

## REVIEW ARTICLE

## CURRENT CONCEPTS

## How Contagious Is Vaccinia?

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**T**HE DEPARTMENT OF HEALTH AND HUMAN SERVICES IS FINALIZING plans for a U.S. vaccination program against smallpox. As more vaccinia virus vaccine has become available, the debate over how many persons to vaccinate has centered on two issues: the safety of the live vaccine and the transmissibility of vaccinia virus from a recently vaccinated person to a susceptible host.

The issue of safety has received substantial attention, given that a predictable number of adverse events will occur among vaccine recipients. Furthermore, an extensive literature has established credible estimates of the complication rates.<sup>1-4</sup> The risk of secondary transmission, however, is discussed much less, perhaps because relatively little is known. A report on vaccine-related deaths in the United States during the 1960s found that 12 of the 68 deaths occurred in unvaccinated persons exposed to recently vaccinated family members or friends, a finding that demonstrates the potential gravity of the problem.<sup>5</sup> A recent reconsideration of the transmission rates during the 1960s concluded that spread is remarkably infrequent; this finding is quite reassuring for immunocompetent persons in the general population.<sup>4</sup>

However, the finding of infrequent transmission may not apply to hospitals, where large numbers of workers will be vaccinated, many for the first time. There is a large concentration of immunocompromised patients in hospitals, a situation distinctly unlike that in 1947, the last time a mass vaccination campaign was mounted in the United States. The prospect that a series of decisions might unwittingly introduce a live, transmissible, and potentially lethal virus into hospitals has dampened the enthusiasm of many for widespread vaccination.

In this article, I review the literature on the secondary transmission of vaccinia virus, including transmission in hospitals, among families, and in other circumstances. Many of the older articles would not pass modern peer review. However, the information they contain cannot be obtained elsewhere — a fact that makes them, however limited, of real value.

## NOSOCOMIAL SPREAD

Nosocomial spread of vaccinia virus has been reported at least 12 times, from 1907 through 1975, and has resulted in 85 secondary cases<sup>6-17</sup> (Table 1). Several additional outbreaks of Kaposi's varicelliform eruption unrelated to vaccinia virus have also been described. The cause of this diffuse skin eruption, whose name is often incorrectly used interchangeably with eczema vaccinatum (a known complication of vaccinia virus vaccination), was debated till the middle of the 20th century. Experts argued whether herpes simplex or vaccinia was the more likely cause; current thinking accepts both these and other viruses as etiologic agents. Studies that clearly demonstrated herpes simplex to be the cause of a patient's Kaposi's varicelliform eruption are therefore not discussed in this article.<sup>18-20</sup>

About three fourths of the cases of secondary vaccinia infection occurred in young

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**Table 1. Reports Describing Nosocomial Spread of Vaccinia.**

Location and Year	Place	Hospital Source Patient	Secondary Cases	Outcome	Comment
Germany, 1907 <sup>6</sup>	Children's dermatology ward	Six-month-old boy with eczema vaccinatum whose sister had received vaccination	Five secondary cases, including 5 of 6 children on the ward who had not previously been vaccinated	One died (underlying skin disorder from congenital syphilis)	None of 10 previously vaccinated children on ward had secondary vaccinia
Glasgow, Scotland, 1935 <sup>7</sup>	Two wards of children's hospital	Three-year-old girl with eczema vaccinatum from an unknown exposure	15 cases, all 8–18 days later, including 11 of 11 children on one ward and 4 on neighboring ward	Five died	Underlying conditions included eczema, seborrheic dermatitis, impetigo, scabies
Germany, 1936 <sup>8</sup>	Burn unit	Eight-year-old girl with extensive burns who received vaccinia vaccine on admission	Three cases from nosocomial spread: 74-year-old woman with burns; previous vaccine; shared room with source patient; 15 days later, vaccinia developed and patient died Six-year-old girl with dermatitis; in room down the hall from source patient (same staff); previous vaccine; rash 24 days after source patient's initial lesions 61-year-old woman with burn; previously vaccinated twice; admitted 3 days after resolution of vaccinia in source patient; vaccinia developed 12 days later	Single death in elderly woman, perhaps from burns	Third and fourth cases were more severe than second; possible passaging effect Spread to girl down the hall from source patient suggests possible aerosol or health care worker-mediated transmission
Sweden, 1940 <sup>9</sup>	Children's hospital	Six-month-old boy with eczema vaccinatum whose sister had recently been vaccinated	Four secondary cases, including 3 with preexisting eczema	All survived; one given "blood" from immune relative	Four of 6 children on ward had disease
Philadelphia, 1944 <sup>10</sup>	Children's "skin ward"	4.5-month-old vaccinated boy without previous known skin problems; eventually progressed to fatal eczema necrosum	Four of 6 children on the ward had vaccinia within 2 weeks after admission of source patient	All survived	Four of 6 children on ward had disease
Brooklyn, New York, 1947 <sup>11</sup>	Infectious-disease hospital	All New York City residents had recently received vaccination	Three reported secondary cases were nosocomial, with a nurse or other health care worker the presumed source	Penicillin given; no vaccinia immune globulin; all survived	Among 16 patients overall, mean incubation period was 10.6 days (5–19 days); substantial eosinophilia (>10%) in 13 of 16
Glasgow, Scotland, 1950 <sup>12</sup>	Children's hospital	Unknown source: cluster of cases in children's hospital after city-wide vaccination	Four secondary cases, each with eczema or irritant dermatitis, all occurring within days	Antibacterial agents given; all survived	Other non-nosocomial transmissions occurred in a normal host with a knee abrasion and another with acne

Table 1. (Continued.)

Location and Year	Place	Hospital Source Patient	Secondary Cases	Outcome	Comment
Marseilles, France, 1952 <sup>13</sup>	Children's hospital	Six-month-old girl with eczema vaccinatum whose sister at home was vaccinated	Four secondary cases: Five-month-old girl with eczema had vaccinia 10 days after admission of source patient and died Six-month-old boy had vaccinia 12 days after admission of source patient; almost died, but responded to vaccinia immune globulin Eight-month-old girl had vaccinia 15 days after source case; received vaccinia immune globulin but died One-year-old boy had vaccinia 16 days after source case; received vaccinia immune globulin and survived	Two died; antibacterial agents given to all; vaccinia immune globulin to 3	Source case was isolated within 5–10 hours after admission; outbreak occurred despite relatively brief exposure and lack of patient-to-patient contact
Italy, 1953 <sup>14</sup>	Children's hospital	13-month-old girl with vulvovaginal vaccinia requiring urinary catheterization, who had been exposed to her recently vaccinated older brother	Within 5 weeks, 23 secondary cases seen, all associated with urinary catheters; all had vulvar lesions and dysuria; many with fever or gross hematuria	All survived	Original urinary catheter incompletely cleaned with Citrosil; soaked in pan with several other catheters
São Paulo, Brazil, 1956 <sup>15</sup>	Dermatology ward for male adults	Man with generalized vaccinia after a recent vaccination	Patient in next bed had generalized vaccinia 8 days after admission of source patient Two additional sub-clinical cases (serologically identified)	All survived	Serologic testing of 6 additional susceptible patients was negative; acute infection in 3 of 9 exposed unvaccinated patients
São Paulo, 1955–1956 <sup>16</sup>	Pemphigus foliaceus hospital	Smallpox cases in adjoining hospital led to decision to vaccinate First wave: 47 inpatients vaccinated Second wave: 140 inpatients and 29 health care workers vaccinated	First wave: 15 unvaccinated patients had generalized vaccinia Second wave: 1 unvaccinated patient had generalized vaccinia	All survived	47 of 187 vaccinated patients had generalized vaccinia Approximate transmission rate: 16 of 187 (9%)
Stanford, California, 1975 <sup>17</sup>	Dermatology ward	19-year-old man from India with atopic dermatitis had recently been vaccinated and had disseminated vaccinia	63-year-old woman with mycosis fungoides and active skin lesions	Two doses of vaccinia immune globulin; patient survived	Patients possibly spent time in a hallway on one day only; otherwise possible health care worker-mediated transmission

children with a dermatologic disorder, usually eczema (currently referred to as atopic dermatitis). These children had eczema vaccinatum, a syndrome of diffuse dermatitis with open vesicles, fever, regional or generalized adenopathy, and (rarely) encephalitis. Vaccinia could easily be cultured from the lesions. Many patients in whom eczema vaccinatum develops have active eczema at the time; the others have only a history of the condition.<sup>4,21</sup> Those without active lesions may have a less severe form of eczema vaccinatum.<sup>4</sup> Other skin conditions that may predispose a patient to secondary acquisition of vaccinia virus include seborrheic dermatitis, impetigo, scabies, burns, and pemphigus foliaceus. Reports of non-outbreak-related disease have described secondary transmission to areas of acne and accidental skin abrasion.<sup>12</sup>

The incidence of secondary transmission of vaccinia virus is not easily calculated. In Glasgow, Scotland, after a three-year-old girl with eczema vaccinatum was hospitalized, all 11 children on her ward and 4 on an adjoining ward had generalized disease.<sup>7</sup> Smaller series from Germany,<sup>6</sup> Sweden,<sup>9</sup> Philadelphia,<sup>10</sup> and São Paulo, Brazil,<sup>15</sup> demonstrated transmission to 16 of 27 susceptible patients (59 percent). In a single outbreak involving adults at a hospital in Brazil where vaccination was given to several patients with pemphigus foliaceus, 16 unvaccinated persons developed secondary disease.<sup>16</sup> However, because many patients on the ward were vaccinated simultaneously, the opportunity for exposure increased. Furthermore, the denominator was not clearly defined but may have included 187 patients whose vaccine history was unknown, yielding an incidence of secondary vaccinia of about 9 percent.

A single French report examined the contribution of the duration of exposure to the risk of vaccinia virus transmission. An infant presented in the daytime with eczema vaccinatum, was hospitalized on an eczema ward, and by evening was transferred to isolation.<sup>13</sup> Despite this, four secondary cases occurred in children on the eczema ward, though none had close contact with the index case.

The exact route of transmission is also uncertain. In the above study,<sup>13</sup> all of the children were confined to cribs and were too ill to interact. In another, after hospitalization of the index patient, several cases of disease occurred in an adjoining ward.<sup>7</sup> Although the affected children did not mix, they were cared for by the same professional staff.

A sore throat developed in three treating nurses, one of whom had several “pustular bullae” on the forearms, but none were formally evaluated.<sup>7</sup> In a carefully studied case of transmission from an adult with disseminated vaccinia to a woman with active mycosis fungoides in California, investigators remained uncertain how the virus moved from the isolation room to the woman, whose room was some 25 m (75 ft) away.<sup>17</sup> They suggested that perhaps health care workers carried the virus or that the two patients occupied the same hall area for several hours, resulting in fomite-based spread. The studies also raise the possibility of aerosol transmission of vaccinia virus.<sup>7,8,13</sup> Any of these potential methods of spread has substantial implications for infection-control teams that may be called on to isolate and care for a patient with eczema vaccinatum.

Yet another route of transmission was demonstrated by a unique outbreak in Italy, where vaccinia was spread by a contaminated urinary catheter.<sup>14</sup> After her older brother received vaccine, a 13-month-old girl had initially undiagnosed genital lesions and dysuria resulting from vaccinia infection. At the hospital, she was catheterized, and the catheter was then placed in a pan of Citrosil solution for sterilization. Several other urinary catheters were soaking in the same pan. Within a five-week period, there were 23 secondary cases with vulvar-urethral vaccinia; each of the patients had been catheterized with one of the contaminated catheters. About half had high fevers, and some had gross hematuria. Virus was cultured from the urine of several children.

Two reports have clearly defined the epidemic curve of vaccinia virus infection. In the 1935 outbreak in Glasgow, all secondary cases occurred between 8 and 18 days after exposure.<sup>7</sup> Examination of patients treated at an infectious-disease hospital in Brooklyn, New York, after the 1947 mass vaccination in New York City found an average incubation period of 10.6 days (range, 5 to 19).<sup>11</sup>

Nine of the 85 reported patients (11 percent) died. Worsening severity of disease with each generation of transmission was seen in one outbreak in Germany.<sup>8</sup> In another report, from Scotland, those in whom disease developed later tended to have milder symptoms.<sup>7</sup> Death was typically due to encephalitis or the development of secondary bacterial pneumonia. Treatment included antibacterial agents and, for several, vaccinia immune globulin.

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 SPREAD WITHIN FAMILIES
 

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Numerous reports have described the spread of vaccinia virus within families. The majority are instances of single transmission, usually from a recently vaccinated child to an unvaccinated younger sibling.<sup>22-25</sup> However, two or more secondary cases have been reported in at least eight reports of family outbreaks published from 1931 to 1981<sup>26-33</sup> (Table 2). Many of the reports describe severe, sometimes fatal eczema vaccinatum in the first family member with secondary disease and substantially milder local inoculation disease in the rest of the family. These latter infections might have been overlooked had medical attention not been sought for the severe case.

These eight reports describe transmission to 27 family members. Only five (19 percent) had previously received vaccine; these persons invariably had milder disease. Of 19 whose skin examination results were noted, 6 had current or previous eczema, including the 3 (11 percent) with fatal disease, none of whom had previously received vaccinia virus vaccine. Death was invariably from fulminant disease, occurring before vaccinia immune globulin could be administered.

In many of the family outbreaks,<sup>27-30</sup> sharing close quarters was a significant factor, suggesting the need for sustained, intimate contact to transmit vaccinia between intact hosts. In one outbreak, a bed was shared by three persons in whom disease developed, further supporting this notion.<sup>27</sup> An unusual aspect of the family outbreaks of vaccinia was the apparent tendency for lesions to be present in similar anatomical areas in all secondary cases, including the mouth<sup>32</sup> and the face.<sup>33</sup>

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 OTHER TRANSMISSION
 

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Scattered reports detail other cases of secondary transmissions of vaccinia, exclusively by inadvertent inoculation.<sup>34-40</sup> Eyelids, lips, nose, and vulva were most commonly reported.<sup>32</sup> Humphrey found 70 cases of vulvar vaccinia in the literature,<sup>37</sup> including the 24 catheter-related cases described above,<sup>14</sup> many due to auto-inoculation and several from sexual transmission.<sup>31,34</sup> The mucosa may be involved because vaccinia can penetrate more easily into this tissue than into skin. Alternatively, vaccinia may have a tropism for mucosal surfaces. This phenomenon may be important, since many currently hospitalized patients, such as those receiving chemo-

therapy, have substantial mucosal abnormalities and therefore may be at higher risk for acquisition of secondary vaccinia virus infection.

Occupational spread to the hands of those working with vaccinia virus vaccine has been described, and many workers have repeated local infection despite previous vaccination.<sup>41</sup> A sustained outbreak occurred among 22 farm workers and 450 cows on a dairy farm in El Salvador.<sup>42</sup> One of the workers had received vaccine and resumed milking cows before his lesions had resolved, thereby spreading the virus to cows and thence to coworkers, including the woman who washed the towels used by the milkers. In all 22 affected workers, lesions were confined to the hands and genitals.

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 IMPLICATIONS FOR VACCINATION POLICY
 

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The rate of adverse events after vaccinia virus vaccination is being carefully scrutinized as a national vaccination policy is developed.<sup>1-4</sup> Relatively little is known, however, about the risk of secondary transmission of this live virus in the hospital setting.<sup>4</sup> A review of the literature indicates that nosocomial transmission does occur and that the outcome may be fatal in up to 11 percent of cases. Nosocomial outbreaks seem to require relatively minor contact with a source case, whereas spread in the home appears to occur only with sustained, intimate exposure, perhaps owing to immunologic and dermatologic differences among the persons exposed.

Information regarding secondary transmission is particularly important for health care facilities, which will need to vaccinate workers while ensuring patients' safety. The composition of hospitalized patients in the 21st century is dramatically different from that in the mid-20th century. Patients treated before the 1950s were very unlikely to be immunosuppressed: cancer chemotherapy was just beginning; transplantation had not yet been performed; the human immunodeficiency virus (HIV) was unheard of; and corticosteroid therapy had only recently been introduced.

Now, approximately 506,154 persons in the United States are known to be living with HIV<sup>43</sup>; 1.2 million new non-skin cancers are diagnosed annually<sup>44</sup>; 2.1 million persons have rheumatoid arthritis and receive therapy with corticosteroids or other immunosuppressive agents<sup>45</sup>; and more than 14 million have asthma, many of whom require intermittent steroid use.<sup>46</sup> Thousands of solid-organ

**Table 2. Reports Describing Spread of Vaccinia to Two or More Members of a Household.**

Location and Year	Source Case	Secondary Cases	Outcome	Comment
Baltimore, 1931 <sup>26</sup>	Older brother	Twin 3-year-old younger brothers with preexisting eczema: First twin had eczema vaccinatum 10 days after older brother's vaccine, died within a few days Second twin had mild disease and survived	One of 2 died	Rapid death typical in family-based transmissions
Baltimore, 1946 <sup>27</sup>	Six-month-old, recently vaccinated girl	Three secondary cases: Unvaccinated 3-year-old brother with history of eczema had eczema vaccinatum 13 days later and died quickly 41-year-old mother, who shared bed with source patient and with patient who died, had several lesions 16 days after vaccination of source patient; remote history of eczema and 3 previous unsuccessful vaccination attempts Four-year-old brother had mild skin lesions 16 days after vaccination of source patient	One of 3 died; antibacterial agents given to patient with fatal case and to mother	Biopsy specimens of lesions contained many eosinophils; closeness of living conditions stressed, including shared bed
England, 1948 <sup>28</sup>	Infant in Polish emigrant camp where many were vaccinated	14-month-old girl "shared hut" with source patient, had history of extensive eczema; eczema vaccinatum developed, and she died within 2 days Mother of 14-month-old, previously vaccinated, had mild case	One of 2 died, despite administration of penicillin	Hygienic conditions were poor, and quarters were crowded Third case in unvaccinated adult with inactive eczema caused severe, nearly fatal disease
Boston, 1966 <sup>29</sup>	Five-year-old boy who received primary vaccination	Four family members had vaccinia, including 2 previously vaccinated: Three-year-old sister; previous eczema without active lesions; no previous vaccine; moderately ill Eight-year-old sister; previously vaccinated; mild disease; no history of eczema Two-month-old sister; no previous vaccination; mild skin involvement; prolonged respiratory illness; no history of eczema 10-year-old brother; previous vaccination; conjunctivitis developed; no history of eczema	All survived; conjunctivitis treated with 5-iodo-2'-deoxyuridine	Secondary cases occurred 14–24 days after vaccination of source patient All 4 patients with secondary cases had normal skin at the time of transmission
Indiana, 1968 <sup>30</sup>	Seven-year-old girl who received primary vaccination	Five other family members, none previously vaccinated: Brother with eczema had "eczema vaccinatum"; given vaccinia immune globulin and survived Mother and 3 other siblings had mild disease 9–16 days later Only source patient had been vaccinated	All survived	Family lived in crowded conditions and had "close and prolonged contact" with source case
Cambridge, England, 1969 <sup>31</sup>	1.5-month-old boy who received primary vaccination	Two other family members (parents), one previously vaccinated: 19-year-old mother had vaginal itching and discharge 10 days later; vaccinia lesions were present 21-year-old father had penile lesions 10–14 days after wife's symptoms; had been previously vaccinated Source patient healed at vaccination site but had perianal lesions Previously vaccinated older brother had no lesions	All survived	Sexual transmission described in several reports
Virginia, 1973 <sup>32</sup>	Recently vaccinated cousin	Three of 6 sons in household, all of whom had oral lesions only, occurring 1–2 weeks apart	All survived	Predilection for oral mucosa unexplained
Newfoundland, Canada, 1981 <sup>33</sup>	18-year-old vaccinated female military recruit	Six secondary cases, 3 in family members: 17-year-old sister had facial lesions 18-year-old female neighbor had facial lesions 40-year-old aunt had facial lesions 15-year-old roommate of source patient had facial lesions 25-year-old man who had kissed the 18-year-old neighbor had facial lesions 19-year-old man who also "had contact" with 18-year-old neighbor had facial lesions	All survived	Exclusive presentation as facial lesions unexplained

and bone marrow transplantations are performed each year and tens of thousands of transplant recipients are alive and still receiving immunosuppressive therapy. Atopic dermatitis is also more common, with prevalence among children ranging from 6.8 percent to 17.2 percent.<sup>47</sup> Finally, there are tens of thousands of patients in intensive care units and newborn nurseries. Current expert opinion recommends that vaccination of such persons should be avoided.<sup>48</sup> Vaccination can be avoided, but contact with a recent vaccinee probably cannot.

Of equal importance are the differences in the modern population of health care workers, some of whom are themselves immunocompromised. Previously, hospitals were staffed with workers who had received at least one vaccinia virus vaccine. Such persons were therefore unlikely to initiate or propagate an outbreak. In contrast, most current health care workers are susceptible to smallpox and vaccinia and so might play a dangerous supporting or even lead part in any nosocomial outbreak.

Both the rate and route of vaccinia transmission remain unknown. The incidence derived from the cited studies (9 to 59 percent) is certainly an overestimation of current risk, owing to erratic infection-control practices in past decades, differences in the virulence of the vaccinia virus used, and a substantial reporting bias. The current plan for an occlusive dressing at the vaccination site and other now-routine infection-control procedures, including hand hygiene and isolation for any patient with unexplained fever and rash, should effectively limit potential spread.<sup>49</sup> Equally important is the need to ensure that the vaccine program develops slowly, with flexibility and ample time to make any necessary adjustments.

The actual route of transmission is not revealed by these outbreaks, but it may include several different paths.<sup>7,8,13,14,17</sup> First, health care workers may carry virus on their clothes, on their hands, or even in the nasopharynx. Other evidence suggests transmission by fomites,<sup>17</sup> and the widespread transmission from contaminated urinary catheters<sup>14</sup> emphasizes the need for rigorous cleaning of any item that comes into contact with a recently vaccinated person. There is also the possibility of transmission of vaccinia virus by the aerosol route,

since some secondary cases have occurred on the same hospital floor as a bedbound source patient.<sup>7,8</sup>

Other than those with underlying skin conditions, it is not known which patients are at high risk for secondary disease. Dozens of reports have described progressive vaccinia (also referred to as vaccinia necrosum and vaccinia gangrenosa) in immunocompromised patients, particularly those with hematologic neoplasms (especially chronic lymphocytic leukemia), hypogammaglobulinemia, or defects in cellular immunity.<sup>50-55</sup> These infections, which are often fatal, may last for months and may respond poorly to frequent doses of vaccinia immune globulin.<sup>50</sup> Progressive vaccinia in a newly vaccinated soldier with advanced, previously undiagnosed HIV infection has also been described.<sup>56</sup> These studies demonstrate that vaccinia may be easily transmitted to hosts with severe dermatologic disorders, with substantial mortality in the absence of appropriate infection-control measures.

An additional important finding from these articles is the observation that secondary disease is manifested exclusively as eczema vaccinatum or contact inoculation. No secondary cases of the most severe complications — progressive vaccinia and postvaccination encephalitis (except in those with overwhelming eczema vaccinatum) — have been reported. Thus, the danger of nosocomial spread, though alarming, is mitigated by the limited range of clinical manifestations in secondary disease.

Because of the risk of secondary transmission of vaccinia, many hospitals remain uncomfortable with the recent recommendation against the provision of administrative leave for newly vaccinated health care workers.<sup>56</sup> Also, the advisability of immunocompromised workers' remaining on the job while colleagues receive vaccine has not been determined. Until these controversies are settled, hospitals must be certain that the rush to vaccinate health care workers does not result in a self-inflicted epidemic — not of smallpox, but of infection with the live, potentially lethal virus, vaccinia.

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