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The use of smallpox virus as a biological weapon: the vaccination situation in France
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In the context of its plan to fight against bioterrorism, the Ministry of Health asked the Institut de Veille Sanitaire to evaluate the epidemic risk from a release of the small pox virus, and to make recommendations on potential vaccination strategies to be implemented. A benefit/risk assessment of various vaccination scenarios, including vaccination of the whole French population, was carried out to evaluate the severity of a terrorist action threat. This analysis concludes that at this stage, vaccination action does not seem to be justified. Even in the case of a real threat, the vaccination of frontline healthcare personnel, and in particular of contacts of cases, must be given priority.

Introduction

In 1980, the World Health Organization (WHO) announced the eradication of smallpox, and since then, no new case has been reported. All countries in the world had stopped smallpox immunisation by the early 1980s at the latest. In the light of recent events, the possibility that viral material could have been extracted from one of the two laboratories in the world authorised to store the smallpox virus has revived concerns about the use of the virus as a biological weapon.

France is one of several countries that have stocks of smallpox virus and can produce the traditional vaccine. With a view to setting up a plan to fight bioterrorism, the French Ministry of Health asked the Institut de Veille Sanitaire (InVS) in early October 2001 for its conclusions on various vaccination scenarios depending on the severity of a threat from a deliberate release, taking into account the epidemic risk and the side effects of the vaccine.

Method

The analysis consisted of three preliminary stages: identifying conceivable vaccination strategies, defining the different risk levels, and evaluating the number and severity of side effects of the vaccine linked to the various vaccination strategies.

The strategies were identified on the basis from data on disease transmission, and on the evaluation of the epidemiological impact that the introduction of the smallpox virus would have in France. The fact that there might be other strategies to fight the disease was taken into account.

Transmission of the disease and implications in terms of control measures

Before the vaccine was introduced, the virus was widespread and highly contagious. In its major form, smallpox was a severe disease, characterised by erupting skin lesions that could kill up to 30% of non-vaccinated patients. Case fatality rates were most notable in very young or old people.

Smallpox is mainly transmitted in aerosolised form, mainly by direct contact from person to person. Transmission from cutaneous lesions has a secondary role.

Smallpox contagiousness is important but less so than that of other acute infectious diseases, such as measles. In a totally susceptible population of average density, the number of secondary cases following one case of smallpox infection was estimated to be around five, compared with 16 for measles. The disease is usually transmitted in the close environment of the patient (family contacts, relatives, or medical staff) (1). This is because transmission of the virus occurs exceptionally before the lesions erupt, which usually occurs two weeks after a patient has become infected. At this stage, patients are usually confined to bed because of their poor general condition and high fever, thus considerably limiting the number of contacts.

The number of secondary cases can be reduced by implementing control measures around the primary case. An early diagnosis, made easy by the specific clinical signs (lesions embedded in the dermis, centrifugal eruption in one ‘crop’), followed by rapid and strict isolation of the patient makes it possible to limit the number of contaminated contacts. Moreover, vaccination of these contacts, if carried out within three to four days after exposure, prevents the disease or results in less severe symptoms. Close monitoring of the contacts enables physicians to detect the disease early in case of vaccination failure. It has been possible to eliminate the disease in densely populated areas, thanks to active research, isolation of cases, and vaccination of patient contacts. In these areas, the level of immunity in the general population needed to allow elimination – around 100% for the most densely populated areas alone – would have been impossible to achieve by immunisation programmes (2).

Evaluation of the epidemiological impact of an exposure to the smallpox virus

The extent of an outbreak of smallpox virus infection resulting from terrorist action in France is difficult to measure. It depends on the number of people infected from the initial source, and on various factors that influence the dynamics of viral transmission, such as the susceptible proportion of the population, the local sociodemographic context, and the nature and timeliness of control measures.

Most of France’s population is probably currently susceptible to the disease. Preventive immunisation was mandatory from 1901 to 1978, and given as primary vaccination during the first two years of life, with boosters recommended at ages 11 and 21, until 1984.

People who were vaccinated before 1984 are likely to have kept a degree of protection that would alleviate the severity of the disease, even though those patients would contribute to transmission. People older than 40 might still benefit from complete protection – although the proportion of the population is not known – provided they received the three doses recommended at 1, 10, and 20 years of age.

In the event of important and unexpected initial contamination in an urban area, the population density and an initially high susceptibility level could lead to a considerable number of secondary cases induced by each index case, possibly reaching 10 to 20 in the first wave of cases, causing an outbreak extending on several generations of cases (1, 3). But an early diagnosis may help limit the

number of patients, provided response strategies – such as isolation of cases associated with vaccination and medical follow up of contacts – are implemented immediately.

Table 1 : Rates of complications associated with smallpox vaccination, by age group (case / million vaccination)

Age and no. of vaccinations	Accidental inoculation	General vaccinia	Vaccinal eczema	Progressive vaccinia	Vaccinal encephalitis
Primary-vaccination					
< 1 years	507,0	394,4	14,1	**0**	42,3
1-4 years	577,3	233,4	44,2	**0,4**	9,5
5-19 years	371,2	139,7	34,9	**1,8**	8,7
>20 years	606,1	212,1	30,3	**6,9**	**3,5**
Revaccination					
<1 years	-	-	-	-	-
1-4 years	109,1	-	-	-	-
5-19 years	47,7	9,9	2,0	0	0
>20 years	25,0	9,1	4,5	6,8	4,5

- *- : sufficient number to calculate rates*
- * : *includes encephalopathies in newborns*

Frequency and severity of side effects of vaccination

The evaluation of the number of deaths and severe adverse events induced by large scale vaccination was carried out from population data of the 1999 census (source: INSEE, Institut National de la Statistique et de Etudes Economiques - National Institute of Statistics and Economic Studies), and from the estimated French population's vaccination history from statistics from INSERM (Institut National de la Santé et de la Recherche Médicale - National Institute of Health and Medical Research) (4). The rates of side effects come from two American studies carried out in 1968, a national survey and a survey carried out in 10 states (5, 6). The survey protocol carried out in the 10 states was stricter, and the estimates are considered as very reliable. We have used data from this study, except where the number of vaccinated people was too low to evaluate the incidence of very rare adverse events, such as progressive vaccinia and vaccinal encephalitis. In these cases, we used the data of the national survey. (table 1)

Table 2 : Fatality rates from smallpox vaccination complications

Vaccinal eczema	6%
Progressive vaccinia	30 à 60 %, median 45 %
General vaccinia	Good prognosis
Vaccinal encephalitis	9 à 57%, median 30%

The data used on case fatality rates from side effects come from a review of the literature and appear in table 2 (2, 7) .

The level of permanent neurological adverse events in patients having survived encephalitis as a result of vaccination is estimated at 25%.

Results

Identification of different vaccination strategies

Four possible vaccination strategies have been identified.

Strategy 1: vaccination or revaccination of the entire French population

In this strategy, we considered that all the population should be vaccinated; available data on protection for more than 20 years are not conclusive about the level of protection, even in those who had been revaccinated twice.

Strategy 2: vaccination of groups at risk (healthcare staff, emergency, or related)

A second preventive vaccination strategy could consist of identifying populations at particular risk from infection, in case the smallpox virus should circulate again. Healthcare staff represent a particularly exposed population. During the last two French outbreaks, 15 out of 42 patients in Marseilles in 1952 and 18 out of 74 in Brittany in 1955 were hospital staff (8). Several vaccination options for healthcare staff may be considered.

Option 1: All healthcare staff likely to be in contact with cases or contaminated equipment: private general practitioners and hospital physicians, other hospital healthcare staff, laboratory staff, hospital laundry and mortuary staff, emergency staff such as ambulance drivers, and public health professionals participating in the control of infectious diseases could be included.
Vaccination options targeting subgroups at highest risk could also be considered.

Option 2: Vaccination of teams taking care of cases in a limited number of hospital facilities (one hospital centre per district, giving priority to university and regional hospitals), including laboratory and mortuary staff.
Option 3: Vaccination of all first line healthcare staff who will be in contact with the first suspected cases, before the diagnosis is confirmed: general practitioners, paediatricians, or hospital emergency staff.
If situation 4 occurred (see below), two additional strategies might be considered.

Table 3.1

Expected undesirable effects of smallpox virus vaccination in the general population

No of vaccinations			Accidental inoculation		General vaccinia		Vaccinal eczema		Progressive vaccinia		Vaccinal encephalitis	
		CV (%) *	Primo	Revac	Primo	Revac	Primo	Revac	Primo	Revac	Primo	Revac
< 1 years	760000	0	385	-	300		11	-	0	-	32	-
1-4 years	2977543	0	1719	-	695		132	-	1	-	28	-
5-19 years	11842842	0	4396	-	1658		414	-	21	-	103	-
20-22 years	2296346	0	1392	-	487		70	-	16	-	8	-
23-29 years	5838621	50	1769	73	619	27	88	13	20	20	10	13
30-34 years	4382967	65	930	71	325	26	46	13	11	19	5	13
35 years and +	32718106	90	1983	736	694	268	99	133	23	200	11	133
Total	60 816425		**12574**	880	**4778**	320	**860**	**158**	**92**	239	**199**	158

* CV = Coverage for primary vaccination

Tableau 3.2

Number of expected deaths following smallpox vaccination in the general population

		Accidental inoculation	General vaccinia	Vaccinal eczema	Progressive Vaccinia	Vaccinal encephalitis
Nb of deaths	**Primo**	0	0	52	41	60
	Revac	0	0	10	108	48
Total	**317**	**0**	**0**	**61**	**149**	**107**

Strategy 3: vaccination of contacts of one case

Strategy 4: regional vaccination around cases

Definition of risk levels

Several situations have been studied, depending on the plausibility of a smallpox outbreak threat.

Situation 1 : (this reflects the situation in mid October 2001): a potential threat exists, but there is no information on whether any terrorist groups are in possession of the virus
Situation 2: information or facts make plausible terrorist action using the smallpox virus
Situation 3: at least one confirmed case was diagnosed outside the national territory
Situation 4: at least one confirmed case was diagnosed inside the national territory
Estimation of the number of severe side effects and deaths associated with vaccination

- Vaccination / revaccination of the whole French population

Tables 3.1 and 3.2 give estimates on the number of severe side effects and deaths that one dose of vaccine given to the entire population might cause.

Table 4

Recommended strategies following the evaluation of a risk of terrorist attack

Situation 1 : **potential threat**	
Strategy 1 Vaccination, revaccination of the whole population	Balance benefit / risk very much in disfavour of vaccination
Strategy 2-1 Vaccination of health care and emergency staff	Balance benefit / risk in disfavour of vaccination
Situation 2 : **plausible threat**	
Strategy 1 Vaccination, revaccination of the whole population	Balance benefit / risk very much in disfavour of vaccination
Strategy 2-1 Vaccination of health care and emergency staff	Balance benefit / risk in disfavour of vaccination
Strategy 2-2 Vaccination of selected dedicated hospital teams	Strategy to consider

Situation 3 **: ≥ 1 confirmed case outside the national territory**	
Strategy 1 Vaccination, revaccination of the whole population	Balance benefit / risk very much in disfavour of vaccination
Strategy 2-1 Vaccination of health care and emergency staff	Balance benefit / risk in disfavour of vaccination
Strategy 2-2 Vaccination of selected dedicated hospital teams	To be considered
Strategy 2-3 Vaccination of health care and emergency staff	To be considered
Situation 4 **: east one confirmed case in France**	
Strategy 1 Vaccination, revaccination of the whole population	To consider if the availability of vaccines allows it, if the outbreak is not contained, if there is a risk of natioanl spread, depending on an updated benefit/risk analysis
Strategy 2-2 Vaccination of health care and emergency staff	Choice depending on the availability of the vaccine, and on the mobilisation of national staff by the authorities
Strategy 2-3 : Vaccination of first line practitioners	
Strategy 3 : Vaccination of contacts	**IMPERATIVE** Depending on the availability of the vaccine and the local spread of the outbreak
Strategy 4 : Regional vaccination	

Vaccination and revaccination of the entire French population would result in around 315 deaths. There would be a further 89 cases with adverse events of encephalitis.

Vaccination and revaccination of all healthcare staff, emergency and related (strategy 2, option 1)

An evaluation of the number of severe side effects and deaths associated with the vaccination of healthcare and emergency staff leads to an estimate of six to eight deaths, depending on actual size of the population and their current vaccination status.

Analysis of the different situations

Situation 1 (the mid October 2001 situation): a potential threat exists, but there is no information on the possession of the virus by terrorist groups.

It seems inappropriate to suggest vaccination or revaccination of healthcare staff (strategy 2 option 1) and a fortiori the whole French population (strategy 1), as the real risk of severe complications associated with vaccination outweighs the theoretical risk of exposure to the smallpox virus.

Priority at this stage should be given to planning methods for the vaccination and control measures of a case made necessary by the intensification or realization of a threat (situation 2 or beyond). Raising awareness among the medical profession and public health professionals on the characteristics of the disease and measures to be taken when faced with a suspected or confirmed case of smallpox would be useful.

Situation 2: information or facts make plausible a terrorist attack using the smallpox virus.

Vaccination strategies for the whole population (strategy 1) and all healthcare staff (strategy 2, option 1) would remain inappropriate, even if the vaccine were available in sufficient quantity. This would expose vaccinated subjects to a disproportionately high risk of severe complications after vaccination since it would be impossible to define geographically the population likely to be affected after a terrorist attack.

A favoured strategy might be selective vaccination of chosen hospital teams from the main hospitals (one hospital per district), which could be put in charge of the potential first suspected or confirmed cases of smallpox (option 2). These teams could play the part of referents, participating in raising awareness among healthcare staff. They would also be able to provide clinical expertise if necessary.

Situation 3: one or several cases of smallpox are confirmed outside the national territory.

In this situation it seems desirable to extend the preventive vaccination strategy beyond dedicated hospital teams to all first line practitioners and healthcare staff who may have to examine or be in contact with patients with smallpox, before the diagnosis is confirmed (general practitioners, paediatricians, and emergency staff) (strategy 2 options 2+3). Priority should be given to the strict planning of methods to implement response strategies around cases. That way, they will be applied without delay, in case situation 4 arises. Methods on the detection and isolation of suspected smallpox cases on entry into national territory will have to be implemented.

Situation 4: Oone or more smallpox cases are confirmed inside the national territory.

The vaccination strategy will depend on the situation, in particular available information on the number of subjects exposed to the source of infection and stocks of available vaccines. The following points, however, need to be emphasised.

In the case of a single attack, when the first cases are symptomatic, the source of the virus will be completely inactivated; the virus does not survive more than two days once spread in the air and exposed to light.
It is likely that a deliberate release would target urban populations first. The level of vaccine coverage necessary to prevent viral circulation would be very high and could not be reached rapidly. People who have been vaccinated, even if a long time ago, should be assigned in priority to take care of the first cases while waiting for vaccines to be available.
Control measures around suspected or confirmed cases will affect the dynamics of the outbreak and should be implemented as soon as possible. They consist mainly of strict isolation of suspected or confirmed cases, if possible in rooms with negative pressure, and on vaccination and monitoring of

body temperature of all those who had close contact with cases, since the occurrence of erupting skin lesions or, as a precautionary measure, fever (strategy 3).
A vaccination strategy for healthcare staff should be implemented as soon as possible. Depending on how many doses of vaccine are available, the number of index cases, the geographical spread of cases, decisions of public health authorities to mobilise a more or less important proportion of the medical profession in the control of the outbreak, this vaccination may or may not interest the whole personnel concerned (strategy 2 option 1) or consist of vaccinating dedicated teams, associated with the vaccination of all first line healthcare staff (strategy 2 option 2 +3).
Extension of the vaccination strategy to a geographical area where cases have been detected may be considered, provided, on the one hand, that enough vaccine is available afterwards to set up the vaccination of potential future contacts in other areas and, on the other hand, of an epidemiological context favouring a wide local circulation of the virus (strategy 4).
Only if the outbreak seems impossible to control rapidly, enough doses of vaccine are available, and all logistical, financial, legal, and ethical issues linked to vaccination are settled, a mass vaccination strategy should have to be considered on the basis of an updated analysis of benefits and risks (strategy 1).
Table 4 summarises the various recommended strategies depending on the evaluation of a terrorist attack risk.

Discussion

Our estimates of the incidence of side effects should be considered carefully, because of diverging data in the literature on the frequency of post-vaccination complications, reflection of different methods, and quality of surveys. Our evaluations, however, are based essentially on a survey whose protocol allowed for exhaustive case finding, and are likely to constitute acceptable estimates. Case fatality rates regarding primary vaccination of 6 per million vaccinated people is similar to the one evaluated in France by Martin-Bouyer et al (5.8 deaths per 1 million vaccinations) from 1968 to1977 for over four million primary vaccinations (9). Data from all surveys might have overestimated the frequency of side effects, as morbidity after vaccination by simple temporal association was not excluded. It is possible that the frequency of complications that would be observed if the old stock of vaccine currently available in France was used has been underestimated. Although regular quality controls carried out on those vaccines by the AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé) have ascertained their biological activity, the occurrence over time of neurotoxic products cannot be excluded.

We do not recommend preventive vaccination at the current risk level. Even in the case of a recognised threat, large scale vaccination, which is likely to be demanded, would lead to the occurrence of severe side effects in populations at no special risk of exposure. Moreover, it would raise the concern of vaccine shortage, stocks of which could be insufficient for targeted vaccination around suspected or confirmed cases, in the event of ongoing transmission. Vaccination of contacts of a case constitutes the most efficacious and efficient vaccination strategy considered, provided it is implemented rapidly.

These conclusions, essentially based on the experience acquired during the reinforced programme for smallpox eradication, are in agreement with the WHO recommendations made in October, and more recently by the Centers for Disease Control in the United States (10).

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