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The Epidemiology of Variola Major

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Abstract

Good studies of the epidemiology of smallpox (Variola major) were conducted in Asia, Africa, and Europe in the late 1960's and early 1970's. These studies showed that transmission is fairly slow and generally to susceptible persons who had prolonged face-to-face contact with patients, often as caregivers. Patients are not infectious during the violent prostrating prodrome caused by intense viremia. The rare exceptions to this pattern include true airborne spread, and spread by aerosols created by shaking out heavily infected bedding.

Vaccination of contacts within two or three days after exposure generally protects them and aborts the disease. Thus contacts must be identified quickly and vaccinated with good vaccine and vigorous technique.

These epidemiologic facts led to the development of the surveillance and containment methodology, which became the main tool for the eradication program. This consisted of active search for patients, effective patient isolation, identification of their close contacts, vaccination of contacts, supervision of the contacts to immediately isolate them if they developed a fever, and if time and staff permitted identification of the contacts of contacts, the "second ring".

In the unlikely occurrence of a bioterrorist attack employing smallpox, surveillance and containment methods should be the mainstay of control efforts.

Keywords: Smallpox; Variola major; Transmission; Case fatality rate; Epidemiology

Introduction

In the late 1960's, the Smallpox Eradication Program switched from a strategy of mass vaccination to intensive surveillance and containment of outbreaks [1,2]. This change brought about rapid success of the eradication program. The switch was based on studies of the epidemiology of smallpox in West Africa [2-4], India [5-9], East and West Pakistan [10-17], Bangladesh [18,19] and Europe [20] conducted in the late 1960's and early 1970's. These studies showed that Variola major was less infectious than previously believed, that its spread was usually quite limited, and that vaccination of the immediate contacts of patients rapidly eliminated the disease. This paper reviews these findings and discusses our current understanding of the transmission and spread of the disease.

Mode of Transmission

Variola major is spread from person to person by direct, usually prolonged, face to face personal contact, during which a non-immune individual inhales virus particles from the exhalations of the infected patient [1,8,21]. There is no animal host of variola virus, and no one can become an asymptomatic carrier. Patients are not infectious during the prodrome despite an intense viremia [1,12,15]. Patients become infectious from the appearance of the rash on the skin and the pharynx, usually two or three days after the onset of the prodrome. The soft tissue in the back of throat has no covering like the squamous layer of the skin, so the virus is shed into the nasopharynx before it is shed from the skin lesions. Most spread is generally to bedside care givers, since most virus is carried in large droplet nuclei which rarely travel more than 6 feet from the patient [1,6,12,16,17]. Most patients can remember being at the bedside of an obviously ill individual [20].

Smallpox rarely can become airborne and infect patients at some distance from the source patient. For instance a patient with a fever and mottled rash was admitted to a hospital in Meschede Germany [22], where he was isolated with a provisional diagnosis of typhoid. The window of his room was open, and patients and visitors on the floor above him became infected. Subsequent studies of air flow showed that air from his room entered windows on the floor above. This incident is highly unusual, but shows the possibility of aerosol spread. There is also good documentation that laundry workers handling heavily contaminated bedsheets from patients with smallpox can become infected when they create an aerosol by shaking out the linen [1,21]. Spread by direct contact with bodies during preparation for funerals has been documented as a rare mode of transmission [4].

Frequency of Transmission

Like most viral exanthems, smallpox is seasonal, following the pattern of measles and varicella, with an upswing in winter and early spring months, and a pronounced downswing in hot humid weather. R_0, the number of susceptible persons infected in the initial wave of transmission, is 2 to 3 during the seasonal upswing of incidence, when each patient spreads the virus generally to more than one new individual. R_0 is less than one during the seasonal downswing, when each patient generally gives rise to less than one new patient. This leisurely flow of smallpox led Dr. Thomas Mack, who has led careful studies of smallpox in East Pakistan, West Pakistan, and Europe, [10-16,20] to declare, "It is my judgment that under contemporary conditions smallpox cannot be said to live up to its reputation. Far

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from being a quick-footed menace it has appeared to be a plodding nuisance with more bark than bite" [20]. Mack's review of outbreaks in Europe after the Second World War identified 47 outbreaks, 13 with no spread at all, and an average of 15 cases and 3 deaths, most of which were accounted for in one large outbreak in Poland and another in the UK. Most transmission was in hospitals, after undiagnosed sick patients were hospitalized [20].

Two patients in the 1972 outbreak in Yugoslavia illustrate the uncommon outliers to this relatively low infectivity of the disease [23]. One adult male patient developed hemorrhagic smallpox with a high fever and prostration, but initially no rash. He was given penicillin and then was misdiagnosed as a patient with allergy to penicillin when he developed a flat hemorrhagic rash. He was hospitalized and demonstrated at his bedside to doctors, nurses, medical and nursing students as an interesting case of severe penicillin allergy. He was then transferred from the initial hospital to a surgical hospital when he began to bleed from all orifices. He was again shown to many of the staff. He spread smallpox to 38 persons, mostly medical staff. A middle aged woman who had been vaccinated as a child was a socially prominent member of her village, and was visited and comforted by dozens of persons from her family and village during her illness. She had a mild illness, but because of her large number of social contacts she spread smallpox to at least 16 and perhaps as many as 23 friends and relatives. These two patients are record setters and are highly unusual, given that it was not known that there was smallpox in Yugoslavia during their illnesses, and Yugoslavia had stopped vaccinating during the Second World War.

Case Fatality Rate (CFR)

CFRs from true Variola major in unvaccinated patients were from 20% to 40%, higher in pregnant women and very young children [1,21,22]. Smallpox was predominantly a pediatric disease prior to the 20th Century, with children commonly infected, and survivors developing life-long immunity. The CFR in hemorrhagic smallpox was nearly 90%+, which is not surprising since the hemorrhagic phenomena were probably from disseminated intravascular coagulation, which was untreatable during the era of smallpox. Fortunately such patients often produced very little spread because of their immediate prostration and rapid mortality. The CFR generally coincided with the extent of the rash, being high in patients with confluent disease, less in high in patients with a discrete rash, and usually quite low in previously vaccinated patients with a minimal rash. This is because the extent and confluence of the rash roughly coincides with the extent of the viremia that initiates the prodrome [1,21,22].

The strain of Variola virus was critical in severity and CFR of the disease. The Asian subcontinent had true Variola major with very high CFR. The disease in West Africa and Indonesia was also considered Variola major, although we now know that they were genetically distinct from the Asian subcontinent strains [23,24]. Hemorrhagic disease was very rare in these areas, and fully confluent disease was uncommon. The CFRs in those areas were generally around 8% to 12%.

Protection from Post-Exposure Vaccination

Successful vaccination with a fully potent strain of vaccinia virus within three days of exposure usually prevents development of disease [1,2,16,19,21,25-29]. Complete and careful isolation was almost as good as vaccination in eliminating transmission of the virus. In the waning days of the eradication program in Bangladesh, armed guards enforced isolation and screened visitors for their vaccination status. Good surveillance is critical to controlling the disease; modern communications should make such finding cases relatively easy. Rapid reporting, case investigation and rapid isolation are essential and would be facilitated by the use of modern media, cell phones, photos of suspect cases transmitted by cell phones, etc. Those who fear rapid and intensive spread of smallpox should remember that SARS, MERS, and Ebola are more infectious than smallpox, can be spread by patients without an obvious diagnosis, have no vaccines or effective antivirals, and yet were controlled by effective isolation of patients alone. Smallpox by contrast is relatively easy to diagnose once the index of suspicion is high, and patients are not infectious in the first two or three days after onset of the prodrome.

Surveillance and Containment

The relatively leisurely spread of smallpox plus the effectiveness of vaccination shortly after exposure led to the development of surveillance and containment as the main strategy for smallpox eradication [1,2,21]. In the unlikely event of a return of smallpox by accident or malign intent, this should be the method used to eliminate the disease. There are six elements of the surveillance and control technique: finding cases, isolating them, identifying contacts, vaccinating contacts, monitoring contacts, and "second ring" vaccination. Each of these should be easier in the United States today than in Africa and the Asian subcontinent during the era of smallpox eradication.

First, cases must be identified. This was done in Africa and Asia by intensive direct search, but in a modern developed nation such as the United States a call via the media including descriptions and pictures of typical cases would bring out notification of suspect cases. Second, the cases must be effectively isolated. The public, political leaders and the medical profession would demand isolation, so it would be prompt and easy. Isolation should ideally be in dedicated facilities outside of hospitals, because nosocomial spread in hospitals where many patients with compromised immune systems are found would be unwise. Third, contacts of the cases must be identified. Modern media including cell phone etc. make this easy, for the bona fide face-to-face contacts want to be found and vaccinated. Publication of the whereabouts of the cases will encourage contacts to come forward. Fourth, the contacts must be vaccinated with good vaccine and vigorous technique. With bona fide documented face-to-face contacts of cases, there should be no contraindication to vaccination, because smallpox would be much worse than any complications of vaccination. Fifth, the contacts must be monitored so they can be immediately isolated before they become infectious. Daily temperatures are the easiest and most effective way to accomplish this. Sixth, the contacts of contacts should be identified, offered vaccination, and monitored. Most likely they will not be infected, and vaccination can be delayed until the prodrome of smallpox develops in their contacts.

In retrospect efforts similar to these had been carried out by CW Dixon is Tripolitania immediately after the Second World War, [22], and by WH Foege in Ogoja Province, Nigeria [2] just before the initiation of the Smallpox Eradication Program. In both cases

a shortage of vaccine led to limiting immunization to immediate contacts, and the rapid cessation of transmission was an unexpected happy outcome.

Variola and Bioterrorism

The specter of the use of Variola major as a weapon for bioterrorism has been discussed a great deal in the 21st century [30-32]. The virus is only known to be in highly Secure labs at the CDC in Atlanta GA USA and at the SRC VB VECTOR in Koltsovo, Novosibirsk region, Russia. The Variola virus can be grown on many biological media, and lyophilized for stability. Creating a stable mixture in a lab and transporting it might be difficult. However its use is unlikely, although it is difficult to prove that there are no such plans. No smallpox was found in Iraq. An attack outdoors sunlight will kill the virus, and it would be hard to deliver a spray with enough concentration of virus to infect many people. An indoor aerosol might result in considerable transmission, but once the first cases are diagnosed their contacts can be rapidly vaccinated and subsequent spread prevented. Terrorists with the technical ability to grow and use Variola as a weapon would realize that they would risk a "blowback phenomenon" in which smallpox would be transported back to their own countries where is would probably be more difficult to control than in the United States. The theoretical threat of a biological attack has been an impetus for developing and stockpiling newer and improved vaccines. A successful attack even if it caused very few cases would have a considerable emotional impact on the general population, so plans have been developed to prepare for such an occurrence.

There is no historical evidence that smallpox has ever been effectively used as a bioweapon. It is known that the British General Lord Jeffrey Amherst wrote to his colonels suggesting that they use smallpox as a weapon against American Indians during Pontiac's Rebellion. There is however no record that any of them did so, and smallpox was known to be already raging among the Indians at the time [33].

Summary and Conclusion

Smallpox caused by true Variola major does not spread rapidly, with R_0 of 2 to 3 in cool dry weather, and generally R_0 less than 1 in hot humid weather. Transmission is usually to bedside caregivers with prolonged face-to-face contact. Patients are prostrated but not infectious during the prodrome, and become infectious with the appearance of the initial rash on the skin. Case Fatality Rates are 20% to 40%, higher in pregnant women and patients with confluent or hemorrhagic disease. Vaccination of contacts shortly after their exposure usually protects them and aborts the disease.

Because smallpox does not spread rapidly, control measures should be based upon vigorous surveillance and outbreak containment techniques, as were utilized during the World Health Organization's Smallpox Eradication Program. While an outbreak caused by a bioterrorist attack is unlikely, if one occurs it should be handled by surveillance and containment.

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