



## Estimated size of the population at risk of severe adverse events after smallpox vaccination in Israel

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### ARTICLE INFO

#### Article history:

Received 13 July 2012

Received in revised form 23 August 2012

Accepted 28 August 2012

Available online 7 September 2012

#### Keywords:

Smallpox vaccine

Variola

Special populations

Bioterrorism

Vaccinia

### ABSTRACT

**Background:** The population at risk of adverse events after smallpox vaccination has increased in recent years. This has important implications for preparedness strategies against bioterrorism with the variola virus. The aim of the study was to estimate the size of this special population in Israel.

**Methods:** The study was conducted in January 2010. Data on patients with contraindications to smallpox vaccination, as delineated by the Israel Ministry of Health for planning post-event strategies, were retrieved from the computerized records of the Department of AIDS and Tuberculosis and the Transplantation Center of the Israel Ministry of Health. In addition, the database of the main Health Maintenance Organization in Israel which insures 60% of the national population was searched using ICD-9 codes and specific medications issued in the last quarter of 2009.

**Results:** Of the 7,563,800 persons residing in Israel in January 2010, 326,318 were at risk of an adverse event after smallpox vaccination.

**Conclusion:** Approximately 4.3% of the Israeli population should not be exposed to the currently used smallpox vaccine. This knowledge is important to ensure the effectiveness of mass vaccination programs in the event of a bioterror attack.

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### 1. Introduction

The concerted effort of the World Health Organization (WHO) to eliminate smallpox was a tremendous achievement. Routine smallpox vaccination was discontinued in the United States in 1972, except, in some cases, for first responders and military personnel, and worldwide, in 1980, when global eradication of the disease was confirmed [1]. In Israel, revaccination of military recruits was performed until 1996 [2]. As a result, today, most of the world's population is not immunized against smallpox. This has raised concerns among authorities because the variola virus may serve as a

potential weapon in bioterrorism. Accordingly, preparedness strategies have been formulated to protect the public health in the event of a terrorist attack [3,4].

In the pre-event program of the Center for Disease Control and Prevention (CDC), smallpox vaccination is contraindicated in the following persons: patients with immunodeficiency, transplant recipients, and patients undergoing chemotherapy or radiotherapy for cancer; individuals with a history of eczema, atopic dermatitis, or exfoliative skin diseases and their household contacts; individuals allergic to vaccine ingredients; and patients with acquired immune deficiency syndrome (AIDS) and carriers of the human immunodeficiency virus (HIV) [5]; pregnant women and children under one year of age; and household contacts of persons who meet the above criteria [5,6].

In Israel, as part of its post-event program based on the CDC recommendations [7], the Israel Ministry of Health listed the following contraindications to smallpox vaccination: primary immune deficiency, HIV infection with CD4+ < 200 cells/mm<sup>3</sup> (or < 15% of total lymphocytes count in children), chemotherapy during the four weeks prior to vaccination, solid organ transplantation with immunosuppressive treatment, one year s/p bone marrow transplantation (with immunosuppressive treatment after this

**Abbreviations:** AIDS, acquired immune deficiency syndrome; CDC, Centers for Disease Control; HIV, human immunodeficiency virus; HMO, Health Maintenance Organization; MVA, modified vaccinia Ankara; VIG, vaccinia immune globulin; WHO, World Health Organization.

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period), high-dose corticosteroid treatment for two weeks in the month prior to vaccination, and active atopic dermatitis or other skin diseases which interrupt the skin barrier [8]. Households of patients with skin diseases, and infants below the age of 1 year and their households are not included in the population with contraindication for smallpox vaccination. The Israeli smallpox preparedness program was originally based on the ring approach with quarantine of contacts [7]. However, the results of an integrative multiorganizational bioterror exercise dubbed Orange Flame 4 indicated that in the event of a bioterror attack with smallpox, contact tracing could not be completed in a timely manner. Therefore, given the small size of the country and the density of the population, mass vaccination is preferable. In addition, there have been considerable changes in the size of the patient groups that should not receive replicating vaccines and in the mobility of the general population, increasing the risk of virus spread.

The aim of the present study was to estimate the size of this special patient population in order to ensure the effectiveness of mass vaccination campaign.

## 2. Methods

National Health Insurance law in Israel entitles all Israeli citizens to compulsory care in one of the four existing Health Maintenance Organizations (HMOs) of their choice. All hospitalizations, family physician visits, and laboratory work-up and imaging results are recorded in the form of electronic health records. To identify the special population at risk of smallpox vaccination, we searched the computerized records of the largest of the four HMOs, Clalit Health Services, which insures 60% of the population. The search was performed in January 2010 using the ICD-9 codes and specific medications issued in the last quarter of 2009. The number of patients with primary immune deficiency (1994–2000) was based on the National Registry published in 2002 [9]. Data on patients with HIV infection (by end 2009) were extracted from the Department of AIDS and Tuberculosis, Division of Epidemiology, Israel Ministry of Health, and on transplant recipients, from the Transplantation Center, Israel Ministry of Health.

## 3. Results

In January 2010, 166,612 persons insured by Clalit Health Services had contraindications for smallpox vaccination (not including HIV infection), accounting for 4.2% of all people belonging to this HMO. According to the National Registry [9], 294 patients were diagnosed with primary immune deficiency in 1994–2000; 31.6% had predominant antibody deficiency; 18%, phagocytic disorders; 16.2%, complement deficiencies; and 7.5%, other deficiencies. The Transplantation Center listed 4628 patients who underwent solid organ transplantation in 1994–2010 (Table 1), of whom 2550 were alive at the time of the study. At the end of 2009, there were 4869 HIV-infected patients in Israel, of whom 2927 had a low CD4+ count (or <15% of the total lymphocyte count in children) (Table 2). Overall, in January 2010, 326,318 persons out of a total of 7,563,800 living in Israel (Israel Central Bureau for Statistics), or 4.3% of the Israeli population, were at risk of an adverse event from smallpox

**Table 1**  
Number of solid organ transplantations performed in the Israeli population during 1994–2010 according to the Center for Transplantation, Ministry of Health, Israel.

Organ transplantations	Number
In Israel	3678
Outside Israel	950
Total <sup>a</sup>	4628

<sup>a</sup> Alive 2550.

**Table 2**

Population with HIV infection in 2009 according to the Division of AIDS and tuberculosis, Israel Ministry of Health.

Age (years)	HIV infection	CD4+ < 200 cells/mm <sup>3</sup> (<15% of total lymphocyte count in children)
0–18	166	99
>19	4703	2822
Total	4869	2921

AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus.

**Table 3**

Estimated size of population at risk for smallpox post-event vaccination.

Population at risk	Number
PID	294
HIV	2921
Solid organ transplantation recipients	2550
Others <sup>a</sup>	320,553
Total	326,318

<sup>a</sup>Malignancies, immunosuppression, high dose steroid treatment, atopic dermatitis and other skin diseases (calculated from the rate reported by the main HMO in Israel).

AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; PID, primary immune deficiency.

vaccination (Table 3). As mentioned in the Introduction, infants below the age of 1 year (153,800 in 2009) are not included in the population with contraindications for smallpox mass vaccination. If we consider this number, 6.3% of the Israeli population were at risk of an adverse event from smallpox vaccination.

## 4. Discussion

To the best of our knowledge, this is the first study in Israel to estimate, on a national level, the number of persons who may be prone to severe adverse events should mass vaccination against smallpox become necessary. In the US alone, an estimated 10 million people fall into this category [10,11]. In these cases, the risk of a severe adverse event after vaccination needs to be weighed against the risk of their contracting the disease. Additionally, plans to treat adverse events after vaccination are needed.

The large-scale smallpox revaccination program for the 21,000 first responders in Israel [12], most of them medical personnel, pre-hospital emergency staff, police and firefighters revealed 13 cases of serious adverse events: generalized vaccinia (2), erythema multiforme (2), optic neuritis (2), retinal branch vein occlusion (1), perimyocarditis (1), polymyalgia (1), urticaria (1), parasthesia of fingers (1), herpes zoster (1), and cervical lymphadenopathy (1). No life-threatening side effects occurred, and no more risk groups were identified [12]. No serious adverse events were noted in 159 soldiers who participated in this program [13]. Previous report on complication rate after smallpox vaccination in a cohort of Israel defense Force recruits enlisted during 1991–1996, demonstrated a low rate of complications (0.4 per 10,000 vaccinees) [14].

The smallpox vaccination program in the United States identified the major severe adverse events of smallpox vaccination: progressive vaccinia (formerly, vaccinia necrosum), generalized vaccinia, post-vaccinal encephalitis and ocular vaccinia. In addition, there has been an alarming increase in reports of post-vaccination myocarditis and pericarditis [15–17]. Following seven cardiac-related events and two sudden deaths in persons vaccinated against smallpox, the CDC issued a Health Alert Notice in 2003 [15].

The new generation of smallpox vaccines may lead to a change in policy and improve smallpox vaccination programs and preparedness. One candidate is LC16m8, a replication competent attenuated

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