the same way, we add up all the numbers of the third column, after reducing the first number, 1300, by half, the sum will now be 18 990, which gives the total quantity of life as it would be if freed from smallpox, up to the age of twenty-five inclusive. To find the remainder of this total life up to the complete extinction, I shall use the number 17 252 corresponding to the natural state, and I shall multiply it by 8/7 [See (c) above]. I shall then have 19 716 as this remainder and consequently the total quantity of life in the state free from smallpox as $18\,990 + 19\,716$ or 38 706. So that the two total quantities of life for the two states are as 34 605 is to 38 706. The two average lives for the two states are in the same ratio. That for the state free from smallpox is 29 years 9 months, whilst that for the natural state is only 26 years 7 months. The gain is approximately 2/17 of the average natural life.

Paragraph 13

Let us now compare the two pictures which I have just displayed, which cannot fail to represent the two states reasonably fairly, and we shall assuredly be touched by the ravages which smallpox by itself wreaks on the human race. I leave it to others who are aware of the truths of mathematics and who at the same time are able to give it all their energy. Above all, I leave it to M. de la Condamine, if he finds these notes worthy of his attention, to apply them to inoculation. But it is to be hoped that the doctors, instead of thwarting him in his enthusiasm, which is as pious as it is enlightened, would wish to help him to perfect the method of inoculation instead of rejecting it without having, perhaps, adequately weighed up the importance of his objective. I said, in Note (c) of the preceding paragraph, that the numbers of the third column, relative to the corresponding numbers of the second column, tend to the ratio 8 to 7, or, more generally, to the ratio m to $m-1$; that is to say, to the ratio of the number attacked by smallpox to the number who recover from it. I admit that I was initially only led to this conclusion by a mere guess. I then immediately applied myself to trying to find out by calculation what this asymptotic ratio ought to be. I will demonstrate this calculation all the more willingly since it will provide us with a general expression for all the numbers of the third column right up to the complete extinction of the generation. This general expression could have served to give these numbers more accurately than we can do by the method of paragraph 11, which is only a kind of approximation.

If we again take the letters x, ξ s, m and n to have the same meanings which I gave to them in paragraph 5, and we take also the final equation of that paragraph, and if in addition we understand by ζ the numbers of the third column, then it will be a question of finding the ratio of ζ to ξ. Now, the total mortality during the element of time dx being $-d\xi$ and the smallpox mortality being $\frac{sdx}{mn}$, we have for the total mortality for the state free from smallpox $-d\xi - \frac{sdx}{mn}$. But this mortality is in respect of the number ξ it is necessary to multiply it by $\frac{\zeta}{\xi}$ to find the mortality in respect of the number ζ. Hence we have $-\frac{\zeta}{\xi}(d\xi + \frac{sdx}{mn}) = -d\zeta$ or $\frac{d\zeta}{\zeta} - \frac{d\xi}{\xi} = \frac{sdx}{mn\xi}$ Substitute for s the value given at the beginning of paragraph 6 and we have

$$\frac{d\zeta}{\zeta} - \frac{d\xi}{\xi} = \frac{\frac{1}{n}dx}{(m-1)e^{\frac{x}{n}} + 1}$$

The integral of this last equation, by the known rules, is

$$\frac{\zeta}{\xi} - \frac{me^{\frac{x}{n}}}{(m-1)e^{\frac{x}{n}} + 1}$$

This expression gives, in a general form, all the numbers of the third column without our having to go through all the preceeding ones, if we put $m = 8$ and $n = 8$; it gives them more accurately, but they do not differ appreciably from those shown in the Table, especially towards the end. It shows us at a glance the nature of the variations, and above all that if we take a fairly big number for x, which represents the age, the ratio of ζ to ξ must be extremely close to m to $m - 1$ or, on our hypothesis, 8 to 7, but without ever exactly reaching it. Let us see, by taking one or two examples, how far our general expression agrees with the numbers of the third column which we determined only by an approximation, passing in succession from one year to another. For example, let $x = 16$ and we shall find $\zeta = 697.4$, whilst the Table gives 700.1. Then let $x = 24$ and the equation will give $\zeta 649.2$ whilst the Table gives 651.7. We see by these two examples that our equation gives almost the same figures as the Table. If, however, the small differences which do exist could cause difficulty in a matter of this kind, we should have to correct the figures of the third column and give them the values which the equation would indicate.

Paragraph 14

Let us try, for the good of humanity, to explain and to determine still more accurately the grounds which should decide us for or against inoculation. If inoculation brought us all the advantages which I have shown to accompany the state of freedom from smallpox, and if it brought them without any risk and without any disadvantage, should one doubt or hesitate about which side to take? Ought one not to inoculate children in the first days after birth? It seems to me that it would be contrary to nature to dare to maintain that, in those circumstances, it ought not to be done. It is, then, only the risk which is attributed to inoculation which should keep us undecided. This consideration leads me to propound and examine this new question: 'What would be the state of the human race if, at the price of a certain number of victims, we could procure for it freedom from natural smallpox?' At first this problem seems difficult; however, it flows quite naturally from our principles and our way of treating the subject.

Let us assume, then, that to be one of the privileged number would cost 1 out of N of them. We have only to consider that the whole generation is decreased in the ratio of N to $N - 1$, and consequently that we must decrease all the numbers of the third column in the same ratio. In this way, the sum of all the numbers which give the total quantity of life will similarly be diminished in the ratio N to $N - 1$. It is then very easy to construct a new Table which shows the state of the human race as it would be if, at the price of a certain small tribute, all the remainder of the newborn children would be absolutely free from all danger of smallpox. I do not include such a Table since we are not sufficiently agreed on the number N which, in the practice of inoculation, shows how many times the number of all those inoculated is bigger than the number who die of artificial smallpox. We only agree that, when we have perfected the practice, the number N is very large. It is true that it might be smaller in respect of children whom we might wish to inoculate in their cradles.

However, this increase in the risk has not yet been established and it is not certain that the risk might not even be smaller. In any case, I think that I should be taking the very worst case if, for example, I took $N = 200$. I am going to include some comments for this example.

The 1300 births will, in this case, first be reduced to 1293.5 and the survivors at the ages of one, two and three completed years will be 1012.1, 877.4 and 831.2 respectively, and so on. Then the differences between these numbers and those of the second column will show the gains for each age after making all deductions for the risk in smallpox innoculation. These gains will, successively, be 12.1, 22.4, 33.2 etc. We can see already, by these examples, that this deduction becomes a very small matter, and we could neglect it for the whole population, which alone merits the attention of the Prince when the wellbeing of the State or the public as a whole is concerned. But let us see what the total quantity of life will be if we make the deduction which we have just explained. We have seen in Note (f) of Paragraph 12 that the total quantity of life for the natural state is 34 605 and that for the state free from smallpox is 38 706 if we make no deduction. This last number must now be reduced by one two-hundredth because of the risk accompanying inoculation. Making this deduction, we obtain the total quantity of life for the state free from smallpox, with the whole tribute paid, as 38 513, which must be compared with 34 605 for the natural state. If we divide these numbers by 1300 we will have the average life for the natural state as 26 years 7 months, for the state without smallpox and without tribute as 29 years 9 months and for the state free from smallpox and with the whole tribute paid as 29 years 7 months. The risk due to inoculation only diminishes the average life by about 1 month 20 days; and notwithstanding this risk, the gain is still 3 years on the average life of 26 years 7 months for the natural state. This gain is once more over one ninth of the average life, and previously it was approximately two seventeenths.

Let us look again at the question of what number we should have to take for N so that inoculation might do neither good nor harm to the population as a whole and so that the natural life might remain the same as in the natural state.

We shall answer this if we put $\frac{38\,706}{34\,605} = \frac{N}{N-1}$, and this gives $N = 9.43$ approximately. We can, then, consider it a moral certainty that, so long as inoculation administered to newborn children carries off less than 100 out of 943, it does more good than harm. It is on this theorem that we should decide whether to reject or to introduce inoculation for newborn children, in so far as we wished to adopt the principle of the greatest use for the whole of mankind. Instead of the ratio 100 to 943 we might have expected the ratio 1 to 8. The difference arises from the fact that those who die of natural smallpox do not die of it at birth.

I am going further, and I do not fear to say that, even if we were to suppose that the risk from inoculation were so great as to carry off 100 out of 943, it would still result in a benefit to society. To understand this paradox it is necessary to examine the change which would result in this case. The 1300 children born would first be reduced to 1162 and then to 909 at the age of one, to 788 at the age of two. In this way, the years are less fertile than in the natural state, but the difference continually becomes smaller. At the age of fifteen it is zero; the natural state has 628 and we would have 630 in the case of general inoculation, however deadly we have supposed it to be. After this, the natural state would always be less fertile than the other, so that at the age of twenty-five, at which there are 565 alive in the natural state, we would have 576 in the other. So that we see that the loss would fall solely on children useless to the State, and that all the gain would come to the age which is most precious. If a generation of 1000 children had 20 000 years before them to be shared, would it be better for the State for them all to arrive at the age of twenty and all die at this age, or for 500 of them to die in the cradle and 500 to reach the age of forty? If that were the fate of humanity, it would soon be extinct in the first case, and perhaps superabundant in the second. So, however we look at the matter, it will always be geometrically true that the interest of Princes is to favour and protect inoculation by all possible means; likewise the father of a family with regard to his children. People who have arrived at the age of reason and not yet had natural smallpox could indeed find themselves in special circumstances demanding special calculations to show them the most advantageous course for them to take in regard to the age most suitable for inoculation; but the public interest will always demand, not only that inoculation should be employed, but even that its employment should be hastened in order to prevent natural smallpox, since we see from our first Table that, at the age of four and a half, it will already have carried off half of all those who would probably die of it, and that there are only 450 persons left who have not yet had it and find themselves in the position of calling the insertion to their aid. If, however, long experience were to give us the knowledge that children were much less exposed to catching smallpox in the first year of life than in subsequent years, this would be a reason for deferring inoculation to the age of one complete year. It is necessary to consult the doctors about this, since the mortality lists do not state the age of those carried off by smallpox. Let us apply ourselves to knowing the nature of smallpox by its (observed—L.B.) phenomena, and not listen to hypotheses when we are working out its pathology and drawing conclusions from this. The hypotheses which I have myself made are not concerned with the essential nature of the disease. They consist solely in assuming certain ratios as adequately determined by a large number of observations, though these ratios may well be susceptible to some small correction, which will depend on new mortality lists for smallpox showing, in particular, the ages of those dying of the disease. I dare to assert, however, that even those corrections will not necessitate any considerable change in our results. It is, then, for experience to decide whether inoculation is more dangerous during the first year of life than during the fifth or sixth. I do not believe, at any rate, that it has been established that this is true for natural smallpox.

COMMENTARY

Any discussion of implementing a public health policy should involve a careful evaluation of the potential risks. In particular when any vaccination campaign is planned it needs to be considered whether any potential risks could outweigh the benefits. For example, mathematical analyses have recently been used to evaluate the conditions under which HIV vaccines could actually increase the severity of HIV epidemics due to either associated increases in risky behaviour (that may occur as the result of the availability of an HIV vaccine) [12] or due to direct effects of vaccine-induced mortality by live-attenuated vaccines [13]. In the current debate concerning whether the United States population should be vaccinated against smallpox (in order to prepare for a possible terrorist attack) critics of mass vaccination have argued that the risks associated with widespread usage of the current smallpox vaccine would outweigh the potential benefits. Over 200 years ago, opponents of smallpox variolation in the 18th century used the same arguments. They argued that: (i) inoculation was risky because ‘artificial smallpox’ could cause mortality, and (ii) inoculation programs could increase the transmission of smallpox (because individuals inoculated with ‘artificial smallpox’ could transmit smallpox). Bernoulli used mathematical reasoning to counter both arguments.

The bane of mathematical modelling—as Bernoulli realised—is that parameter values are rarely known precisely. Mathematical modellers now deal with these difficulties by using sophisticated uncertainty and sensitivity analyses to explore parameter ranges rather than simply focusing on specific parameter values (see for example [13]). Bernoulli conducted a form of sensitivity analysis by changing assumptions and parameter values and then presenting a series of analyses. In Bernoulli’s first series of calculations he assumed that 100% of newborns would be inoculated, that inoculation would induce complete immunity to infection by the wild-type strains of smallpox, and that inoculation would carry no risks. Under these assumptions he calculated that an individual's expectation of life at birth would increase from 26 years 7 months to 29 years 9 months. Bernoulli then repeated his calculations including the assumption that one individual out of every 200 inoculated individuals would die as the result of 'artificial smallpox'. These calculations showed that the inclusion of a mortality risk due to 'artificial smallpox' reduced the gain in life expectancy by only one month. Bernoulli also quantified the risk that mass inoculation could cause an increase in the transmission of smallpox. He determined the magnitude of this risk by assuming that if universal inoculation was adopted then more individuals would be infected with 'artificial smallpox' than were currently infected by 'natural smallpox' (he calculated a ratio of 13:8), but that 'artificial smallpox' was 13 times less severe and four times less transmissible than 'natural smallpox' (based upon the assumption that 'artificial smallpox' generated fewer pustules than 'natural smallpox'). Therefore, he concluded that infection of individuals with 'natural smallpox' was 32 times as great as infection with 'artificial smallpox' would be if universal inoculation was adopted (and inoculated individuals were able to transmit the virus).

Bernoulli's analyses provided considerable insight into the historical epidemiology of smallpox, and the severity of the pathogen. Recently, concerns about the utility of smallpox as a potential weapon of bioterrorism has led to considerable speculation about the potential rate of spread of smallpox. The initial rate of spread of an epidemic can be summarised by the basic reproduction number (R_0), which is defined as the average number of secondary infections caused by one case in a wholly susceptible population [14]. Dietz and Heesterbeck have calculated, using Bernoulli's parameter values, that only 15% of the population in the 18th century escaped infection with smallpox, and hence that the R_0 for smallpox was approximately 7 [8]. Others have used more recent datasets to estimate that the R_0 for smallpox was between 4 and 5 [14]. A comprehensive analysis of datasets collected from a variety of smallpox outbreaks and epidemics suggest that the R_0 for smallpox during the time period from the 1700s to the 1900s ranged from 3.5 to 6, but sometimes reached as high as 10 or 12 [15]. The extremely high values of R_0 were suggested to be the result of crowding and poor nutrition (in 18th century outbreaks) and hospital-associated transmission (in late 20th century outbreaks) [15]. These estimates of R_0 are valuable for quantifying the potential of smallpox to generate an epidemic in the absence of any intervention strategy (such as vaccination or quarantine). Although, in evaluating the risk of a potential attack based upon smallpox it needs to be considered that: (i) the virus might be genetically modified to increase transmissibility and virulence and hence increase the value of R_0, and (ii) an attack could involve initial widespread dissemination of the virus.

The numerical estimates of the value of R_0 are also useful to understand the vaccination coverage levels that were necessary to eradicate smallpox. Bernoulli assumed that 100% of newborns would be inoculated in his calculations; however, universal vaccination is not necessary for eradication. The critical vaccination coverage level necessary for eradication (p_c) can be calculated from the equation $p_c = 1-(1/R_0)$ [14]. Since the estimates of R_0 range from 3.5 to 12, the estimates of the critical vaccination coverage level necessary for eradication range from 71% to 92%. Interestingly, the reported vaccination coverage levels that occurred during the smallpox eradication campaign ranged from 77% to 95% [14]. Recent mathematical modelling analyses have shown the magnitude of public health interventions that would be necessary if a smallpox epidemic reoccurred as the result of a bioterrorist attack [1–4]. These mathematical analyses have evaluated the relative benefits of targeted versus universal vaccination against smallpox, and the relative effects of vaccination and quarantine [1–4].

The epidemiology of smallpox in the 17th and 18th century was fairly complex, and showed considerable differences between urban and rural settings. Duncan and colleagues have conducted a series of detailed quantitative analyses of the historical epidemiology of smallpox by using time series analyses to analyse historical birth and death records [11,16–18] in England during the time period 1600–1800. Their analyses have shown that there were three possible types of epidemiological situations: (i) in London (and other large cities) smallpox was endemic but epidemics occurred every 2–3 years, (ii) in medium-sized rural towns (with a population of approx 4000) smallpox was not endemic but periodic severe epidemics occurred every 5 years, and (iii) in small rural communities smallpox was not endemic and epidemics did not occur. The transmission dynamics of smallpox, and these urban-rural differences, can be understood by using a standard system of ordinary differential equations; the SEIR model [14]. In this model individuals can exist in one of four states: Susceptible (uninfected with smallpox), Exposed (infected with smallpox but not yet infectious), Infectious (infectious with smallpox) and Recovered (recovered and immune to smallpox).

By analysing the SEIR model (using parameter values that reflect the biology of smallpox) it can be seen that a smallpox epidemic will quickly infect a high proportion of the population and that therefore almost all of the surviving population will be immune. Hence, before another epidemic of smallpox can occur it is necessary to build up the pool of susceptibles by birth in order to attain a critical threshold population level (i.e. so that $R_0 > 1$). In the 17th and 18th centuries replenishment of the susceptible pool took several years as it was dependent upon the birth rate and the population size. The susceptible pool was more quickly replenished in the urban centres than in rural towns; hence, the observed inter-epidemic period between smallpox epidemics was shorter in cities (on average 2 years) than in medium-sized rural towns (on average 5 years). Analysis of the SEIR model shows that smallpox epidemics should show damped oscillations and fade away over time, however, the data show that smallpox epidemics exhibited fairly regular cycles over a 150 year time period [16–18]. Duncan and colleagues [18] have shown that only a small (8%) annual variation in host susceptibility would have been sufficient to cause oscillating undamped epidemics every 2 years. They have suggested that variation in host susceptibility to smallpox occurred as the result of periodic famine and food shortages [18].

In England, variolation against smallpox began to be widely administered after about 1750; vaccination was introduced in 1796 and was made compulsory for infants in 1853. During the 19th century as the pool of susceptibles was drastically reduced: (i) the endemic level of smallpox fell steadily, (ii) the amplitude of smallpox epidemics decreased, and (iii) the interepidemic interval increased. Thus public health measures led to the disappearance of smallpox in England by the end of the 19th century. It is not clear how influential Bernoulli's paper was in influencing public health policy, but it remains a classic paper as it was the first known mathematical analysis that was used to try to influence public health policy. Bernoulli was the first to use a series of sophisticated mathematical analyses in order to carefully evaluate the potential risks as well as the potential benefits of a public health intervention. Bernoulli argued that universal inoculation would not only be of benefit to the individual, but would also be of benefit to the population. He introduced the concept of 'Civil Life', which he defined as the time when an individual became mature enough to contribute to the State and Society (which Bernoulli decided was at age 17). He calculated that, by adopting universal inoculation against smallpox, France would gain 25 000 additional useful 'Civil Lives' which would benefit the state and society. Echoes of Bernoulli's arguments—that substantial population-level benefits can accrue as the result of a public health intervention—are now being used to argue for the widespread availability of antiretrovirals for treating HIV-infected individuals in developing countries [19–21].

REFERENCES

1. Meltzer MI, Damon I, LeDuc JW, Millar JD. Modelling potential responses to smallpox as a bioterrorist weapon. *Emerg Infect Dis* 2001; **7**: 959–969.
2. Kaplan EH, Craft DL, Wein LM. Emergency response to a smallpox attack: the case for mass vaccination. *Proc Natl Acad Sci USA* 2002; **99**: 10935–10940.
3. Halloran ME, Longini IM, Nizam A, Yang Y. Containing bioterrorist smallpox. *Science* 2002; **298**: 1428–1432.
4. Bozzette SA, Boer R, Bhatnagar V, *et al.* A model for smallpox-vaccination strategy. *N Engl J Med* 2003; **348**: B1–10.
5. Mortimer PP. Review of 1902 Classic Paper by J C McVail. *Rev Med Virol* 2002; **12**: 267–278.
6. Baxby D. Review of 1913 Classic Paper by W Hanna. *Rev Med Virol* 2002; **12**: 201–209.
7. Bernoulli D. Essai d'une nouvelle analyse de la mortalite causee par la petite verole. *Mem Math Phy Acad Roy Sci Paris* 1766. (English translation entitled 'An attempt at a new analysis of the mortality caused by smallpox and of the advantages of inoculation

to prevent it' In *Smallpox Inoculation: An Eighteenth Century Mathematical Controversy*, Bradley L. Adult Education Department: Nottingham, 1971, 21).

8. Dietz K, Heesterbeek JAP. Daniel Bernoulli's epidemiological model revisited. *Math Biosci* 2002; **180**: 1–21.
9. Creighton C. *A History of Epidemics in Britain*, 2nd edn. Cambridge University Press: London, 1894.
10. Razzell P. *The Conquest of Smallpox*. Caliban Books: Sussex, 1977.
11. Scott S, Duncan SR, Duncan CJ. Infant mortality and famine: a study in historical epidemiology in northern England. *J Epidemiol Community Health* 1995; **49**: 245–252.
12. Blower SM, McLean AR. Prophylactic vaccines, risk behavior change and the probability of eradicating HIV in San Francisco. *Science* 1994; **265**: 1451–1454.
13. Blower SM, Koelle K, Kirschner DE, Mills J. Live attenuated HIV vaccines: predicting the trade-off between efficacy and safety. *Proc Natl Acad Sci* 2001; **98**: 3618–3623.
14. Anderson RM, May RM. *Infectious Diseases of Humans: Dynamics and Control*. Oxford University Press: Oxford, 1991.
15. Gani R, Leach S. Transmission potential of smallpox in contemporary populations. *Nature* 2001; **414**(6865): 748–750. Erratum in *Nature* 2002; **415** (6875): 1056.
16. Duncan SR, Scott S, Duncan CJ. An hypothesis for the periodicity of smallpox epidemics as revealed by time series analysis. *J Theor Biol* 1993; **160**: 231–248.
17. Duncan SR, Scott S, Duncan CJ. Modelling the different smallpox epidemics in England. *Philos Trans R Soc Lond B Biol Sci* 1994; **346**(1318): 407–419.
18. Duncan CJ, Duncan SR, Scott S. Oscillatory dynamics of smallpox and the impact of vaccination. *J Theor Biol* 1996; **183**: 447–454.
19. Velasco-Hernandez JX, Gershengorn HB, Blower SM. Could widespread use of combination antiretroviral therapy eradicate HIV epidemics? *Lancet Infect Dis* 2002; **2**: 487–493.
20. Blower SM, Farmer P. Predicting the public health impact of antiretrovirals: preventing HIV in developing countries. *AID Science* 2003; **3**(11).
21. Blower SM, Schwartz EJ, Mills J. Forecasting the future of HIV epidemics: the impact of antiretroviral therapies and imperfect vaccines. *AIDS Rev* 2003; **5**(2): 113–125.