



## **Smallpox Bibliography March 2004**

1: Am Fam Physician. 2003 Sep 1;68(5):889-96.

Smallpox vaccine: contraindications, administration, and adverse reactions.

Maurer DM, Harrington B, Lane JM.

Family Practice Residency Program, Darnall Army Community Hospital, Ft. Hood, Texas 76544, USA. douglasmaurer@netscape.net

Since the terrorist attacks of September 11, 2001, and the anthrax exposures in the following weeks, concern that smallpox could be used as a biologic weapon has increased. Public health departments and the U.S. military have begun the process of vaccinating soldiers and civilian first-responders. Smallpox vaccination carries some serious risks: approximately one in 1 million primary vaccinees and one in 4 million revaccinees will die from adverse vaccine reactions. The most serious side effects of smallpox vaccine include progressive vaccinia, postvaccinial central nervous system disease, and eczema vaccinatum.

Some of these reactions can be treated with vaccinia immune globulin or cidofovir. Proper patient screening and site care are essential. Family physicians must learn to screen potential vaccinees for contraindications (e.g., immunodeficiency, immunosuppression, certain skin and eye diseases, pregnancy, lactation, allergy to the vaccine or its components, moderate or severe intercurrent illness) and to treat vaccine-associated adverse reactions.

Publication Types:

Review

Review, Tutorial

PMID: 13678138 [PubMed - indexed for MEDLINE]

2: Am J Transplant. 2003 Jul;3(7):786-93.

Smallpox and live-virus vaccination in transplant recipients.

Fishman JA.

Transplant Infectious Disease and Compromised Host Program, Infectious Disease Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. jfishman@partners.org

Recent bioterrorism raises the specter of reemergence of smallpox as a clinical entity. The mortality of variola major infection ('typical smallpox') was approximately 30% in past outbreaks. Programs for smallpox immunization for healthcare workers have been proposed. Atypical forms of smallpox presenting with flat or hemorrhagic skin lesions are most common in individuals with immune deficits with historic mortality approaching 100%. Smallpox vaccination, even after exposure, is highly effective. Smallpox vaccine contains a highly immunogenic live virus, vaccinia. Few data exist for the impact of variola or safety of vaccinia in immunocompromised hosts. Both disseminated infection by vaccinia and person-to-person spread after vaccination are uncommon. When it occurs, secondary vaccinia has usually affected individuals with pre-existing skin conditions (atopic dermatitis or eczema) or with other underlying immune deficits. Historically, disseminated vaccinia infection was uncommon but often fatal even in the absence of the most severe form of disease, "progressive vaccinia". Some responded to vaccinia immune globulin. Smallpox exposure would be likely to cause significant mortality among immunocompromised hosts. In the absence of documented smallpox exposures, immunocompromised hosts should not be vaccinated against smallpox. Planning for bioterrorist events must include consideration of uniquely susceptible hosts.

Publication Types:

Review

Review, Tutorial

PMID: 12814470 [PubMed - indexed for MEDLINE]

3: Bull World Health Organ. 2003;81(10):762-7. Epub 2003 Nov 25.

Smallpox and bioterrorism.

Pennington H.

Department of Medical Biology, University of Aberdeen, Medical School Building, Foresterhill, Aberdeen AB25 2ZD, United Kingdom. t.h.pennington@abdn.ac.uk

Smallpox was declared to be eradicated on 8 May 1980, during the Thirty-third World Health Assembly. However, concerns about the possible use of the virus as a weapon of bioterrorism have increased in recent years. Governments have responded by initiating selective vaccination programmes and other public health measures. This review uses historical data from 20th century outbreaks to assess the risks to current populations (which have declining immunity) from a deliberate release of virus. The data presented supports the conclusion of a previous reviewer (Mack) that "smallpox cannot be said to live up to its reputation. Far from being a quick-footed menace, it has appeared as a plodding nuisance with more bark than bite." Its R value (the average number of secondary cases infected by a primary case) is lower than that for measles, human parvovirus, chickenpox, mumps, rubella, and poliomyelitis; only the value for severe acute respiratory syndrome (SARS) is lower. Like SARS, close person-to-person contact is required for effective spread of the disease, and exposure to the virus in hospitals has played an

important role in transmission for both viruses. In the present paper the dangers of mass vaccination are emphasized, along with the importance of case isolation, contact tracing, and quarantine of close contacts for outbreak control. The need for rapid diagnosis and the continued importance of maintaining a network of electron microscopes for this purpose are also highlighted.

Publication Types:

Review

Review, Tutorial

PMID: 14758439 [PubMed - indexed for MEDLINE]

4: Clin Infect Dis. 2004 Feb 15;38(4):536-41. Epub 2004 Jan 28.

Risk of vaccinia transfer to the hands of vaccinated persons after smallpox immunization.

Talbot TR, Ziel E, Doersam JK, LaFleur B, Tollefson S, Edwards KM.

Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, USA. tom.talbot@vanderbilt.edu

Transmission of vaccinia virus after smallpox vaccination is a concern. We conducted a prospective examination of the protection afforded by vaccination-site bandages in recently vaccinated individuals. After smallpox vaccination, inoculation sites were covered with 2 occlusive dressings. Site assessment and bandage changes occurred every 3-5 days until the site was healed. At each visit, specimens from the vaccination site, outer dressing surface, and contralateral hand were obtained for vaccinia culture. For 148 vaccinated subjects, vaccinia was detected from vaccination lesions of every subject on several occasions. Only 6 (0.65%) of 918 dressing (95% CI, 0.24%-1.4%) and 2 (0.22%) of 926 hand (95% CI, 0.03%-0.78%) specimens tested positive for vaccinia. The mean number of bandage changes was 9.6 (95% CI, 9.17-10.0). Vaccinia autoinoculation did not occur. The rate of vaccinia recovery outside occlusive bandages covering smallpox vaccination sites was remarkably low, suggesting excellent protection against inadvertent transmission.

PMID: 14765347 [PubMed - indexed for MEDLINE]

5: Clin Infect Dis. 2004 Jan 1;38(1):86-9. Epub 2003 Dec 08.

Comment in:

Clin Infect Dis. 2004 Jan 1;38(1):90-1.

Age distribution for T cell reactivity to vaccinia virus in a healthy population.

Hsieh SM, Pan SC, Chen SY, Huang PF, Chang SC.

Division of Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan.

The potential for bioterrorism involving smallpox has led to a debate about the durability of protective immunity against smallpox from vaccination. By assessing the T cell reactivity to vaccinia virus in a healthy population, we show that subjects who were vaccinated within the past 3 decades and who have a visible vaccination scar had remarkable T cell reactivity. However, person who were vaccinated within the past 3 decades but who do not have a scar and those who were vaccinated >4 decades ago had responses as low as those in unvaccinated subjects. Thus, we estimate that the significant T cell memory response to vaccinia virus from successful vaccination may persist for only 20-30 years. Furthermore, we found the vaccinia-specific cellular immunity could be easily assessed by determination of the frequencies of vaccinia-specific CD69 expression on T cell subsets. These data may help in the development of public health strategies to counter bioterrorism threats associated with smallpox.

PMID: 14679452 [PubMed - indexed for MEDLINE]

6: Clin Infect Dis. 2004 Jan 1;38(1):90-1. Epub 2003 Dec 08.

Comment on:

Clin Infect Dis. 2004 Jan 1;38(1):86-9.

New data in a 200-year investigation.

Bray M.

Publication Types:

Comment

Editorial

Historical Article

PMID: 14679453 [PubMed - indexed for MEDLINE]

7: Conn Med. 2004 Jan;68(1):27-35.

Bioterrorism preparedness--Part II. Smallpox vaccination in a hospital setting.

Jacobs LM, Emanuelsen K, McKay C, Burns K.

Department of Traumatology and Emergency Medicine, Hartford Hospital, 80 Seymour Street, P.O. Box 5037, Hartford, CT 06102, USA. Ljacobs@harthosp.org

The threat of using smallpox as an agent for bioterrorism resulted in a directive for the creation of smallpox response teams. In Connecticut, The Commissioner of the Department of Public Health convened public health and hospital leadership to plan for the vaccination of these teams. The purpose of this paper is to provide a description of the vaccination program at Hartford Hospital, a Center of Excellence for Bioterrorism Preparedness, and to report the results of a

survey of the vaccinees regarding the vaccination experience. Ninety persons were vaccinated. Six individuals experienced low-grade fever and 10 had axillary node swelling. One individual experienced significant fatigue. A total of six persons lost time from work. Four lost one day and two persons lost between four to five days of work. There was no autoinoculation, transfer inoculation, vaccinia or any other significant complication. Survey results indicate that most vaccinees felt positive about the experience.

Publication Types:

Review

Review, Tutorial

PMID: 14752914 [PubMed - indexed for MEDLINE]

8: Emerg Infect Dis. 2003 Nov;9(11):1489-90.

Frequency of revaccination against smallpox.

Baron S, Pan J, Poast J.

University of Texas Medical Branch, Galveston, Texas 77555-1019, USA.  
sabaron@utmb.edu

PMID: 14725257 [PubMed - indexed for MEDLINE]

9: Emerg Infect Dis. 2003 Nov;9(11):1468-70.

Flow cytometry and T-cell response monitoring after smallpox vaccination.

Poccia F, Gioia C, Montesano C, Martini F, Horejsh D, Castilletti C, Pucillo L, Capobianchi MR, Ippolito G.

National Institute for Infectious Diseases "Lazzaro Spallanzani," Rome, Italy.  
poccia@inmi.it

Orthopoxvirus zoonosis or smallpox as result of bioterrorism or biological warfare represents a risk for epidemic spread. By monitoring T-cell responses by flow cytometry, we observed a recall response after recent vaccination against smallpox. When the high similarity between the orthopoxviruses is considered, this rapid assay that uses vaccinia antigens could identify recently exposures.

PMID: 14718095 [PubMed - indexed for MEDLINE]

10: Emerg Infect Dis. 2003 Nov;9(11):1363-70.

Risks and benefits of preexposure and postexposure smallpox vaccination.

Meltzer MI.

Centers for Disease Control and Prevention, Atlanta, Georgia 30345, USA.  
qzm4@cdc.gov

This article presents a model and decision criteria for evaluating a person's risk of pre- or postexposure smallpox vaccination in light of serious vaccine-related adverse events (death, postvaccine encephalitis and progressive vaccinia). Even at a 1-in-10 risk of 1,000 initial smallpox cases, a person in a population of 280 million has a greater risk for serious vaccine-related adverse events than a risk for smallpox. For a healthcare worker to accept preexposure vaccination, the risk for contact with an infectious smallpox case-patient must be  $>1$  in 100, and the probability of 1,000 initial cases must be  $>1$  in 1,000. A member of an investigation team would accept preexposure vaccination if his or her anticipated risk of contact is 1 in 2.5 and the risk of attack is assumed to be  $>1$  in 16,000. The only circumstances in which postexposure vaccination would not be accepted are the following: if vaccine efficacy were  $<1\%$ , the risk of transmission were  $<1\%$ , and (simultaneously) the risk for serious vaccine-related adverse events were  $>1$  in 5,000.

PMID: 14718077 [PubMed - indexed for MEDLINE]

11: *Epidemiol Infect.* 2004 Jan;132(1):19-25.

Modelling responses to a smallpox epidemic taking into account uncertainty.

Legrand J, Viboud C, Boelle PY, Valleron AJ, Flahault A.

Epidemiology and Information Sciences, INSERM U444, CHU Saint-Antoine, Universite Pierre et Marie Curie, 27 rue Chaligny, 75012 Paris, France.

Epidemiology and modelling are currently under pressure to build consistent scenarios of control in case of deliberate release of biological weapons. In order to assess the key parameters for the control of a smallpox outbreak in a large city (2 million inhabitants), we built a stochastic model to simulate the course of an epidemic controlled by ring vaccination and case isolation. Assuming a reference scenario with 100 index cases and implementation of intervention 25 days after the attack, the model forecasts an epidemic of 730 cases with an epidemic duration of 240 days. Setting intervention 20 days later would result in an almost fourfold increase in the epidemic size. A multivariate sensitivity analysis has selected three key parameters: the basic reproduction number (i.e. the number of secondary cases infected by one case in an entirely susceptible population, equal to 3 in the reference scenario), time to intervention, and proportion of traced and vaccinated contacts.

Publication Types:  
Validation Studies

PMID: 14979585 [PubMed - indexed for MEDLINE]

12: *Harv Health Lett.* 2003 Mar;28(5):6.

The smallpox vaccine: frequently asked questions.

[No authors listed]

PMID: 12777221 [PubMed - indexed for MEDLINE]

13: Hastings Cent Rep. 2003 Sep-Oct;33(5):26-33.

The smallpox vaccination of health care workers: professional obligations and defense against bioterrorism.

May T, Aulisio MP, Silverman RD.

Center for the Study of Bioethics, Medical College of Wisconsin, USA.

PMID: 14696277 [PubMed - indexed for MEDLINE]

14: Immunol Allergy Clin North Am. 2003 Nov;23(4):731-43.

Smallpox vaccine: problems and prospects.

Poland GA, Neff JM.

Mayo Vaccine Research Group, Mayo Clinic and Foundation, 611C Guggenheim Building, 200 First Street SW, Rochester, MN 55905, USA.  
poland.gregory@mayo.edu

Smallpox justifiably is feared because of its morbidity and mortality. Wide-spread population-level susceptibility to smallpox exists, and the only effective tool against the virus is a live, attenuated vaccine that is highly reactogenic and controversial. A significant minority of the population has contraindications that prevent preexposure use of this vaccine. Newer, safer, and equally immunogenic vaccines must be developed and licensed. Several live, attenuated vaccines are in clinical trials. Although these vaccines may prove to be less reactogenic, they still may not be administered safely to a significant portion of the population because they contain live, attenuated viruses. Newer vaccines will be needed if routine preexposure vaccination is to be instituted universally. The idea of a subunit or peptide-based vaccine is appealing, because it obviates potential safety concerns. It may be possible to use a more-attenuated, live vaccine strain for a large segment of the population on a preexposure basis and accept the morbidity and mortality that would result from its use on a postexposure basis, if necessary. The need for widespread population-level protection against variola infection is apparent. The use of the new biology tools to predict or define who might experience serious reactions to the smallpox vaccine and why these reactions occur is an area ripe for additional research. The reason why an individual develops postvaccinal encephalitis remains unknown, and the development is unpredictable and untreatable. In the future, if the mechanism behind such adverse events is defined, it may be possible to screen persons who are likely to experience such events. Although the authors remain proponents for use of the vaccine in alignment with the CDC vaccination program and recommendations, the previous concerns indicate that new knowledge must be gained and shared. Further research on attenuated vaccines and nonliving or peptide

vaccines with equal efficacy should remain the goal, as it is apparent that smallpox vaccine once again will become part of the vaccinologist's and public health official's armamentarium in the decades to come.

Publication Types:

Review  
Review, Tutorial

PMID: 14753389 [PubMed - indexed for MEDLINE]

15: J Immunol. 2003 Nov 15;171(10):4969-73.

Cutting edge: long-term B cell memory in humans after smallpox vaccination.

Crotty S, Felgner P, Davies H, Glidewell J, Villarreal L, Ahmed R.

Emory Vaccine Center and Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, GA 30322, USA.

Memory B cells are a central component of humoral immunity, and yet little is known about their longevity in humans. Immune memory after smallpox vaccination (DryVax) is a valuable benchmark for understanding the longevity of B cell memory in the absence of re-exposure to Ag. In this study, we demonstrate that smallpox vaccine-specific memory B cells last for >50 years in immunized individuals. Virus-specific memory B cells initially declined postimmunization, but then reached a plateau approximately 10-fold lower than peak and were stably maintained for >50 years after vaccination at a frequency of approximately 0.1% of total circulating IgG(+) B cells. These persisting memory B cells were functional and able to mount a robust anamnestic Ab response upon revaccination. Additionally, virus-specific CD4(+) T cells were detected decades after vaccination. These data show that immunological memory to DryVax vaccine is long-lived and may contribute to protection against smallpox.

PMID: 14607890 [PubMed - indexed for MEDLINE]

16: J Law Med Ethics. 2003 Winter;34(4 Suppl):39-40.

Workshop on smallpox legal preparedness: what have we learned from smallpox legal preparedness?

Matthews GW, Murphy AM, Lopez W, Orenstein WA.

Office of General Counsel, Centers for Disease Control and Prevention, Atlanta, GA, USA.

Publication Types:

Addresses

PMID: 14968617 [PubMed - indexed for MEDLINE]

17: JAMA. 2004 Feb 11;291(6):725-7.

Tertiary contact vaccinia in a breastfeeding infant.

Garde V, Harper D, Fairchok MP.

Department of Pediatrics, Madigan Army Medical Center, Tacoma, Wash 98431, USA.

On May 4, 2003, a US Army soldier received primary smallpox vaccination and experienced a primary uptake reaction at the inoculation site on days 6 through 8. The vaccinee reported observing all of the standard precautions to avoid household spread. In mid May, his breastfeeding wife developed vesicles on both areolas. On May 29, their infant daughter developed a papule on her philtrum. Contact vaccinia was confirmed by positive polymerase chain reaction and culture for vaccinia of both the maternal and infant lesions. This is the first documented case of inadvertent contact vaccinia transmission from a mother to her infant through direct skin-to-skin and skin-to-mucous membrane contact while breastfeeding. The mechanism of transfer from the vaccinee to the spouse is uncertain. This report demonstrates that breastfeeding infants living in close contact with smallpox vaccinees are at potential risk for contact vaccinia, even if the vaccinee is not the breastfeeding mother, and highlights the need for special precautions to prevent secondary transfer to breastfeeding mothers.

Publication Types:

Case Reports

PMID: 14871916 [PubMed - indexed for MEDLINE]

18: Lab Invest. 2004 Jan;84(1):41-8.

Detection and identification of Variola virus in fixed human tissue after prolonged archival storage.

Schoepp RJ, Morin MD, Martinez MJ, Kulesh DA, Hensley L, Geisbert TW, Brady DR, Jahrling PB.

Diagnostic Systems Division, United States Army Medical Research Institute of Infectious Diseases, Frederick, MD 21702-5011, USA.  
randal.schoepp@amedd.army.mil

Smallpox disease has been eradicated from the human population since 1979, but is again a concern because of its potential use as an agent of bioterrorism or biowarfare. World Health Organization-sanctioned repositories of infectious Variola virus are known to occur in both Russia and the United States, but many believe other undeclared and unregulated sources of the virus could exist. Thus, validation of improved methods for definitive identification of smallpox virus in diagnostic specimens is urgently needed. In this paper, we describe the discovery of suspected Variola infected human tissue, fixed and preserved for decades in largely unknown solutions, and the use of routine histology, electron microscopy, and ultimately DNA extraction and fluorogenic 5' nuclease (TaqMan) assays for its identification and confirmation.

PMID: 14631381 [PubMed - indexed for MEDLINE]

19: Lancet. 2003 Dec 20;362(9401):2104-9.

Benjamin Jesty: new light in the dawn of vaccination.

Peard PJ.

Molecular Microbiology and Infection, University of Southampton, Southampton General Hospital, Southampton, UK. pjpeard@yahoo.co.uk

Publication Types:  
Biography  
Historical Article

Personal Name as Subject:  
Jesty B

PMID: 14697816 [PubMed - indexed for MEDLINE]

20: MMWR Morb Mortal Wkly Rep. 2004 Feb 13;53(5):103-5.

Erratum in:  
MMWR Morb Mortal Wkly Rep. 2004 Feb 20;53(6):133.

Secondary and tertiary transfer of vaccinia virus among U.S. military personnel--United States and worldwide, 2002-2004.

Centers for Disease Control and Prevention (CDC).

In December 2002, the Department of Defense (DoD) began vaccinating military personnel as part of the pre-event vaccination program. Because vaccinia virus is present on the skin at the site of vaccination, it can spread to other parts of the body (i.e., autoinoculation) or to contacts of vaccinees (i.e., contact transfer). To prevent autoinoculation and contact transfer, DoD gave vaccinees printed information that focused on hand washing, covering the vaccination site, and limiting contact with infants (1,2). This report describes cases of contact transfer of vaccinia virus among vaccinated military personnel since December 2002; findings indicate that contact transfer of vaccinia virus is rare. Continued efforts are needed to educate vaccinees about the importance of proper vaccination-site care in preventing contact transmission, especially in household settings.

Publication Types:  
Case Reports

PMID: 14961003 [PubMed - indexed for MEDLINE]

21: MMWR Morb Mortal Wkly Rep. 2004 Feb 13;53(5):106-7.

Update: adverse events following civilian smallpox vaccination--United States, 2003.

Centers for Disease Control and Prevention (CDC).

During January 24-December 31, 2003, smallpox vaccine was administered to 39,213 civilian health-care and public health workers in 55 jurisdictions to prepare the United States for a possible terrorist attack using smallpox virus. This report updates information on vaccine-associated adverse events among civilians vaccinated since the beginning of the program and among contacts of vaccinees, received by CDC from the Vaccine Adverse Event Reporting System (VAERS) during August 9-December 31.

PMID: 14961004 [PubMed - indexed for MEDLINE]

22: N Engl J Med. 2004 Feb 12;350(7):e6.

Images in clinical medicine. Use of multinucleated giant cells to diagnose a viral eruption.

Koranda FC.

University of Kansas Medical Center, Kansas City, KS 66160, USA.

Publication Types:  
Case Reports

PMID: 14960757 [PubMed - indexed for MEDLINE]

23: Nursing. 2004 Jan;34(1):30.

Administering smallpox vaccine: a two-pronged risk.

Perry J, Jagger J.

International Health Care Worker Safety Center, University of Virginia, Charlottesville, VA, USA.

PMID: 14738067 [PubMed - indexed for MEDLINE]

24: Sci Am. 2004 Feb;290(2):27.

AIDS resistance thanks to smallpox?

Choi C.

Publication Types:  
News

PMID: 14982099 [PubMed - indexed for MEDLINE]

25: US News World Rep. 2004 Jan 19;136(2):64.

Smallpox mixes make a stir.

Boyce N.

Publication Types:  
News

PMID: 14959542 [PubMed - indexed for MEDLINE]