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PERSPECTIVE

Pre-event smallpox vaccination for healthcare workers revisited—the need for a carefully screened multidisciplinary cadre

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Summary As healthcare institutions are a focus of smallpox transmission early in an epidemic, several mathematical models support pre-event smallpox vaccination of healthcare workers (HCWs). The deciding factor for HCW voluntary vaccination is the risk of disease exposure versus the risk of vaccine adverse events. In a United States military population, with careful screening to exclude atopic dermatitis/eczema and immunosuppression, over 1 million vaccinia (smallpox) vaccinations were delivered with one fatality attributed to vaccination. Among 37 901 United States civilian volunteer HCWs vaccinated, 100 serious adverse events were reported including 10 ischemic cardiac episodes and six myocardial infarctions — two were fatal. This older population had a higher rate of adverse events due to age-related coronary artery disease. T-cell mediated inflammatory processes induced by live vaccinia vaccination may have a role in the observed acute coronary artery events. With exclusion of individuals at risk for coronary artery disease, atopic dermatitis/eczema, and immunosuppression, HCWs can be smallpox vaccinated with minimal risk. A carefully screened multidisciplinary cadre (physician, nurse, infection control practitioner, technician), pre-event vaccinated for smallpox, will supply the necessary leadership to alleviate fear and uncertainty while limiting spread and initial mortality of smallpox.

Introduction

Several mathematical models of smallpox (variola virus) outbreaks have been proposed.[1–6] All have appropriate information to offer public health response planners, although their conclusions vary due to differing assumptions and statistical methods. The models attempt to minimize outbreak morbidity and mortality through various vaccination policies and procedures. Smallpox vaccination complication rates with the currently available live vaccinia virus are of significant concern to individuals and public health response planners. More recent information on vaccination complication rates, especially for healthcare workers (HCWs), is now available from the experience of vaccinia virus vaccination in the USA over the last five years. Combining the more recent knowledge on vaccination complications and potential immunologic mechanisms with

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the mathematical models will allow public health leaders and HCWs opportunities for the most informed decisions. No model can be truly predictive, no one control measure identified as best, but evidence exists for the prevaccination of HCWs prior to the first recognized case.

The article by Longini et al., *Containing a large bioterrorist smallpox attack: a computer simulation approach*, is a discrete time, stochastic computer simulation model that offers additional planning guidance for a smallpox outbreak.[1] Although interpretation of the model's information may differ, the article concludes "Given that surveillance and containment measures are in place, preemptive vaccination of hospital workers would further reduce the number of smallpox cases and deaths, but would require large numbers of prevaccinations" for the greatest effectiveness. In their computer simulation, the hospital had 686 workers (a relatively small facility compared to many tertiary care institutions) and 133 of these made close contact with smallpox cases prior to the initiation of isolation measures. Of 828 cases, 50% originated in the hospital and 13% of the contacts were untraceable. Preemptive smallpox (vaccinia virus) vaccination of 10% of the hospital workers, in addition to surveillance and containment, had a small effect on the average number of cases; however, preemptive vaccination of 50% of the hospital workers had a relatively large effect on case reduction. The larger number of preemptive vaccinations required less contact tracing and 'ring' containment vaccinations. A delay of one day in fully implementing surveillance and containment resulted in a large epidemic.

Ferguson's 2003 synopsis stated "historically, most infections occurred in caregivers to symptomatic individuals, whether in households or hospitals," and Bozzette's 2003 findings conclude "the analysis favors the prior vaccination of healthcare workers...but would cause 25 deaths nationally."[5,6] A death rate less than one per million (nine deaths: six primary and three revaccinees) was reported in 1968, the last year for mass smallpox vaccination in the USA.[7] With continued attention to the pre-event smallpox exclusionary criteria of atopic dermatitis/eczema and immunosuppression, and additional exclusion of those with significant coronary artery disease risk factors, an even lower fatality rate may be possible based upon review of the United States smallpox vaccination experience from the past five years.

Vaccinia vaccine complications—United States recent experience

Vaccinia (smallpox) vaccine can be safely delivered to a carefully screened population. As of April 28, 2006, the United States Department of Defense (DoD) has administered over 1 004 000 Dryvax™ (Wyeth; New York City Board of Health strain vaccinia) live virus vaccinations to military operational forces and HCWs. Most adverse events were at rates below historical values, and the death rate directly attributed to vaccination was one per million in this select population of male and female military members.[8] Other vaccinia strains, such as the Lister strain utilized in some European countries, may have higher estimated complication rates (8.4 deaths per million vaccinations).[9] Of the initial screened military population, ninety thousand members were medically exempt, a majority for a history of atopic dermatitis/eczema or family member with the condition. The one unfortunate attributable death was a 22-year-old female United States Army Reservist undergoing mobilization. A lupus-like syndrome developed a month after receiving five vaccinations including smallpox and anthrax. The evidence favored a causal relationship to the vaccinia vaccination. Pathology showed a lymphocytic pericarditis with eosinophils and diffuse alveolar damage.[10] As of October 2004, 24 DoD vaccinees were hospitalized with myocardial ischemia 2—24 days post vaccination. Myocardial infarction occurred in 13 military members, with one fatality. Many individuals presenting with cardiac ischemia had significant preexisting cardiovascular disease.[11] The coronary events were judged unrelated to smallpox vaccination. An expert panel also concluded that the ischemic events did not exceed the expected level of 40 cardiac admissions in unvaccinated DoD personnel. The authors of the myocardial ischemia review, which included the senior leadership of the DoD smallpox vaccination effort, concluded that the available data "do not support a causal relation between ischemic cardiac events and receipt of the smallpox vaccine; however this possibility cannot be excluded."

In addition, the 114 myopericarditis cases (1.14/10 000) in over 1 million vaccinated were an unexpected complication. All cases resolved to the best of available knowledge. Detailed follow-up was possible in 64 patients; all had normal electrocardiograms (EKGs), echocardiograms, and treadmill stress tests.[12,13] The incidence (1/10 000) of vaccinia myocarditis in Finnish conscripts during the late 1970s was similar.[14] An additional Finnish study showed asymptomatic EKG changes suggestive of inflammatory myocarditis in eight of 234 (3%) conscripts receiving multiple vaccinations including the live vaccinia virus. Those with EKG changes more often had a history of atopy.[15] Myopericarditis should be considered in the differential diagnosis of chest pain for those 4—30 days post smallpox vaccination.

In the DoD population of one million vaccinees, "There were no cases of live vaccinia virus transmission in the workplace; most importantly, among 27 700 healthcare workers, there were no cases of provider to patient transmission."[8] Contact transmission did occur in 55 cases, principally at home among spouses and intimate partners with no known serious consequences, including resolution of a vaccinia keratitis case. Due to an effective education and deferral program for those with a history of atopic dermatitis/eczema or immunosuppression, there were no cases of eczema vaccinatum or progressive vaccinia. A detailed description of the first 450 293 vaccinations (70.5% primary and 29.5% revaccinations) in the initial five months of the program which commenced on December 13, 2002, has been published.[16]

The National Smallpox Preparedness Program sponsored by the Department of Health and Human Services (HHS) through the Centers for Disease Control and Prevention (CDC) primarily ran January through October 2003 and was targeted to civilian HCWs and public health response teams. During this time period, 37 901 civilian volunteers received vaccinia Dryvax™ vaccination and 100 suffered serious adverse events.[17] In this significantly different population from military members, 64% of the vaccinees were women. More than 75% of the vaccinees were between 40 and 64 years of age and had previously received vaccinia vaccination. The serious events included 21 cases of myopericarditis and 10 cardiac ischemic events. The 10 ischemic events included

four cases of increased angina and six myocardial infarctions with two fatalities among women, ages 55 and 57 years old, one and four days after vaccination, respectively. The interval between vaccination and cardiac symptoms was seven to 14 days with a median of eight days in the majority of cases. Two cases of insidious onset dilated cardiomyopathy occurred two to three months after vaccination. Statistically speaking, the rate of ischemic cardiac events in civilian vaccinees did not appear to exceed the rate in a comparable unvaccinated population. The older revaccinees had a higher risk of adverse events due to age-related underlying chronic disease, especially coronary artery disease. Among the nearly 38 000 live virus vaccine recipients, there was no transmission of vaccinia to others; specifically, no nosocomial transmissions occurred.

After the Health Alert Notice of March 26, 2003, deferring vaccination for those at risk for coronary artery disease, no further ischemic cardiac events were reported. Cardiac deferral criteria included the following: a history of cardiac disease, or three of the five major risk factors for atherosclerotic heart disease (hypertension, diabetes, hypercholesterolemia, smoking, or history of heart disease in a first degree relative less than 50 years old).[17] Publication of the cardiac deaths associated with vaccination resulted in a rapid decline in volunteers. As of October 31, 2005, the total number of HCWs vaccinated according to the CDC is 39 608.[18] The rates of expected, preventable, noncardiac adverse events in the civilian vaccinees were similar to the military program.

Reported neurological events were generally mild and self-limited in a combined analysis of the vaccine adverse event reporting system among approximately 665 000 persons vaccinated against smallpox by the DoD (590 400) and HHS (64 600) during 2002 to 2004.[19] Serious neurological events included the following cases: suspected meningitis (13), suspected encephalitis or myelitis (3), Bells palsy (11), seizures (9), and Guillain—Barre syndrome (3). Of the 39 events, 27 (69%) occurred in primary vaccinees usually within 12 days of vaccination. No neurological syndrome was identified above baseline estimates. The data indicate that mild neurologic adverse events may be temporally but not necessarily causally associated with smallpox vaccination.

Vaccinia virus immunology and adverse events

The 10 cardiac ischemic events with two fatalities within a 14-day post vaccination period among nearly 38 000 civilian HCWs may have a causal relationship to vaccination. A vaccinia virus-induced inflammatory response may have a role in acute coronary events following smallpox vaccination. Supporting evidence for generalized inflammation post vaccination includes vigorous cytotoxic T-cell and interferon-gamma (IFN-γ) responses after the appearance of inoculated vaccinia skin vesicles.[20] In 107 naïve volunteers receiving the Aventis-Pasteur vaccinia formulation, levels of INF-γ, interleukin (IL)-10 and tumor necrosis factor-alpha (TNF-α) were significantly elevated with dramatic increases in INF-γ at one week in nearly 50% of cases.[21]

A vulnerable atheromatous plaque contains T-lymphocytes, macrophage foam cells, and 'activated' intimal smooth muscle cells. In patients with fatal myocardial infarction, the acute plaque rupture site is marked by a coordinated 'cross talk' inflammatory response of these cells. T-lymphocytes activate the macrophages, and T- cell activation is likely an important mechanism in the pathophysiology of the acute coronary syndrome (ACS). Unstable plaques show a tenfold increase in T-cell content by PCR indicating specific antigen driven recruitment of T-cells in unstable lesions. Marked INF-γ upregulation can be observed in unstable plaques and the consequent Th1 response (INF-γ, TNF) may have a critical role in the outcome of the lesions.[22]

Fracture of the atheromatous plaque's fibrous cap is best understood as a mechanism for an acute coronary event. Inflammation causes various forms of plaque disruption including endothelial cell death due to cytolytic attack by activated killer T-cells. Most of the tensile strength of the fibrous cap is conferred by interstitial collagen molecules. Collagen production by smooth muscle cells can be inhibited by proinflammatory cytokines such as INF-γ.[23]

The above immunological data support a possible mechanistic link between smallpox vaccination and acute myocardial infarction in high-risk ACS individuals several days after smallpox vaccination; further study in this area is warranted. Smallpox vaccination deferral in individuals with multiple risk factors for atherosclerotic coronary artery disease is certainly a prudent policy. Older essential HCW personnel with cardiac risk factors desiring smallpox vaccination may consider a cardiac exercise stress test to detect high-grade atherosclerotic coronary plaques.

Vaccinia pericarditis is not related to fixed obstructive coronary artery lesions and may be immunologically mediated or the result of a direct cytotoxic effect of the vaccinia virus. The possible increased incidence of vaccinia pericarditis with an atopic history noted by the Finns in the 1970s may hold a clue to the pathogenesis.[14]

The immunology of vaccinia virus in the dermis offers insight into the adverse reactions in individuals with atopic dermatitis and the complication of eczema vaccinatum. The live virus inoculation method by scarification (multiple superficial punctures to the skin with a bifurcated needle) induces a diffuse dermal immunologic response. Langerhans cells, at the base of the epidermis, are implicated as antigen processing sites, and replication of the vaccinia virus in the lower epidermis is important to developing effective immunity. The skin of atopic individuals involves multiple abnormal immunologic responses including increased expression of Th2 cytokines such as IL-4.[24] Atopic individuals also have keratinocytes producing abnormal chemokines favoring Th2 lymphocyte production of IL-4, IL-10, and IL-13. Higher levels of IL-4 inhibit production of INF-γ; lower levels of INF- γ contribute to the overgrowth of the vaccinia virus.

Decreased cytotoxic T-cell generation is also noted in atopes. IL-4 has been shown to downregulate antiviral cytokine expression and cytotoxic T-cell responses to vaccinia virus. In addition, overexpression of the Th2 cytokines in atopic dermatitis resulted in decreased human cathelicidin LL-37, an antimicrobial peptide that kills the vaccinia virus.[25] As atopic dermatitis and eczema are increasing in frequency in the population, further investigation into the T-cell immunology of the vaccinia virus will benefit the increasing numbers of at-risk patients.

Reasons for a pre-event smallpox vaccinated healthcare worker multidisciplinary cadre

In 2002, attitudinal research on HCWs showed that the relative weight of the risk of disease exposure versus the risk of vaccine adverse events is the deciding factor for voluntary smallpox vaccination.[26] Four variables were significant in favor of vaccination: perceived risk of smallpox attack, self-assessed knowledge of smallpox vaccination, previous smallpox vaccination status, and male gender.

In addition, HCWs well informed on smallpox vaccination should know that the vaccination is required within three days of exposure to prevent disease. Successful 'ring vaccination' (isolation of symptomatic patients and vaccination of all contacts which includes HCWs) requires rapid diagnosis. Time to diagnosis is an essential parameter in determining intervention strategies.[27] Unfortunately, survey data in 2003 revealed poor smallpox diagnostic skill among primary care and emergency room physicians in a large urban academic medical center. Only 36% correctly answered three of four differential diagnosis questions and only 17% reported comfort in diagnosing smallpox.[28] In the age of globalization with rapid air and ground personal travel, a few individuals can spread smallpox infection over large areas, especially during their contagious 24 hour prodromal period prior to the initial outbreak of vesicles. In the recent mumps virus outbreak in the central United States (Iowa), 11 persons possibly infected with mumps traveled by aircraft on 33 commercial flights operated by eight different airlines, potentially exposing 575 persons.[29] Two cases of infection may have been transmitted in flight.

A multidisciplinary cadre team (physician, nurse, infection control practitioner, technician) will safely be able to evaluate and care for suspected initial smallpox patients, along with being called upon to quickly initiate vaccinia vaccinations for their healthcare facility. Today's HCWs, although well-meaning professionals, are still human beings vulnerable to self-preservation, with concerns of risks to spouses and children, or threats to their economic livelihood. A survey of nearly 6500 HCWs in New York City showed that they were most willing (80%) to report to work during a snowstorm and least willing during a severe acute respiratory syndrome (SARS) outbreak (48%). Willingness to report in a smallpox outbreak was 61%. Ability to report for a mass casualty event was 81%; ability to report for a smallpox outbreak was one of the lowest at 67%.[30] The human factor of fear when facing a fatal contagious disease is difficult to model mathematically.

A smallpox prevaccinated multidisciplinary cadre, known and trusted by the institutional staff, will supply the invaluable leadership that a smallpox crisis will demand to maintain an effective healthcare facility and minimize the mortality rate.

United States 'lessons learned' on the preemptive civilian smallpox vaccination program

The USA can share 'lessons learned' regarding poor participation in the smallpox vaccination program for civilian HCWs. When implementing an emergency response plan with some degree of inherent individual risk for a low likelihood high consequence event, the scientific evidence and analysis must also include a balance of information available to the public involving national security.[31] A unifying theme of trust is required for effective communication and information sharing between intelligence agencies, public health organizations, and citizens of the country. Commitment and attitude of the implementation staff is also critical to success.

Specific missteps in the HHS initiated program included rapid implementation without a compensation plan for the inadvertently injured, lack of effective data systems for recording vaccine utilization and adverse events, and no evidence for imminent smallpox attack.[31] Poor risk communication, unfavorable media perceptions, and differing recommendations by the Advisory Committee on Immunization Practices (ACIP) resulted in conflicting messages. Volunteers rapidly declined after the March 2003 Health Alert Notice deferring vaccination for those with cardiac risk factors. A more successful preemptive smallpox vaccination program should be possible.

Preemptive vaccination of HCWs against smallpox is a risk versus benefit decision. This low probability high consequence event weighs the risk/benefits of HCW pre-event vaccination versus the consequences of morbidity and mortality for providers and patients with increased dissemination in an outbreak. Healthcare providers and public health planners now have recent data on the adverse events from over 1 million vaccinia vaccinated individuals, including nearly 28 000 military and 38 000 civilian HCWs. Continued careful screening and exclusion for atopic dermatitis/eczema, immunosuppression, and coronary artery disease will minimize the risk of pre-event smallpox vaccination adverse events for HCWs. Mathematical models are invaluable planning tools, but do not replace our human cognitive abilities to assess risk and evaluate our local healthcare institutions and health departments. Local preparedness is the most important factor for an effective response in a healthcare crisis. A small multidisciplinary cadre of carefully screened and preemptively smallpox-vaccinated HCWs in each institution and public health district, knowledgeable and confident with smallpox vaccination, may limit the spread and initial mortality of smallpox.

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