Preparation for an Outbreak of Smallpox in Israel*

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Abstract

Because of its high case-fatality rate, its very high transmission potential, and the worldwide shortage of effective vaccine, smallpox tops international lists of over a dozen possible bioterror and biologic warfare agents. In a scenario involving aerosol variola virus release, tens to hundreds of first-generation cases would ensue, as would hundreds to thousands of subsequent cases resulting from person-to-person transmission. A smallpox outbreak in Israel must not be regarded as a doomsday event: the methods of smallpox outbreak control are known and will be implemented. The rapidity with which organized outbreak control measures are competently executed will determine how many generations of cases occur before the outbreak is brought under control. Planning, vaccine stockpiling, laboratory expansion, professional training and public education, all carried out well in advance of an epidemic, will minimize the number of casualties. The reinstitution of routine smallpox vaccination in Israel, as in other countries, must be given serious consideration, since it has the potential for eliminating the threat of smallpox as a bioterror agent.

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Following the certification by the World Health Organization in December 1979 that smallpox had been eradicated from the world [1], the routine smallpox vaccination program in Israel was disbanded in mid-1980 [2]. According to articles published in recent years, clandestine supplies of variola virus exist in various locations, in addition to the two designated WHO laboratories in Russia and the USA. It is likely that variola virus has been obtained by international terror organizations and has already been prepared for delivery to civilian population centers as an aerosol [3–5]. The threat of an attack using smallpox virus is felt by many experts to be real, and any western country could be the target of such an attack at any time [3–5]. The recent anthrax emergency in the United States [6] adds a measure of immediacy to the topic. Thus, our purpose in penning this article is to acquaint the Israeli medical community with some of the issues facing us in the event that a smallpox attack is actually carried out, and our thoughts concerning preparations needed to mitigate its effects.

Although about half of the Israeli population possesses at least partial immunity to smallpox, we must assume that in the event of a smallpox outbreak, no matter how small, vaccination of the entire Israeli population will need to be carried out. If our experience in the minor 1988 polio outbreak [7] is relevant, the demand for smallpox vaccination by the population will be overwhelming, and the designation of some groups or geographic areas for vaccination and others not for vaccination will not hold for long: if public health officials vacillate, political authorities will quickly force the issue. As recently as 1972, a single imported case of smallpox in Yugoslavia, which resulted in 38 secondary cases, necessitated the vaccination of 18 million of the country's 21 million citizens [1].

Since Israeli public health officials maintain close professional ties with their counterparts in the Palestinian Authority, we can anticipate a request to assist in the provision of vaccine and organizing the vaccination of the contiguous Arab population. These three million persons probably have the same age-specific smallpox immunity as Israelis, and ensuring their protection against smallpox in the event of an outbreak would be of obvious public health benefit to the entire region.

Smallpox: clinical features [1,8]

Following an incubation period of 10–14 days, there is a 2–4 day severe but non-specific prodrome of sudden onset characterized by high fever, chills, severe headache and backache, and vomiting, followed by a typical eruption in 88% of cases. This eruption is a centrifugal macular rash that progresses through papular, vesicular, pustular, scab and scar stages in about 2 weeks, with all lesions on any one part of the body passing through the various stages together. In 6–7% of cases, primarily children, a "flat" eruption occurs in which the lesions are not raised but rather flush with the skin. In 2–3%, rapidly fatal hemorrhagic smallpox occurs, which may not be recognized as smallpox because the typical lesions do not develop. Another 2–3% of patients have only the prodrome without the rash. Overall, naturally occurring smallpox is 30% fatal, death being attributed to "overwhelming toxemia" or "massive viremia." Persons with partial immunity from vaccination many years in the past may have a less serious illness that is not fatal. If a strain more virulent than natural variola is released, morbidity may be even more severe, and mortality accordingly higher.

A potent antiviral agent, cidofovir, has been shown to be effective against poxvirus infections [9], and has the potential of being developed as a treatment for smallpox, as well as for use as post-exposure prophylaxis. Meanwhile, smallpox treatment is supportive only.

* The opinions expressed in this article are those of the authors alone and do not purport to be the official position of the Israel Ministry of Health.

WHO = World Health Organization

Transmission

Person-to-person transmission of smallpox is by direct contact, droplets and aerosol and, less commonly, by fomites, such as contaminated bed linens. In an uncontrolled smallpox outbreak, one contagious case typically generates 10–20 secondary cases [8,10] – a community transmission potential almost as high as that of measles and chickenpox. The secondary attack rate in susceptible household members is 50%. As in most infectious diseases, lighter cases of smallpox may be the most dangerous transmitters because the victims will be ambulatory for longer and will have many more contacts than those cases that result in early collapse.

If the initial exposure is by the intentional release of an aerosol, the virus may survive in the environment (on the ground, although not in the air) in an infectious state for 6 hours in hot weather to 48 hours in the cold. The designation of an area as "contaminated" with residual infectious material will depend on whether the attack is discovered immediately or only after the first clinical cases begin to appear, a minimum of 10 days after exposure. If the first signal of an attack is the appearance of cases, the physical environment will by then be non-infectious [8].

Vaccination

The vaccine is administered transdermally, traditionally by 15 perpendicular strokes of a bifurcated needle through a droplet of vaccine placed on the skin. Needle-free jet injection devices exist, which may be better suited to mass vaccination than the multiple puncture method [11]. Three days after primary vaccination a red papule appears at the vaccination site, which develops into a vesicle and then a pustule over the next 4 days. At least one day of fever between days 4 and 14 occurs in 70% of primary vaccinees. Neutralizing antibodies develop 10–13 days following vaccination, a time span corresponding to the incubation period of smallpox, meaning that post-exposure vaccination will sometimes, although not always, be protective. In vaccinees with partial immunity, the response to revaccination is accelerated, peaking at 3–7 days [8].

Under normal circumstances, the vaccination site would be inspected after one week to verify that a "major reaction" had occurred, and non-reactors would then be revaccinated. It is likely that in an emergency national vaccination campaign, inspection of vaccinees would have to be waived. Very few working nurses in Israel have experience with either vaccination method. A preferred method should be decided upon at once, vaccination devices procured immediately, and the training of nurses using the device selected should be organized.

Vaccination complications [8]

- Postvaccinal encephalitis occurs in 1/300,000 primary vaccinees, carries a significant case fatality rate and leaves many survivors with permanent neurologic sequelae. There is no treatment for this complication.
- Progressive vaccinia (vaccinia gangrenosa) is a rare but potentially fatal complication in which necrosis of the initial vaccination lesion spreads to adjacent skin as well as to other organs. This complication occurs in vaccinees with immune deficiency from any cause. Vaccinia immune globulin has been used for the treatment of progressive vaccinia, but not with great success.
- Eczema vaccinatum may occur in vaccinees or their contacts over parts of the body with current or healed eczema. It is characterized by high fever, toxicity and extensive vesicular and pustular eruption in areas of active or healed dermatitis. VIG is therapeutic.
- Generalized vaccinia, a blood-borne systemic disease and eruption caused by vaccinia virus, may occur in primary vaccinees. It is usually self-limited, but VIG may be needed in severe cases.
- Inadvertent inoculation is the accidental transmission of vaccine to contacts or the autoinoculation of skin sites in the person vaccinated. It is a self-limited complication, but VIG may be used in severe cases.

Methisazone (Marboran), a drug once useful in treating the complications of smallpox vaccination, is no longer produced.

Contraindications to smallpox vaccination [8]

- Eczema or other exfoliative skin conditions in the vaccine candidate or his/her household. If we estimate that 2% of the population suffers from eczema (130,000 individuals), the number excluded from vaccination, including household members, would be about half a million.
- Pregnancy: Approximately 150,000 women, but not household members.
- Immune deficiency from any cause, including disease, chemotherapy, radiation therapy, high dose corticosteroids. Our estimate of the number of such persons in Israel is approximately 100,000. If household members of immunosuppressed persons are also excluded from vaccination, the number of vaccination exclusions will rise substantially.

If, because of known or unavoidable smallpox exposure, vaccine must be given to people with contraindications, it is given together with VIG, 0.3 ml/kg body weight, i.e., 20–25 ml for an adult, 10 ml for a child.

Vaccine production

Smallpox vaccine, based on the Lister strain vaccinia virus grown on chorioallantoic membrane of fertilized eggs, was produced in the past by the Central Laboratories of the Israel Ministry of Health for domestic use [12]. In the event of a smallpox outbreak in Israel in the near future, vaccine is not likely to be available from any other country. We believe that to ensure an adequate smallpox vaccine supply for Israel, mass production of smallpox vaccine by the Ministry of Health should be authorized and budgeted and should be resumed as soon as possible. Moreover, in view of the U.S. plan to commission the production of 280 million doses of vaccine by the end of this year [13], the Ministry of Health should also explore avenues of smallpox vaccine acquisition from commercial sources. Nine million doses would be needed for the Israeli and contiguous Arab populations.

VIG = vaccinia immune globulin

Vaccinia immune globulin production

It is estimated that even after the exclusion of vaccine candidates with known contraindications, for every 1 million doses of vaccine given, 250 persons would subsequently require VIG for the treatment of unforeseen vaccine complications [8]. The therapeutic dose of VIG (as distinct from the preventive dose) is 0.6 ml/kg, or 40–50 ml for an adult, and about 20 ml for a child. Thus, about 45,000 ml of VIG would be needed to treat the vaccination complications of 6 million vaccinees in Israel. If we include the population of the Palestinian Authority, we would need 65,000 ml of VIG. Since the presence or absence of immune deficiency will be equivocal in enormous numbers of the sick and sickly, it can be anticipated that the demand for VIG, in the event of a mass vaccination campaign, will greatly exceed these legitimate estimates, and strict rationing will be needed unless a very large supply of VIG is available.

The production of 65,000 ml of VIG would involve the recruitment of 2,500 volunteers who were vaccinated in the past. These persons would be revaccinated to achieve maximum personal antibody levels and would undergo plasmapheresis twice, 4 and 6 weeks after revaccination. In order to begin revaccination of the volunteers, an initial small supply of VIG would have to be obtained from the Centers for Disease Control and Prevention in Atlanta, Georgia. These activities should be authorized, budgeted and should begin at once.

Immunity of the Israeli population against smallpox, 2002

Universal smallpox vaccination was mandated by law in Palestine/Israel from 1918 until 1980, and a national mass vaccination campaign was carried out in 1949 [2]. From then until mid-1980, children were vaccinated at ages 1 and 8 years, as were most new immigrants. Children born since 1979 were not vaccinated. The size of the cohort born in 1979–2002 is 2.6 million, and, as there is no naturally acquired immunity to smallpox, these young adults and children have no smallpox immunity. It must also be recalled that Israel has absorbed over 2 million immigrants since 1980, and as most western countries discontinued smallpox vaccination in the early 1970s, the majority of immigrants under age 30 must be assumed to be non-immune. Thus, most persons born in Israel before 1979 were vaccinated once, and many born before 1972 were vaccinated twice. Although vaccine-induced immunity against smallpox is relatively short-lived and wanes substantially by 10 years after the last dose [8], persons vaccinated in the distant past may possess sufficient immunity to prevent death, if not disease, in the event of exposure.

Smallpox containment

Smallpox containment is based upon two essential activities: a) *isolation* of patients to minimize spread of disease to others, and b) *vaccination* and subsequent surveillance of potentially infected individuals and isolation of those who develop disease.

All personnel involved in patient care or in face-to-face case or contact interviewing or vaccine administration will have to be vaccinated before embarking on these tasks. Persons who cannot receive smallpox vaccine will be excluded from these activities.

Epidemiologic investigation and surveillance services

Interviewing patients and possible case contacts will be under the supervision of the various public health offices. In the first instance, nurse-epidemiologists will perform these tasks, but if the numbers become too great they will be supplemented by community nurses, volunteer nurses and Israel Defense Forces medics. Daily follow-up of contacts for febrile illness or rash would similarly be the responsibility of the public health office. As in peacetime, notification of new suspect smallpox cases would be by phone or telefax to the local public health office and from there by phone, telefax or email to the Department of Epidemiology in Jerusalem, which would maintain the national morbidity maps and epidemic curve. The Israel Center for Disease Control as well as standing and ad hoc advisory committees will also require full and immediate access to morbidity and epidemiologic data. The appearance of confirmed smallpox in Israel would be immediately reported by the Ministry of Health to the WHO, as is required by international health regulations.

Isolation of cases and contact surveillance

Smallpox spreads through air ducts and via air-conditioning systems, and a large hospital outbreak has been described [14]; thus, the presence of a smallpox patient in a general hospital could be catastrophic for other inpatients. While the first few patients in a smallpox outbreak will undoubtedly end up in one or more general hospitals, suspect smallpox cases must not intentionally be admitted to any open general medical facility [8]. The care of a relatively small number of smallpox patients could be in one or more military-type field hospitals or in a single hospital or isolated hospital wing that has been emptied of its general patients. An alternative to full hospital care for those only moderately ill would be admission to one or several "convalescent hospices" that could be dedicated to smallpox patients. Smallpox admission facilities need to be designated and prepared far in advance of a smallpox emergency. In any event, if and when the number of smallpox patients outstrips the health system's smallpox bed capacity, patients will be have to be isolated and treated at home.

Case contacts, defined as persons with face-to-face contact with a case following development of fever in the case, as well as members of their immediate households, will be vaccinated. Thereafter, they will perform daily temperature measurements for the 17 day maximum smallpox incubation period and will be isolated at home if they develop fever or rash, until the significance of their symptoms is clarified. This policy will result in the ultimate voluntary isolation of many of the contacts, since vaccination itself will cause fever in most of them. Daily telephone surveillance of these individuals would be the responsibility of the public health offices, but could be carried out by community nurses or other trained personnel.

Vaccination priorities

At whatever stage the release of a smallpox aerosol is discovered, a spontaneous mass exodus from the attack area can be anticipated and cannot be prevented by physical means, in our opinion. The

imposition of large-scale quarantine is an undesirable option [15], unlikely to be enforceable in any event. Rapid deployment of vaccination centers in the hot zone will give the public confidence in the determination and capability of the government to fight the epidemic and will encourage those possibly exposed to remain near home to be vaccinated. The availability of VIG for the treatment of vaccination complications will provide an additional measure of reassurance to an exceedingly anxious citizenry.

As we have indicated, a confirmed case of smallpox anywhere in Israel will signal the need to vaccinate the entire population. Nevertheless, if inadequate vaccine supplies are available, priorities for vaccine use will have to be established. Even if the total vaccine supply is adequate, not everyone can be vaccinated at once – the hurried mass immunization campaign in 1988 in which 3 million Israeli citizens received oral polio vaccine took 18 days [7]. Thus, our suggested priorities for smallpox vaccination are:

- All medical, paramedical, laboratory, emergency and first responder personnel (police, firefighters, ambulance crews, including volunteers), as well as burial workers, everywhere in the country
- Case contacts: household members or anyone with face-to-face contact with a case following the development of fever in the case
- Household members of bona fide case contacts
- All active duty soldiers as well as reservists called to active duty
- The settlement/town/city/subdistrict/district containing a case
- The entire population.

Mass vaccination

Supervision and execution of mass vaccination, either limited or nationwide, will be by the Public Health Services of the Ministry of Health, the only civilian agency with experience in carrying out such an operation. Ministry of Health nurses will be supplemented by community nurses and by IDF nurses and medics. Vaccination centers operating 24 hours a day will be designated by the district health officers; large clinics, schools and other suitable community buildings are logical sites to carry out mass vaccination.

- ***Pre-outbreak vaccination of professional personnel***

The emergency staffing of one or more smallpox hospitals would require full hospital staffs immune to smallpox on day one of the outbreak. If smallpox hospitals are planned, potential staff should be designated and vaccinated as soon as possible. Moreover, public health nurses and other personnel responsible for screening and counseling case contacts should also be vaccinated immediately.

- ***Mass media education campaign***

An aggressive public and professional education initiative will be needed for any smallpox containment plan to succeed, since sick and worried Israelis are known to hasten to the nearest emergency room and demand hospital admission. Public education needs to begin long before an outbreak occurs [16], and we believe that preparation of the public for a smallpox contingency should begin immediately. The enormous public interest and concern over the recent anthrax episode suggests that the Israeli population is ready to receive well-construed information about a smallpox emergency. The topic of smallpox preparedness needs to be down-classified or declassified so that these activities can begin in earnest.

- ***Clinical consultants***

The number of physicians in Israel who have seen smallpox in their professional lives is small and is shrinking by natural attrition. A list of possible consultants, now in their seventies or older, must nevertheless be compiled and kept up to date. Consideration should be given to offering vaccination to these physicians as well as to all infectious disease specialists and dermatologists in the country, any of whom may be called upon to offer an opinion regarding a suspected case.

- ***Clinical specimens***

Rapid preliminary diagnosis is by electron microscopic demonstration of orthopoxvirus from scrapings of lesions, vesicular or pustular fluid or crusts. Confirmation is by identification of smallpox virus grown on chorioallantoic membranes or in tissue culture, and virus strain characterization is by polymerase chain reaction [17]. Biologic specimens will be placed in labeled dry vacutainer tubes and transported by automobile in metal containers to a designated laboratory.

- ***Laboratory facilities***

It must be appreciated that any outbreak of smallpox will occur on a background *national chickenpox incidence of over 300 cases per day.* Once the first smallpox cases are detected, the demand for laboratory services to distinguish between smallpox and chickenpox will be enormous. If excessive public confusion and anxiety are to be minimized, arrangements for the swift transfer of specimens to competent laboratory facilities must be immediately available at the onset of the outbreak. Necessary laboratory expansion must be budgeted and should begin at once, since the upgrading of laboratory capability may take months to accomplish.

- ***Supreme authority for control of the outbreak***

During the Persian Gulf War of 1991, a supreme medical authority, consisting of the Director-General of the Ministry of Health, the Surgeon General of the IDF, the Director of the Emergency Services Branch of the Ministry of Health and selected other professionals, took overall responsibility for the wartime allocation of medical resources. Presumably such a body would take general responsibility for provision of medical services and smallpox outbreak control, as well as coordination with international health agencies, in the context of the global health emergency. In the event of an intentional attack, it may be assumed that the Ministry of Defense would supervise military, police and other vital national activities.

IDF = Israel Defense Forces

- ***Press spokesperson***

A single government spokesperson, supported by a team of professional experts, will have to be designated to provide ongoing authoritative health information to an exceedingly apprehensive public. In the Gulf War, when gas masks and atropine syringes were distributed to the entire population [18], a physician member of Parliament and former host of a popular television medical show was designated and rehearsed for this function. In the event of an intentional smallpox attack, undoubtedly a cabinet-level personality would be appointed to this vital task. The provision of accurate information to the public in a national smallpox emergency is a crucial component of outbreak control whose importance cannot be sufficiently emphasized.

Postscript: the resumption of routine smallpox vaccination

A serious smallpox preparedness proposal cannot ignore the logical and obvious option of reinstituting routine smallpox vaccination in Israel. This would entail a one-time campaign to vaccinate the entire population, an operation that could be spread comfortably over a year or two or more and, begun in parallel, the routine vaccination of 140,000 infants each year. Many will find it difficult to justify such a course of action in the absence of a real and present smallpox threat, in view of the complications of smallpox vaccination already discussed. In the event of an attack, they will say, then and only then will the formidable risks of mass vaccination be an acceptable alternative to a rapidly expanding nightmare of smallpox morbidity and death. Moreover, the international implications of Israel *unilaterally* resuming routine smallpox vaccination cannot be taken lightly. To others, the immediate resumption of routine vaccination, coupled with an unhurried mass catch-up campaign, is far easier to contemplate than the emergency vaccination of the same number of citizens in an atmosphere of alarm and impending doom after the disease has already claimed its first victims. Indeed, one outspoken expert has suggested such a policy for Israel repeatedly over the last 25 years [19], in words that have begun to sound prophetic. The first calls for preemptive voluntary vaccination of the U.S. population have been sounded [20], and their arguments ring true. The most cogent and appealing justification of such a policy is that it would effectively "eliminate the threat of smallpox as an agent of bioterrorism" [21]. One can only hope that the new smallpox vaccines currently under development [22] will have a more favorable safety profile so that the reinstitution of routine vaccination will be an option palatable to a greater number of experts and policy makers, in Israel and in the international community.

Summary

The intentional release of smallpox virus on a partially susceptible civilian population is a distinct possibility, in Israel as well as in other countries. In a scenario involving aerosol variola virus release, tens to hundreds of first-generation cases would ensue, as would hundreds to thousands of subsequent cases resulting from person-to-person transmission [23]. Hardest hit would be never-vaccinated persons born after 1979, and the case-fatality rate would be, as it has always been, 30%, if not higher.

The methods of smallpox outbreak control are known and can be implemented – in fact they were successfully carried out in Israel in 1949 [2]. The rapidity with which organized outbreak control measures are competently executed will determine how many generations of cases occur before the outbreak is brought under control.

Planning, vaccine stockpiling, laboratory expansion, professional training and aggressive public education, all carried out well in advance of an epidemic, will minimize the number of casualties. The economic cost of preparation is relatively small. Vaccine production capability already exists, but it needs to be reactivated and expanded. Existing excellent laboratory facilities need to be augmented. Professionals who already carry out relevant public health functions in peacetime need to be trained and drilled for a smallpox outbreak. An astute author has pointed out that the preparations for the investigation and control of a smallpox outbreak are appropriate for any naturally occurring epidemic situation and serve to strengthen the existing public health infrastructure, even if never used for smallpox control [24]. The public needs to be psychologically prepared to cooperate in the event of an outbreak. This is the hardest nut to crack, but we must go public if we are to succeed.

A new smallpox outbreak in Israel must not be regarded as a doomsday event. If it occurs, it can and will be overcome. If we make the necessary commitment now to vaccine production and stockpiling, laboratory preparation, planning, professional training and public education, the losses, although substantial, can be minimized. Moreover, the reinstitution of routine smallpox vaccination in Israel must be given serious consideration, now and in the future, as improved vaccine becomes available.

References

1. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID, eds. Smallpox and its Eradication. Geneva: World Health Organization, 1988.
2. Slater PE, Leventhal A, Anis E. The elimination of smallpox from Israel. *IMAJ* 2001;3:71–2.
3. Zilinskas RA. Iraq's biological weapons, the past as future? *JAMA* 1997;278:418–24.
4. Siegrist DW. Threat of biological attack, why concern now? *Emerging Infect Dis* 1999;5:505–8.
5. Davis CJ. Nuclear blindness, an overview of the biological weapons programs of the former Soviet Union and Iraq. *Emerging Infect Dis* 1999;5:509–12.
6. Jernigan JA, Stephens DS, Ashford DA, Omenaca C. Bioterrorism-related inhalational anthrax, the first 10 cases reported in the United States. *Emerging Infect Dis* 2001;7:933–44.
7. Slater PE, Orenstein WA, Morag A, et al. Poliomyelitis outbreak in Israel in 1988. *Lancet* 1990;335:1192–8.
8. Henderson DA, Inglesby TV, Bartlett JG, et al. Smallpox as a biological weapon. *JAMA* 1999;281:2127–37.
9. DeClercq E. Vaccinia virus inhibitors as a paradigm for the chemotherapy of poxvirus infections. *Clin Microbiol Rev* 2001;14:382–97.
10. Kortepeter MG, Parker GW. Potential biological weapons threats. *Emerging Infect Dis* 1999;5:523–7.
11. CDC website on needle-free jet injection technology: www.cdc.gov/nip/dev/jetinject.htm.
12. El-Ad B, Roth Y, Winder A, et al. Persistence of neutralizing antibodies after revaccination against smallpox. *J Infect Dis* 1990;161:446–8.

13. Breman JG, Henderson DA. Diagnosis and management of smallpox. *N Engl J Med* 2002;346:1300–8.
14. Wehrle PF, Posch J, Richter KH, Henderson DA. Airborne outbreak of smallpox in a German hospital and its significance with respect to other recent outbreaks in Europe. *Bull WHO* 1970;43:669–79.
15. Barbera J, Macintyre A, Gostin J, et al. Large-scale quarantine following biological terrorism in the United States. *JAMA* 2001;286:2711–17.
16. Holloway HC, Norwood AE, Fullerton CS, Engel CC, Ursano RJ. Threat of biological weapons, prophylaxis and mitigation of psychological and social consequences. *JAMA* 1997;278:425–7.
17. Ropp SL, Jin Q, Knight JC, Massung RF, Esposito JJ. PCR strategy for identification and differentiation of smallpox and other orthopoxviruses. *J Clin Microbiol* 1995;33:2069–76.
18. Danon YL, Shemer J, eds. Chemical Warfare Medicine. Jerusalem: Gefen Publishing House, 1995.
19. Michaeli D. Has smallpox finally been eradicated? *Public Health Rev* 1998;26:305–7.
20. Bicknell WJ. The case for voluntary smallpox vaccination. *N Engl J Med* 2002;346:1323–5.
21. Fauci AS. Smallpox vaccination policy – the need for dialogue. *N Engl J Med* 2002;346:1319–20.
22. Rosenthal SR, Merchlinsky M, Kleppinger C, Goldenthal KL. Developing new smallpox vaccines. *Emerging Infect Dis* 2001;7:920–6.
23. O'Toole T. Smallpox, an attack scenario. *Emerging Infect Dis* 1999;5:540–6.
24. McDade JE. Addressing the potential threat of bioterrorism – value added to an improved public health infrastructure. *Emerging Infect Dis* 1999;5:591–2.

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