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CLASSIC

PAPER

Studies in smallpox and vaccination†

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INTRODUCTION

Satisfaction at the eradication of smallpox was always tempered by concern that illicitly held supplies of smallpox virus might be used as a weapon by terrorists or 'rogue' states [1]. This concern was increased in the late 1990s by information provided by a defector from the Russian bioweapons programme. Consequently, plans to manage the deliberate release of smallpox virus were being modelled before the events of September 11 and the subsequent still unexplained deliberate release of anthrax spores in the USA [2–5]. However, these latest events add an important contemporary edge to the value of assessing historical studies on smallpox.

The work discussed here, published in 1913 by William Hanna of Liverpool, though not a 'paper' and not all wholly original, deserves 'classic paper' status. His monograph is one of the earliest, objective, and certainly most impressively presented expositions of the duration of vaccine immunity and the effect of post-exposure vaccination. As such, it is clearly of considerable historical and current interest.

In the UK during the second half of the 19th century, the imposition of compulsory vaccination and increasing evidence that smallpox was occurring in adults vaccinated in childhood caused considerable controversy [6]. Supporters of vaccination pointed to the lower mortality and attenuated disease in the partially protected [6,7]. Opponents, citing the Jennerian dogma of complete lifelong protection, regarded any case of smallpox, no matter how mild or how long after vaccination, as 'proof' that vaccination did not work [6,8]. Both sides selected and manipulated data to serve their own ends in ways that now would not be acceptable, and the value of these studies is difficult to assess. Also, because vaccine was maintained by arm-to-arm transfer, quality control was impossible and there was concern about the safety and efficacy of vaccination [6].

Lobbying by opponents led to the appointment of a Royal Commission and then the 1898 Vaccination Act. This replaced arm-to-arm vaccination by the use of safer, more reliable, animal vaccine and vaccination was no longer made compulsory. Consequently, although some opposition continued, the start of the 20th century heralded an era when more objective views became dominant [6]. A large outbreak of smallpox in Liverpool during 1902–3 was studied in great detail, due to controversy over the possible role of smallpox hospitals in the spread of the disease [9,10]. Vaccination was not an issue although naturally information on it was collected. This provided the raw data that Hanna, Assistant Medical Officer of Health for the port, analysed so impressively in his monograph. Cases were assigned to vaccinated and unvaccinated groups on the certain presence or absence of vaccination scars. This was more reliable than 'proof' on paper, and uncertain cases were not included. Infant vaccination was in theory compulsory up to 1898, with optional revaccination of children or adults recommended only after that date. Hanna's data therefore concern the effects of childhood primary vaccination only on subsequent smallpox. Reference to vaccination 'scars' (in the plural) relates to the fact that up to five or six insertions were commonly used for a primary vaccination at the time [11]. Hanna uses the term 'de-vaccination' to denote the diminishing protective effect of vaccination with time. The monograph is too long to reproduce in full, but the most important and currently most relevant extracts are reproduced verbatim.

†*Reproduced from a monograph* Studies in Small-Pox and Vaccination *by W. Hanna, 1913. John Wright and Sons Ltd: Bristol, with permission of Blackwell's: Oxford. Please note that only relevant excerpts are presented; the paper is not reproduced in full.*

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STUDIES IN SMALL-POX AND VACCINATION

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(Reprinted from the monograph published by John Wright and Sons Ltd, Bristol, 1913)

INTRODUCTION

A study of the early history of small-pox, before vaccination was introduced, shows that the disease was one of extensive prevalence and great malignancy. In the 18th century it reached its highest point of intensity and distribution in Europe, the mortality from small-pox in England at that period being one-tenth of the total mortality. In London it was constantly present, and the deaths averaged, during the period 1761–1796, from 3,000 to 15,000 yearly; indeed, in the latter half of the century the deaths seldom fell below 1,000. The great malignancy of the disease when introduced into fresh countries in later years has also been frequently recorded. The decrease in small-pox prevalence since the beginning of the 19th century, and the marked reduction in its fatality, have been shown to be due to the protection afforded by the process of vaccination.

...Small-pox still continues to invade our shores from abroad, the extensive movements of populations, the rapid means of communication, and the travelling facilities afforded by fast steamships, enabling the disease to jeopardize our ports and the country generally, even more so than heretofore. Countries such as Canada, the United States of America, Spain, Russia, Egypt, etc., are well within the incubation period of the disease, and from time to time persons have been landed in our ports in the incubation stage.

...After a long spell (seven years) of comparative quiescence, the disease broke out in epidemic form in Britain in 1902–3; it carried off a large number of persons; in the City of Liverpool alone there were during that period 2,280 cases, with 161 deaths.

...The series of small-pox cases under consideration has been collected from amongst those which have been admitted to the hospitals of the City and Port of Liverpool during the past ten years. The large majority occurred during the above-mentioned epidemic period (1902–3), and since then the cases admitted have been chiefly imported from abroad.

...A STATISTICAL STUDY OF 1,163 CASES OF SMALL-POX, WITH SPECIAL REFERENCE TO VACCINATION IN MODIFYING THE DISEASE.

The examination of a large series of cases of small-pox is of value as affording additional testimony to the efficacy of vaccination as a prophylactic measure, as an estimate of the severity of the disease, and of the mortality generally in the vaccinated and unvaccinated; and in particular, the measure of the efficiency of the vaccination in the case of the vaccinated. Some new methods have been adopted in recording and comparing this series of cases.

...The cases of small-pox numbered 1,163, consisting of 943 vaccinated in infancy and 220 unvaccinated.

The method adopted was that of tabulating the age, the presence or absence of vaccination scars, and in the former case of measuring the area in square inches.

The cases were placed in ten age-groups, and arranged in order to show the proportion of vaccinated and unvaccinated in each. These have been set out in Tables I and II, where the extent and severity of the disease are also revealed. The influence of vaccination on the mortality will be first considered.

Influence of vaccination on the case-mortality

Whilst there are several criteria of the severity of the disease, such as extent of eruption, temperature, etc., the one of most value is the case-mortality. When, therefore, a comparison is made of the influence of vaccination on the case-mortality of small-pox, it will be seen that amongst the 943 cases which were vaccinated in infancy, there were twenty-eight deaths, or 2.9 per cent, and amongst the 220 unvaccinated cases there were sixty deaths, or 27.2 per cent; that is, the ratio of deaths to attacks is ten times as great in the unvaccinated as in the vaccinated (see Table II).

...On *Chart A* and in the accompanying tables, the cases have been arranged into suitable age periods, so as to show clearly the value of vaccination on the mortality in passing from infancy to adult and old age. An examination of the deaths recorded amongst the vaccinated under each age-group reveals the interesting fact that no death occurred until the 20–30 year group is reached, and the case-mortality for this group is only 0.9 per cent. It will be observed, however, that the percentage case-mortality amongst the vaccinated steadily rises from this point onwards in life, but never exceeds 10 per cent.

On contrasting these figures with those amongst the unvaccinated, we observe a striking difference. Under 2 years of age the deaths are 58 per cent of the cases attacked, for 2–5 years 30.6 per cent, and the figure then falls until 10–15 years, when it is 3.2 per cent.

This decrease may be attributed to the gradual development of the natural resistance and recuperative power of youth enabling the patient to recover from the disease; this may be compared with what is observed in other infections diseases. From adolescence onwards the mortality in the unvaccinated gradually increases, until it reaches 50 per cent at the periods from 40 years and upwards. This high ratio of deaths to attacks amongst the unvaccinated, especially at the early and late periods of life, compares with what is well known of this

Table I. TABLE SHOWING NUMBER OF SMALL-POX CASES (943 VACCINATED AND 220 UNVACCINATED) AT EACH AGE-PERIOD, WITH RELATIVE DEGREES OF SEVERITY.

	Under 2 years		2–5		5–10		10–15		15–20	
	Vaccd.	Unvaccd.	Vaccd.	Unvaccd.	Vaccd.	Unvaccd.	Vaccd.	Unvaccd.	Vaccd.	Unvaccd.
A. Modified discrete and discrete	No cases	3	7	3	31	6	54	9	89	1
B. Profuse discrete and semi-confluent	No cases	9	No cases	15	3	15	8	19	14	20
C. Confluent and death	No cases	17	No cases	8	No cases	5	No cases	3	No cases	9
Total	No cases	29	7	26	34	26	62	31	103	30
Deaths alone	0	17	0	8	0	5	0	1	0	4

20–30		30–40		40–50		50–60		60 and up		Total	
Vaccd.	Unvaccd.	Vaccd.	Unvaccd.	Vaccd.	Unvaccd.	Vaccd.	Unvaccd.	Vaccd.	Unvaccd.	Vaccd.	Unvaccd.
249	11	163	No cases	63	1	20	2	10	1	686	37
77	21	72	5	29	3	13	3	8	No cases	224	110
7	10	13	9	9	6	2	5	2	1	33	73
333	42	248	14	101	10	35	10	20	2	943	220
3	6	13	8	9	5	1	5	2	1	28	60

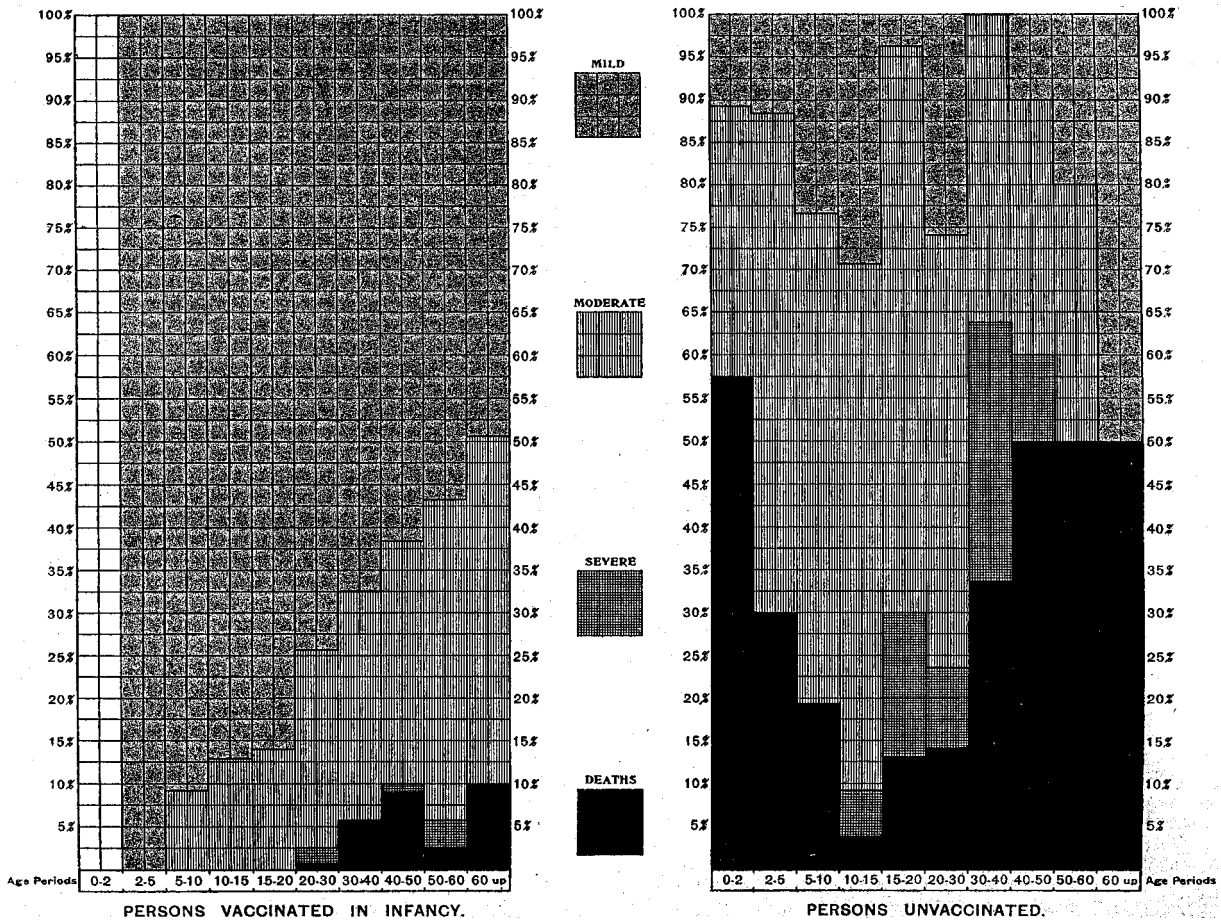
Table II. TABLE SHOWING PERCENTAGE OF VACCINATED AND UNVACCINATED CASES RESPECTIVELY AT EACH AGE-PERIOD AFFECTED WITH SMALL-POX IN DIFFERENT DEGREES OF SEVERITY.

	Under 2 years		2–5		5–10		10–15	
	Vaccd.	Unvacc.	Vaccd.	Unvacc.	Vaccd.	Unvacc.	Vaccd.	Unvacc.
A. Modified discrete and discrete	No cases	10.3%	100%	11.5%	91%	23%	87%	29%
B. Profuse discrete and semi-confluent	No cases	31%	No cases	57%	9%	57%	13%	61.3%
C. Confluent and death	No cases	58%	No cases	30.7%	No cases	19%	No cases	9.7%
Percentage casemortality vaccinated and unvaccinated	—	58%	—	30.6%	—	19%	—	3.2%

15–20		20–30		30–40		40–50		50–60		60 and up		Total	
Vaccd.	Unvacc.	Vaccd.	Unvacc.	Vaccd.	Unvacc.	Vaccd.	Unvacc.	Vaccd.	Unvacc.	Vaccd.	Unvacc.	Vaccd.	Unvacc.
86.4%	3.3%	74.7%	26.2%	65.7%	No cases	62.3%	10%	57.1%	20%	50%	50%	72.7%	16.8%
13.6%	66.6%	23.1%	50%	29%	35.7%	28.7%	30%	37.1%	30%	40%	No cases	23.7%	50%
No cases	30%	2.1%	23.8%	5.2%	64.3%	9%	60%	5.8%	50%	10%	50%	3.6%	33.2%
—	13.3%	9	14.2%	5.2%	33.3%	8.9%	50%	2.8%	50%	10%	50%	2.9%	27.2%

CHART *A*. SMALL-POX IN LIVERPOOL DURING TEN YEARS 1902-1911.

Showing the Relative Severity of the Disease as it affects Vaccinated and Unvaccinated persons, based on the Records of 1,163 Cases.



disease in pre-vaccination days, viz., that the severity and mortality lay heaviest on infants and young children under ten years of age.

...De-vaccination

The length of the period of protection can be fairly well gauged by an examination of the appended Tables.

The period will vary a good deal for each individual, but from the figures given, the highest resistance lasts only a short time. After a few years those who become susceptible develop the disease only in a mild form, and further on in years greater severity manifests itself in the type of the disease, but no cases of severe and fatal small-pox appear in this series of cases until over 20 years of age. It is evident, then, that following a primary vaccination in infancy, the period of greatest protection in childhood probably does not cover more than three to five years, and after this, the absolutely preventive efficiency of vaccination rapidly diminishes, and cases of small-pox begin to appear amongst the vaccinated. The power to modify the disease, however, still continues to remain considerable until adolescence, and even into later life, as will be seen by comparing the severity and the percentage case-mortality in different age-groups of vaccinated and unvaccinated cases.

...Observations on the interaction of concurrent variola and vaccinia.

It has been abundantly shown by the experiments of Thiele and Ceely, and more recently by Klein and Copeman, that cow-pox or vaccinia may be considered as an attenuated descendant of small-pox; and in connection with this close relationship, if not absolute identity, of these two affections, the examination of the following series of 75 cases of small-pox with a concurrent vaccination will prove of interest. The cases have been collected during the past ten years in the City and Port of Liverpool. Many of them were persons who were landed incubating or suffering from the disease, and were removed to the Port Isolation Hospital; these were chiefly

cattle-men from Boston, who landed incubating small-pox during the severe outbreak in that city in 1902–3.

The cases may be examined in the light of the relative effects produced on one another by each of these conditions: (1) As regards the success of the vaccination when performed subsequently to infection with small-pox; and (2) As regards the effect of the vaccination on the course and severity of the disease. Cases of concurrent variola and vaccinia have rarely been given the prominence which they deserve, and it was with this object that the present series was collected. The series, then, gives information of the effect of *vaccination or re-vaccination* periormed after exposure to infection and running *concurrently* with the course of the disease.

The success of the vaccination.

The success of the process may first be considered, and the series may be conveniently divided into two groups, viz.: (1) Those who have never been vaccinated until infected with small-pox, *Chart B*; (2) Those who have been primarily vaccinated in infancy, *Chart C*.

On examining the charts it will be seen that the period of twelve days has been taken as the duration of the incubation period: this has been found to be practically correct for all the cases; they were all carefully investigated both as to the symptoms of onset and initial rash, and found to correspond to the period set forth in the charts.

...The cases have been set out showing those vaccinated and re-vaccinated on different days: first, during the period of incubation, and second, after the onset of symptoms, and even until three days after the rash had appeared. It is unnecessary to say that vaccination efficiently performed in susceptible people before exposure to infection of small-pox will, almost without exception, prove successful, and will protect the individual from developing any symptoms or signs of the disease.

Vaccination during Incubation.—On examining the charts it will be found that all the vaccinations and re-vaccinations have been *successful if performed during the incubation period* and even up to the day of onset of symptoms. When the term ''successful'' is used, it must be understood that the phenomena at the site went through the typical and normal course of human vaccination.

...Vaccination after onset of the disease.—The operations performed subsequently to the onset of symptoms were unsuccessful.

...Influence of concurrent vaccination on the course of the disease.

The remarkable antagonism of these two diseases can only be explained by a consideration of the question of immunity or concurrent immunities. It may suffice to say that in small-pox with a concurrent vaccination, it is a race between the virulent and the modified organisms; the less virulent and the more saprophytic forms grow faster and produce immunity more quickly than the more virulent ones. Protection is not acquired at any particular time, but there is a gradual accumulation of

CHART *B.*

CONCURRENT VARIOLA AND VACCINIA.

Cases unvaccinated before infection with Small-pox.

No.	Probable Day of Infection	Day of disease on which vaccination was performed — Incubation Period 1	2	3	4	5	6	7	8	9	10	11	Onset 12	13	14	Rash 15	16	17	18	19	Severity of Disease — Mild	Moderate	Severe	Remarks
1	V	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	No	Development		
2	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	No	Development		
3	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	A few papules
4	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	A few papules
5	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	Papules few and scattered
6	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	A few papules—face, arms, legs, &c.
7	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	
8	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	
9	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	Very few papules
10	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	
11	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	
12	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	
13	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	
14	–	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	X	–	–	
15	–	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	X	–	
16	–	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	X	–	
17	–	–	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	X	
18	–	–	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	X	–	
19	–	–	–	–	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	X	
20	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	Death	–	–	–	–	–	–	X	Death
21	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	–	–	–	–	–	–	X	
22	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	–	–	–	–	–	X	
23	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	–	–	–	–	–	X	
24	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	–	–	–	–	X	
25	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	–	–	–	X	
26	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	–	–	X	–	
27	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	–	–	X	–	
28	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	–	–	X	–	
29	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	Death			–	–	X	Death
30	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	Death		–	–	X	Death

V —Successful Vaccination. Λ—Unsuccessful Vaccination,

CHART *C.*

CONCURRENT VARIOLA AND VACCINIA.

Cases with Primary Vaccination before infection with Small-pox.

No.	Probable Day of Infection	DAY OF DISEASE ON WHICH RE-VACCINATION WAS PERFORMED — Incubation Period 1	2	3	4	5	6	7	8	9	10	11	Onset 12	13	14	Rash 15	16	17	18	19	Severity of Disease: Mild	Moderate	Severe	REMARKS
1	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	Six or seven papules
2	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	A few papules
3	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	
4	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	Thirty or forty papules
5	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	Ten or twelve papules
6	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	
7	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	
8	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	
9	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	
10	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	Few papules
11	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	Few papules
12	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	
13	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	Only a few papules
14	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	Few papules
15	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	
16	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	
17	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	
18	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	
19	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	
20	–	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	X	–	–	
21	–	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	X	–	–	
22	–	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	X	–	–	
23	–	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	–	–	–	X	–	–	Aorted papules
24	–	–	–	–	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	X	–	–	
25	–	–	–	–	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	–	X	–	–	
26	–	–	–	–	–	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	X	–	–	
27	–	–	–	–	–	–	–	–	–	–	–	–	V	–	–	–	–	–	–	–	X	–	–	
28	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	–	–	–	–	X	–	–	
29	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	–	–	–	X	–	
30	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	–	–	X	–	–	
31	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	–	–	X	–	–	Few papules
32	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	–	–	X	–	–	
33	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	–	–	X	–	
34	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	–	–	X	–	
35	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	–	–	X	–	
36	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	–	–	X	–	
37	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	X	–	–	
38	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	X	–	–	
39	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	X	–	–	
40	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	–	X	–	
41	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	–	X	–	
42	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	X	–	
43	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	X	–	
44	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	–	X	–	
45	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Λ	–	X	–	–	

V—Successful Vaccination. Λ—Unsuccessful Vaccination.

immunity in the blood, which usually shows itself to be completed by the beginning of the second week after vaccination.

It would seem from an examination of the charts, that nine days after vaccination is the period required to give real evidence of the increasing protection against small-pox.

...On referring to *Chart B* of unvaccinated cases, it will be seen that cases of small-pox vaccinated within three days after infection will develop very slight or no symptoms of small-pox; and a reference to *Chart C* shows no cases occurring within the first three days. One may safely infer, therefore, that vaccinations performed within the first three days of infection in persons with a primary vaccination will not develop small-pox, and in those who are unvaccinated the chances are that the disease will not develop; or, in other words, vaccination requires nine days to develop an immunity which will absolutely prevent or minimise and attack of small-pox....

COMMENTARY

In addition to the extracts reproduced and analysed here, Hanna also included information relating the area of vaccination scars to the duration of immunity. This is omitted here because, although Hanna showed a positive correlation, the subject was not pursued further; improvements in the production of vaccine and improved vaccination techniques soon made multiple and large vaccination lesions unnecessary [6,11].

Hanna's data on the duration of immunity, well displayed in Tables I and II and particularly in Chart A, are self-evident. He discussed them appropriately, and they require little in the way of comment here. Because the vaccinated population of Liverpool was much higher than the unvaccinated [9,10] there were inevitably more cases among the former. The most obvious difference between the two sets of patients was the much lower mortality in the former (2.9% vs 27.2%; Table II). In the vaccinated cases severity and mortality increased with age, whilst in the unvaccinated cases increased severity and higher mortality occurred at the extremes of age (Chart A). In each age group mortality and severity were

higher in the unvaccinated (Table II, Chart A). The results showed clearly that vaccination conferred protection from serious illness and death for up to 20 years. They also showed that, when compared with the unvaccinated, some protection was evident for very much longer. Although similar and more extensive data were collected later, Hanna's results continued to be favourably discussed and his figures and tables were reproduced by smallpox experts through to the official WHO account [1,12,13].

Of course, in terms of Jennerian dogma, these results show the failure of vaccination to protect all individuals completely — and this should be the ultimate goal. However, they do show considerable attenuating effects which can only benefit the infected individual. There is also a hidden but most important benefit. The results show the effect of smallpox in the partially immune. However, not pointed out by Hanna, and always a tantalising unknown is how many other individuals were completely protected from an otherwise infectious dose. Because of this, the results of these and similar studies underestimate the total level of immunity in the population. Unfortunately however, there was a drawback to the community from partially protected individuals. Infection spread from these ambulatory and undiagnosed cases was an important means of transmission [1,12–14].

Results such as those collected by Hanna are particularly important because they relate directly to immunity to smallpox, something which is otherwise extremely difficult, if not impossible, to assess properly. Revaccination is too severe a challenge in this respect, and can produce a 'primary' response a short interval after the initial vaccination [15]. The vaccine is placed directly in a favourable site for replication, whereas smallpox virus would have to travel a tortuous path of nonspecific and residual specific immune barriers in order to infect. Although there is recent evidence that there may be considerable long term immunological memory of vaccination [16,17], such results are not necessarily related to actual immunity. Virions released naturally from infected cells (so-called 'extracellular, enveloped' virions) play an important role in pathogenesis [18]. However, long lasting immunity has been detected with the traditional neutralisation test [16]. This is done with artificially extracted virions, (so-called 'intracellular, naked' virions) which lack important neutralisation sites present on the naturally released extracellular virions [17,18]. Also, it is not known with certainty whether long lasting cytotoxic T-cell activity [17] detects viral antigens in general rather than those that induce immunity [16].

As well as protecting the individual, pre-exposure vaccination is also intended to reduce the overall impact of smallpox in the community. Such impact can be reduced further, and needless mass vaccination avoided, by the detection and isolation of cases and contacts — the so-called surveillance-containment strategy that ultimately proved so successful [1]. The risk of disease in these contacts can be reduced by post-exposure vaccination as early in the incubation period as possible. The considerable effects of post-exposure vaccination in those who had never been vaccinated and in those who had been vaccinated in childhood are shown by Hanna. The charts (B and C) with the patients arranged sequentially to show the effect of vaccination in relation to the interval between exposure and vaccination are most impressive, and require little comment. Vaccination during the first 11–12 days after exposure was usually 'successful'—here, Hanna was referring only to a take rather than any protective effect. If the post-exposure vaccination was in fact a re-vaccination it offerred significant protection against moderate and severe disease if done during the first 11–12 days (Chart C). If it was primary vaccination it offered significant protection if done during the first week (Chart B). Again, what cannot be determined with any certainty is the number who were protected completely, because the total number exposed and the degree of exposure is unknown. However, Hanna included two such completely protected contacts as Cases 1 and 2 of Chart B. These were newborn children born to infected mothers and in these particular instances the risk of infection must have been extremely high. Post-exposure vaccination became a standard procedure [1,12,13], would play an important role in the management of any future episode, and would be an effective use of limited vaccine supplies.

Both the UK and USA abandoned routine vaccination in the early 1970s. Consequently those born since then will be fully susceptible. However, to regard the level of immunity in those over

30 years old as low or non-existent may be unduly pessimistic [20]. The data collected by Hanna, and amply confirmed by others, suggest that there should be a considerable degree of protection against serious illnesss in a large proportion of those aged over 30. Also, as mentioned above, there will be a further, unknown proportion with complete immunity. This is not to infer that a sensible programme of revaccination should not be implemented for the over-30s.

It has been stated rather pessimistically that the smallpox database is over 20 years old [20]. So it is, but this does not make it obsolete. Indeed, analysis of data such as Hanna's mostly collected 100 years ago still has considerable value when smallpox control measures are being debated.

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