Jpn. J. Infect. Dis., 55, 112-116, 2002

Review

Duration of Immunity after Smallpox Vaccination: A Study on Vaccination Policy against Smallpox Bioterrorism in Japan

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(Received July 4, 2002. Accepted August 29, 2002)

CONTENTS:

SUMMARY: The success of global smallpox eradication in 1980 led all the nations of the world to discontinue smallpox vaccination. To date, however, the threat of deliberate release of smallpox virus has led health authorities to reconsider smallpox vaccination and at the same time, to urge to evaluate duration of the immunity of the population vaccinated before 1980. Although available data is scarce and incomplete, the study suggests that protective immunity lasts longer in a good percentage of vaccinees, although the real percentage and duration are not known. Accordingly, how to establish a national vaccination policy for preparedness in Japan and elsewhere was discussed. The study is intended to cause interest and debate among the medical and public health community.

1. Introduction

It is somewhat surprising that information regarding the duration of immunity after smallpox vaccination is scarce and incomplete, posing difficulty when we have to formulate a national vaccination policy against the threat of smallpox bioterrorism. These days a few health policy experts are contemplating a nationwide vaccination program (1,2). The World Health Organization (WHO) recommended, immediately after the incidents of 11 September 2001 and anthrax terrorism attacks in the United States (U.S.), a limited area vaccination program in case of smallpox introduction for the reason that complications due to vaccination itself may exceed the anticipated disaster to a greater or lesser extent if a nationwide campaign is initiated involving a large population.

Until 1980 when the WHO declared the global eradication of smallpox and recommended the cessation of routine smallpox vaccinations worldwide, all countries had established a routine two-dose vaccination program and, as needed, administered vaccinations for containing outbreaks. Although some such as the U.S., United Kingdom (U.K.), or Japan had already discontinued smallpox vaccination in the early or mid-l970s, almost two-thirds of the entire populations of the majority of the nations that had previous routine vaccination programs may have some residual immunity as of 2002. Vaccine quality as well as coverage may have varied in each state and area, but it would be important to evaluate residual immunity when contemplating the creation of a new vaccination policy.

In this respect, we have gathered pertinent historical data relevant to this issue. The results presented here may be useful for health policy makers in Japan and elsewhere.

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2. How to assess duration of vaccinal immunity

Smallpox vaccination is the oldest among many vaccinations. Thus, its use was started before the concept of biological standardization including a seed virus system, potency, safety, and assay of the level and duration of immunity. Much of the observed effectiveness of vaccination for smallpox came to the result of empirical connotation. Meanwhile, its protective effectiveness had been splendid, specifically when it was used for an epidemic control campaign. These, perhaps, were reasons why the actual duration of vaccinal immunity did not receive much attention, whilst the interruption of smallpox transmission rapidly progressed worldwide, resulting in successful eradication of the disease.

In this paper, vaccinal immunity is defined as prevention of infection by the smallpox virus. (Vaccinal immunity certainly modifies the severity of the disease, but we prefer to limit the definition as a clear-cut effect, namely prevention of infection among nearly all the vaccinees.) The Centers for Disease Control and Prevention (CDC), U.S. indicated after the September 11th incident, “It is not known exactly how long the immunity from the smallpox vaccination will last. Most estimates suggest that immunity lasts from 3 to 5 years.” (Full text is available on Web site at http://www.bt.cdc.gov/DocumentsApp/FAQSmallpox.asp?link=2&page=bio, as of 20 May 2002) (3). International Health Regulation when in practice before the eradication, determined the validity of immunity protection to be 3 years, requiring the vaccination certificate to be renewed by that duration (4). However, it is interesting to note that during a few decades before the smallpox eradication of 1980, many industrialized states where health services were competent set up laws for smallpox vaccinations, namely primary vaccination at 1 year and thereafter revaccination at 10 to 13 years, suggesting their acceptance that primary immunity may last up to 10 years

(5,6). This policy might have resulted from an old study of smallpox outbreak conducted by Hanna in the U.K. early 20th century, showing that booster doses were needed around every 10 years (7). In Japan, at that time, the law set up primary vaccination at 1 year, revaccination at 6 years, and revaccination again at 12 years.

During the smallpox eradication campaign those who were engaged in the actual program did try to collect information regarding the duration of vaccine immunity. At that time, the CDC prepared an "operational manual" for the eradication campaign in the late 1960s. It indicated, based on Dixon's estimate, that the duration of immunity, namely, a protection effectiveness of 99.5% 3 years after vaccination, at 87.5% in 10 years and 50% in 20 years (8). It also introduced Marsden's study, namely, a study including 1,753 variola minor cases from 1928 to 1934, showing that only 3.0% developed the disease 19 years after the primary or revaccination, 11.7% developed the disease after 29 years, and 23.6% after 39 years (9) (Table 1).

Specifically remarkable is the extremely small portion of the cases that developed the disease after revaccination despite the fact that the potency of the smallpox vaccine at that time would not be as strong as it was during the smallpox eradication program of 1967-1980. One might think that since at that time, smallpox was endemic, immunity induced by natural infection might have played a role on the booster effect in older individuals. But the extremely low frequency of cases affected after revaccination makes one think that residual immunity played a major role.

A. R. Rao, an Indian health officer in Madras, studied this question during the eradication campaign (10). His results grew out of his personal investigation as chief of an Infectious Diseases Hospital in smallpox-endemic area. Rao's data is based on the age, not years having elapsed since vaccination as studied by Marsden. Assuming the all vaccinations were conducted at very young ages, however, the age distribution of cases may suggest the duration of immunity level (10) (Table 2).

Thus, it is assumed that only 7.95% of vaccinees up to the age of 10 years contracted the disease, and 25.87% of vaccinees up to the age of 19 years contracted the disease. Table 2 also shows the corresponding figures of the unvaccinated as a good contrast, namely up to 10 years of age, 79.2%, and up to 19 years, 87.6%. However, it should be noted that in Rao's data, at up to 19 years of age, vaccinal immunity appears to prevent smallpox infection effectively, but unlike Marsden's data, at up to 29 years of age, immunity has already waned causing about a total of 70% of cases among vaccinees.

Experience further indirectly supporting the above observations is provided by an investigation of European outbreaks by Mack et al. (11). Of 680 cases of variola major of reported outbreaks in Europe from 1950-1971, case fatality rate was 52% among the unvaccinated whilst only 1.4% those vaccinated before 10 years or less died and 11% before 20 years or more died. These case mortality rates can be regarded as effect of residual immunity for long periods although immunity had waned. Mack's data is consistent with that of Marsden and Rao. Similar observations were made by Gayton. Of 2,085 cases of variola major, the case mortality rate of those vaccinated was less than 4% up to 20 years of age in contrast to about a 50% fatality rate among the unvaccinated (12).

As regards the effectiveness of revaccination as shown in Marsden's study, the small number of cases revaccinated may broadly suggest that a significant protective effect could be anticipated for long period of time. The principal problem in this would be whether the experience concerning variola minor is applicable to that in variola major. There is no way to test this today. An attempt to elucidate this point failed, namely comparisons of clinical types based on Rao's data show no clear tendency (Table 3). Note that variola major

Table 1. Variola Minor, River Hospitals, London County Council, 1928-1934

Elapsed time (years) since vaccination or revaccination	Number of cases occurring after:		Total cases (%)
	Primary vaccination	Revaccination	
0-3	0	0	0 (0)
4-9	6	1	7 (0.4)
10-19	38	7	45 (2.6)
20-29	147	5	152 (8.7)
30-39	204	5	209 (11.9)
40-49	520	4	524 (29.9)
50+	813	3	816 (46.5)
Total	1,728	25	1,753 (100)[1)]

(Based on reference 9)

[1)] Of total of 13,686 cases reported, 1,753 cases had been vaccinated before.

Table 2. Age distribution of smallpox cases among the vaccinated and the unvaccinated

Vaccination status	Cases in all years	Cases by years of age					
		0-4	5-9	10-19	20-29	30-39	40+
Vaccinated	3,398	90	180	609	1,525	634	360
(%)	(100)	(2.6)	(5.3)	(17.9)	(45.0)	(18.6)	(10.6)
Unvaccinated	3,534	2,091	708	297	260	91	87
(%)	(100)	(59.2)	(20.0)	(8.4)	(7.4)	(2.5)	(2.5)

(Based on reference 10)

Table 3. Clinical variety and age distribution of smallpox cases among the vaccinated

Clinical variety	Number of cases (%)	Age group in years (%)		
		0-19	20-39	40+
Hemorrhagic[1)]	115 (100)	17 (14.8)	80 (69.6)	18 (15.6)
Flat[1)]	45 (100)	7 (15.6)	27 (60.0)	11 (24.4)
Ordinary[2)]	2,377 (100)	555 (23.4)	1,546 (65.0)	276 (11.6)
Modified[2)]	861 (100)	300 (34.8)	506 (58.8)	55 (6.4)
Total	3,398 (100)	879 (25.9)	2,159 (63.5)	360 (10.6)

[1)] Hemorrhagic and flat types are rare.
[2)] Ordinary resembles variola major and modified, minor.

tends to have much greater number of more severe skin lesions (ordinary type) as compared with variola minor (modified type). Also at that time, variola minor or variola major had to be diagnosed based on clinical picture; hence, we cannot exclude the possibility that in Marsden's and Rao's data there might be mixture of major or minor. Thus, unless further evidence comes up, the finding based on Marsden's study could be applicable to estimate the effectiveness of revaccination to date.

In summary, these findings described above suggest that immunity did decline after vaccination, but that it still significantly prevented a portion of infections as a number of years elapsed after vaccination. Parenthetically, an attempt failed to identify experiences showing shorter duration of vaccinal immunity which would be contrary to the above described findings.

3. Vaccination policy in Japan

Smallpox vaccination in Japan was discontinued in 1976. Hence, as of 2002, the age group of younger than 26 years, born in 1977 and thereafter, have never been vaccinated, and are thus susceptible to smallpox infection if it were deliberately introduced to Japan (Fig. 1). Also estimated is the immunity level of older population with vaccination history. It is obvious that Japan requires effective preparedness, namely, development of an emergency surveillance and containment system in order to cope with possible smallpox bioterrorism. On the other hand, despite every effort to cope with disaster we will have to admit the impossibility of perfect control measures. This consideration as such leads to second thoughts regarding the reinstitution of a nationwide vaccination program despite the significant frequency of complications, as expressed in a few of medical journals (1,2).

In the circumstance, based on the experience mentioned in proceeding section, an attempt was made to estimate the over-all vaccinal immunity in the Japanese population as shown in Table 4 and Fig. 1.

In each Group A, B, and C, residual immunity was broadly estimated as shown in the footnotes of Table 4. It is theoretical, but shows the extent of herd immunity. The frequency of complications is also estimated based on data from the CDC national survey in the U.S. (4). One death would occur in each 1 million primary vaccinees (3). However, here we should note that Japan is prepared to use tissue culture freeze-dried vaccine with LC16m8 strain. This strain appears to be of less neuropathogenicity, whilst producing good skin reaction and neutralizing antibody (4). However, as the vaccine was developed in mid-70s, it was not used as an actual control measure for a smallpox outbreak.

This review suggests the following strategy.

1. Unless imminent threat of smallpox bioterrorism is recognized, it would not be wise to initiate nationwide vaccination program because of the significant complications expected in Group A. Further, residual immunity in Groups B and C would apparently be greater than health regulations have previously implied, especially in Group C, although a number of years have elapsed since the year of revaccination.
2. These estimates should be modified on an individual basis,

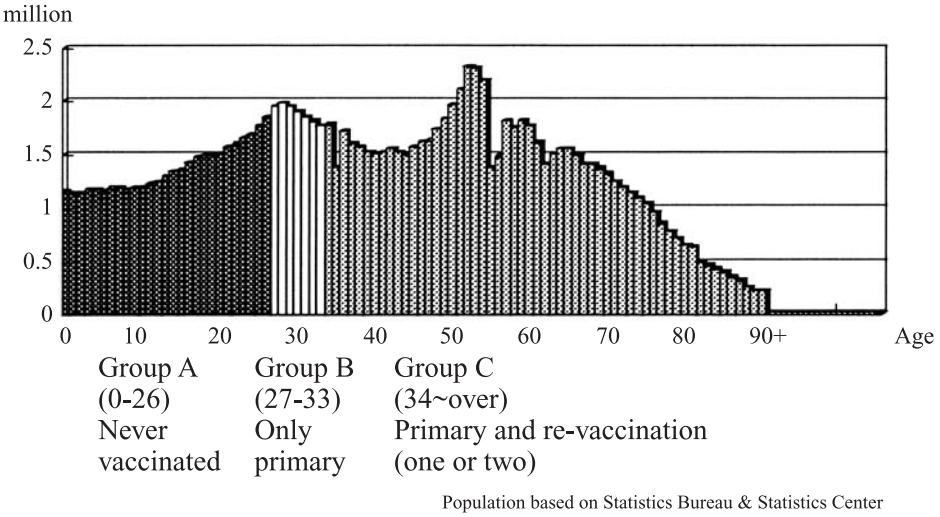

Fig. 1. Japanese population age distribution and smallpox vaccination history as of April, 2002.

Table 4. Vaccination priority of population by age as of 2002

	Age	Population (Million) As of 2001	Postvaccinal encephalitis[1)]	Progressive Vaccinia[1)]	Eczema vaccinatum[1)]	Immunity estimated[3)]	Priority
Group A Never vaccinated, born after 1976	<1	1.16	8[2)]	–	10	Nil	High
	1-4	4.67	11[2)]	2	53		
	5-9	5.95	20[2)]	4	43		
	10-19	13.61	–	35	101		
	20-26	11.66	41[2)]	81	284		
Group B Vaccinated, but primary only born between 1969-1975	27-33	13.23	–	15	–	Circa 30-80%	Medium
Group C Vaccinated first revaccination, born between 1962-1968	34-40	11.15	–	13	–		
Vaccinated, first & second revaccination, born before 1961	41+	64.44	–	71	–	Circa >90%	Low

[1)] Frequency estimated based on Table 7.4 Complication of smallpox vaccination, data expressed as cases per million vaccinations. US national survey, 1968 (reference 4).
[2)] With current Japanese vaccine strains LC16m8, the estimates of post-vaccinal encephalitis would be much lower (reference 4).
[3)] Mainly based on Marsden, Rao, and Mack (Tables 1, 2). Estimate is theoretical. Low vaccination coverage may reduce the immunity level of a group as a whole. Group B estimate is broad; 30% based on Rao's data and 80% based on Marsden's data, examining proportions of cumulative total of those protected, up to the similar age group.

since, in the past, vaccination status could have varied according to the number of those which had been left unvaccinated, which may be as high as 30-40%.

3. From national security purposes, it would be desirable to set up effective task force system to conduct investigations as well as perform containment vaccinations (on a larger or smaller scale). In order to do this, it is recommended that selected personnel from health and medical circles as well as those from fire brigades be vaccinated so that they are already immune in the case of an emergency. The complication would not pose a significant risk if they are recruited from Group C which is composed of those who have been revaccinated.
4. If the world political situation rapidly deteriorates and some nations prepare nationwide vaccination campaigns, Japan's vaccination strategy would first focus on Group A and then Group B. The LC16m8 vaccine can be first used for such a program. It would be urgently desirable to ascertain the immunogenicity of this vaccine.

4. Discussion

Bioterrorism using smallpox virus is unprecedented. There are great uncertainties as to when, how, and where it could occur. It is also clear that first, vaccination is the sole practical preventive measure, and secondly that surveillance and containment operations can effectively stop disease transmission if it does not occur simultaneously over wide areas. Once it occurred, however, there might be unpredictable events such as panic, shortage of vaccine, breakdown of health measures, unexpected humans errors, etc. Hence, preparedness will have to be established, and it is very important that, on a practical level, a specific priority be determined regarding which segment of the population is most at risk. The paper presented here is an attempt to do this, focusing on duration of vaccinal immunity based on the vaccination history of a population. Although the data is scarce and the quality of available data does not fully meet modern scientific assessment (for instance, unknown vaccine quality, heat stability of vaccine, lack of cold chain, lack of suitable denominators, etc.), it is believed that the priority presented here would not be far from the actual case. In fact, an absolutely accurate picture would be difficult to create now and in the foreseeable future.

Vaccinal immunity is refined as preventing infection by the smallpox virus; namely, it refers to protective immunity. This definition is practical for the assessment of available field data for the following reason: in smallpox, subclinical infection is rare in unvaccinated individuals and of no epidemiological significance. This is, in fact, the reason why eradication succeeded. There was no smallpox outbreak without a human source of manifested infection. The eradication strategy was not dependent on herd immunity by naturally induced infection among the unvaccinated, as observed in varicella or polio.

The CDC's statement-that the duration of the vaccinal immunity lasts 3-5 years-indicates that nearly all the vaccinees can enjoy protective immunity against smallpox infection during that period. This paper discussed what would happen after 3-5 years. It showed that up to 10 years or to 20 years, a certain proportion of vaccinees still maintain protective immunity as broadly estimated in Table 4, namely 30% to 80% in Group B and >90% Group C. The wide range in the Group B is noted. Unfortunately, few data are available to examine this, but it would be constructive to present this wide range as it is, because it suggests that vaccinal immunity was sustained in Madras and London among a good proportion of vaccinees despite its waning over a long period of time after vaccination.

An ethical problem also existes; namely, those who personally wish to have vaccination cannot be ignored during an emergency situation. Extensive public education is needed before and during the preparedness phase. With that, individuals should weigh the benefit of vaccination and its complications. In the past, for primary vaccination, a vaccination scar

was clear indication that it was successful. Experience in revaccination was that whether it was a good "take" or an allergic reaction or something else was often difficult to determine. Thus, history of revaccination may have involved uncertainty.

In Rao's data (Table 2), the 45% of vaccinated cases of 20-29 years of age is rather difficult to interpret, as the age group of 30-39 years and more did not show a larger number of cases. However, this is not unusual if we see other data, namely age distribution of smallpox cases among vaccinees such as Marsden's findings (in addition to his variola minor data shown in Table 1) (9). Two variola major outbreaks (7,616 cases) and the others (5,665 cases), all with vaccination scars, showed the highest percentages of cases ranging 15% to 18% in the 20-30 year-old age group. Thereafter, they started to decline down to age groups 50-60 years, showing around 4-5 % in both. Rao suggested that, they might have been revaccinated, but this is not convincing since the data including Marsden showed a similar tendency. The reducing population size (or shorter life span) at that time or the increase in the number of smallpox survivors or some social factors that reduced the frequency of exposure to the disease might have played a major role.

It would be productive, if research institutions are conducting some seroepidemiological study that involves the collection of serum samples, that the tested vaccinia antibody titers be combined so that we may be more certain as to how we create a priority of need. Interpretations of serological data such as neutralizing antibody according to the year elapsed since the vaccination may shed further light on the problem of residual immunity (13).

5. Conclusion

Experiences in the duration of primary smallpox and revaccination have been reviewed in order to prioritize population groups having different vaccination histories in Japan against bioterrorism. This review suggests that residual vaccinal immunity even when it has elapsed over many years after vaccination, still prevents good percentage of vaccinees from contracting smallpox. Although as of to-date, no nationwide vaccination program may be required, good preparedness is needed for building a strategy and system which includes a vaccination policy. Further study of LC16m8 is most desirable. The effectiveness of any measures related to preparedness depends upon how effectively the agencies concerned can assess the extent and imminence of the threat. This is difficult, but it has to be mentioned here, and be done with vigorous effort.

ACKNOWLEDGMENTS

I am grateful to Dr. D. A. Henderson and Dr. Mineo Arita for their valuable comments and advise for improving the paper. I thank Ms. Miyuki Nakane and Ms. Yoshiko Kobayashi for searching and collating a number of references for preparation.

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