Effectiveness of Postexposure Vaccination for the Prevention of Smallpox: Results of a Delphi Analysis

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We estimated the effectiveness of postexposure smallpox vaccination in preventing or modifying disease in naive and previously vaccinated adults, using the formal Delphi technique. For persons not previously vaccinated, the median effectiveness in preventing disease with vaccination at 0–6 h, 6–24 h, and 1–3 days after exposure was estimated as 93%, 90%, and 80%, respectively, and effectiveness in modifying disease among those who develop illness was estimated as 80%, 80%, and 75%, respectively. Effectiveness was greater for those vaccinated previously. High postexposure vaccination effectiveness for preventing or modifying smallpox is consistent with the limited data available, is biologically plausible, and is similar to that seen for other viral vaccine-preventable diseases. These estimates support the Advisory Committee on Immunization Practices recommendations and provide a key parameter for mathematical models on which policy decisions may be based.

With increased concern about a potential bioterrorist attack, plans are being formulated for smallpox (vaccinia) vaccination before a possible event and for outbreak response should a smallpox reintroduction occur. In 2001 and 2002, the Advisory Committee on Immunization Practices (ACIP) recommended that pre-event vaccination be of limited scope and endorsed the use of surveillance and containment—the strategy that was used to eradicate smallpox globally—if a reintroduction occurs [1, 2]. Both of these recommendations are based, in part, on the assumption that vaccine administered to persons shortly after exposure to smallpox would be protective or would modify the severity of disease and, possibly, its communicability.

Although postexposure vaccination was part of the World Health Organization smallpox eradication strategy, only limited data exist on its effectiveness. Studies in India, Pakistan, and Bangladesh of transmission within families or compounds have shown that the vaccination of contacts during the week after onset decreases the rate of secondary attack [3–6]. However, few details on the timing of postexposure vaccination or the vaccination history of contacts exist, making the interpretation of results difficult. We know of no published data that have evaluated the protective effectiveness of vaccination during shorter periods after exposure, and discussions with several of the authors of the few published studies did not identify unpublished data that have addressed this question. Such information is important for 2 reasons. First, the location of a potential smallpox reintroduction is unpredictable, so unless all health care workers are vaccinated before an event, some unvaccinated health care workers would be exposed. The effectiveness of postexposure vaccination is important in considering the potential benefits versus the risks of pre-event vaccination in this population. Second, postexposure vaccine effectiveness is an important parameter in mathematical models that predict the consequences of a smallpox attack and that may inform the development of national policy.

Because data from the smallpox eradication era are not available, we conducted a formal Delphi analysis to develop a quantitative assessment of postexposure vaccination effectiveness from a group of smallpox experts who were involved in the eradication campaign.

Methods. The Delphi method, which was developed by the RAND Corporation in 1948, is a method to systematically obtain expert opinion and build consensus in a way that maximizes the impact of the strength of experts’ arguments while minimizing that of individual personalities and group dynamics [7, 8].

We identified potential panel members from public health officials who participated in smallpox eradication activities. Several had participated in the training of public health response teams at Centers for Disease Control and Prevention, and others had authored peer-reviewed articles on smallpox control. None of the participants at the time of the study (or currently) had a smallpox decision- or policy-making role. Potential participants received a screening questionnaire that requested information on the duration and type of field experience, including the use of vaccination after exposure in household and medical settings.
Table 1. Effectiveness of postexposure smallpox vaccination by prior vaccination status and time since exposure.

<table>
<thead>
<tr>
<th>Time between exposure and vaccination</th>
<th>Prevent disease, No prior vaccination, %</th>
<th>Modify disease, No prior vaccination, %</th>
<th>Prevent disease, Vaccinated &gt;30 years prior, %</th>
<th>Modify disease, Vaccinated &gt;30 years prior, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25th</td>
<td>50th</td>
<td>75th</td>
<td>25th</td>
</tr>
<tr>
<td>0–6 h</td>
<td>75</td>
<td>93</td>
<td>98</td>
<td>65</td>
</tr>
<tr>
<td>6–24 h</td>
<td>65</td>
<td>90</td>
<td>95</td>
<td>58</td>
</tr>
<tr>
<td>1–3 days</td>
<td>55</td>
<td>80</td>
<td>89</td>
<td>40</td>
</tr>
<tr>
<td>4–7 days</td>
<td>8</td>
<td>25</td>
<td>35</td>
<td>18</td>
</tr>
<tr>
<td>8–14 days</td>
<td>0</td>
<td>2</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

* Those in whom disease was not prevented.

After selection of the panel, the study coordinator (L.B.) distributed a questionnaire to panel members requesting quantitative estimates of vaccine effectiveness in preventing or, for those in whom disease was not prevented, modifying smallpox, on the basis of when vaccination occurred relative to exposure (available on request from the authors). We collected estimates for persons without prior immunity to smallpox and for those who had been vaccinated >30 years ago. We tabulated the estimates and calculated 25th, 50th, and 75th percentiles. The coordinator obtained explanations for the responses from panelists whose estimates were <25th or >75th percentiles and anonymously distributed them to the other participants, along with the 25th, 50th, and 75th percentiles for each question. Where necessary, the anonymity of all responses was preserved by editing explanations so that the respondent could not be identified (e.g., references to countries in which respondents had administered smallpox vaccinations were changed to “country x” and “country y”). This process was then repeated for a second iteration, with participants having the opportunity to change their responses on the basis of the quartile data and to explain extreme values.

Results. Of 18 veterans of smallpox eradication initially contacted, 9 agreed to participate, 3 indicated that they had had little experience with postexposure vaccination, 3 had insufficient time, and 3 did not reply to the initial request. Among participants, field experience in developing countries that are endemic for smallpox ranged from ∼3 months to >8 years (median, 2 years and 4 months). All 9 participants had experience providing vaccinations after exposure in families and villages and assessing its impact on disease.

Panel members were unanimous in their estimate of the effectiveness of vaccination at least 2 weeks before exposure in preventing disease. Among those not previously vaccinated, the median predicted vaccine effectiveness was 95%, with an interquartile range (IQR; 25th–75th percentile) of 90%–98.5%. The median estimate for protection by vaccination immediately before exposure to was also 95%, with a wider IQR (80%–96%).

The estimates of median predicted postexposure vaccine effectiveness remained high for the first 3 days but dropped substantially thereafter (table 1). Two panel members consistently provided lower effectiveness estimates (figure 1). One panelist’s explanations for these lower estimates included concern about accurately determining the time of first exposure, uncertainty whether vaccination would prevent all prodromal symptoms in addition to the rash, and his observational experience. The other panelist explained his low estimates as concern that the...
response to vaccine would be lower in a population that includes a higher proportion of immunocompromised persons who may receive vaccine and the estimated time for developing a maximal immune response relative to the incubation period of the disease. The estimated protection was consistently higher for those with prior vaccination >30 years ago, compared with those never vaccinated (table 1). In this group too, however, estimates of protection rates of vaccine given >3 days after exposure declined substantially, to a median of <50% for vaccination between 4 and 7 days after exposure.

Panel members also estimated the effectiveness of postexposure vaccination in modifying the severity of illness among those vaccinated who nonetheless develop clinical illness (table 1). Combining the median estimates of disease prevented with those of disease modified yielded an estimate of the proportion of vaccinees who would develop disease of normal severity despite postexposure vaccination (figure 2). For totally susceptible and previously vaccinated persons who were vaccinated 1–3 days after exposure, the proportion developing disease of normal severity would be 5% and 2%, respectively; with vaccination given 4–7 days after exposure, the proportions are 52% and 25% (figure 2).

Discussion. The results of our Delphi analysis suggest that vaccination within 3 days of exposure to smallpox is effective in preventing disease and that, when disease prevention and modification are combined, few who are vaccinated within that period will develop disease of normal severity. These findings support the assumptions that underlie current ACIP recommendations for only limited pre-event vaccination and for the use of a surveillance and containment strategy should a smallpox reintroduction occur. These findings are based on a systematic method to quantify expert observation rather than on prospectively collected data, so the confidence that health care workers, policy makers, and the public should place on these results may be open to question.

The Delphi method has been used successfully in a variety of public health settings and other disciplines in which hard data have been scarce or absent [9]. Our panel members all had substantial experience in smallpox eradication activities, and all reported observational—if not systematic—experience in providing vaccinations after exposure and in assessing whether disease subsequently occurred. Although unanimity was not achieved among panel members regarding the effectiveness of postexposure vaccination, estimates were generally similar for 7 of 9 participants. Concern by 1 panel member that postexposure vaccination might not prevent prodromal smallpox symptoms may reflect a gap between the definition of “prevention” and “modified disease,” which, for smallpox, is defined as a less severe rash illness that resolves more rapidly than typical smallpox. Among a group of children vaccinated after exposure to prevent measles—another viral infection that is acquired through the respiratory tract and has a 14-day incubation period—some remained well, some developed fever alone, and others developed fever and rash [10]. Another panel member’s concern that immunocompromised persons might respond less well to vaccine is reasonable. With pre-event vaccination, persons with these conditions would be deferred from vaccination because of an increased risk of severe adverse events, although, if they were exposed to disease after a reintroduction of smallpox, they would be recommended for vaccination [1].

High levels of protection with postexposure vaccination are plausible biologically and are consistent with postexposure vaccination experience in other diseases. Smallpox infection usually occurs after exposure to respiratory secretions from a patient with oral lesions, which follow the febrile prodrome and precede the development of the typical smallpox rash. Virus initially infects mucosal cells in the upper and lower respiratory tracts and alveolar macrophages. After ∼3 days, it spreads to regional lymph nodes and lymphoid organs, where it replicates, and, at ∼8 days after exposure, a dramatic secondary viremia occurs. Prodromal clinical symptoms, including fever, myalgia, and malaise, occur concomitantly with this secondary viremia, and rash occurs 2–3 days later [11]. Vaccinia vaccination, in bypassing the respiratory tract and having a shorter incubation period, results in a more rapid development of cell-mediated immunity and neutralizing antibody. In a susceptible person, cell-mediated immunity is present by ∼8 days and antibody by ∼10 days after vaccination and would thus be present before the development of smallpox symptoms, even in the case of vaccination several days after exposure [11]. Because of the more rapid kinetics of the antibody response in a person vaccinated previously, it is plausible that protection would be greater among those vaccinated a second time. By analogy, in a randomized, controlled trial, the protective effectiveness of
have suggested residual immunity among the population. Although some data were prevalent. In this setting, low levels of transmission at- also came from developing countries, where endemic smallpox resulted in different estimates. The experience of the panelists of smallpox eradication whom we contacted and invited to participate in the study did so; their inclusion might have re-

References


postexposure vaccination for varicella was 90% within 3 days of exposure and 67% within 5 days [12].

Data from the smallpox eradication era support the use of postexposure vaccination. Heiner et al. [5] studied postexposure vaccination in rural Pakistan during 1968–1970. Among 464 household and compound contacts identified, 52 were vaccinated or revaccinated within 7 days of exposure. Only 1 (1.9%) of 52 who were vaccinated developed illness, compared with 90 (21.8%) of 412 contacts who were not vaccinated or were vaccinated >1 week after exposure. Although the apparent efficacy of postexposure vaccination was 91.3%, the postexposure vaccination group included both unvaccinated and previously vaccinated persons. In 1968, Rao et al. [4] evaluated secondary transmission among contacts in 254 infected families in Madras, India. Of 61 contacts who were vaccinated, 18 (29.5%) became infected, compared with 20 (47.6%) of 42 unvaccinated persons. Finally, in a 1972 investigation in Bangladesh, Sommer [6] found that the attack rate in families for whom vaccinations were provided during the first week after exposure was only 1.2 per 100, a rate that is one-third of the expected minimum. Because the longest interval between vacci-

Acknowledgments

We thank the Delphi panelists: Edward Brink, Stanley Foster, Don Francis, Donald Hopkins, Michael Lane, Thomas Mack, Al Sommer, Jason Weisfeld, and Bruce G. Weniger.