Evaluation of 21st-Century Risks of Smallpox Vaccination and Policy Options
J. Michael Lane, MD, MPH, and Joel Goldstein, MD

The United States stopped vaccinating against smallpox in 1972 because the risks were judged to outweigh the benefits. The possibility of a terrorist attack using smallpox has led to renewed interest in a vaccination program. Smallpox vaccination carries considerable risks, which may be of greater concern today than in the late 1960s because of the increased prevalence of immunosuppression and atopy in the population. This paper reviews the clinical presentations of major adverse events after vaccination and the rates of occurrence of these events observed in the 1960s. The normal dynamics of the spread of smallpox is slow, and usually only persons who have had close personal contact with an overtly ill patient are affected. There are several preattack vaccination policy options, but immunization of medical workers, especially those who might have close contact with infected patients, is sufficient in the absence of a known threat of a bioterrorist attack or the identification of a smallpox-infected person.

For author affiliations, see end of text.

The United States stopped routine vaccination against smallpox in 1972. Studies performed in the 1960s documented that the risk for serious complications from smallpox vaccination was greater than the estimated risk for reintroduction of smallpox itself (1). Studies of European outbreaks after reintroduction of smallpox showed that spread of the disease was usually minimal once public health containment efforts were instituted (2, 3). In the 1960s and 1970s, inadvertent importation from endemic nations posed a risk for smallpox. Concerns about bioterrorism now raise the possibility that the risk from intentional release may justify resumption of vaccination (4–7).

A spectrum of vaccination strategies should be considered before an initial case has occurred or a specific threat of a bioterrorist attack has been received. We could resume routine vaccination of the entire population. We could vaccinate “first responders” who might care for or investigate persons suspected of having smallpox and their contacts. We could allow individual citizens to make their own choices concerning immunization after informing the public about the risks of vaccination and the potential threat for smallpox. We could continue to pursue the current policy that considers the risk for smallpox to be too low to justify the risks of vaccination. The Advisory Committee on Immunization Practices initially suggested vaccinating a very limited number of persons who might be involved in the early investigation of possible smallpox cases (8) but is now suggesting a more widespread program for first responders (9).

We describe the smallpox vaccine; review risks from vaccination; and briefly discuss preattack vaccination policy options.

SMALLPOX VACCINE (VACCINIA VIRUS)

Vaccinia is a live-virus vaccine. In the United States, vaccine is made by using the New York City Board of Health (NYCBOH) strain of vaccinia, which was the safest of the strains in common use in the 20th century (3). The virus was grown on the skin of cows and then purified in production laboratories to produce the final product. Wet, glycerinated lymph was often used in smallpox vaccine in the 1960s and earlier, but after about 1970, most smallpox vaccine was lyophilized to preserve its stability when exposed to heat. Good vaccine has a titer of about 10 × 8 pock-forming units per mL (3). Successful vaccination (reported as take rates) will be achieved in almost 100% of previously unvaccinated persons and will be high in previously vaccinated persons. Vaccine of this titer that is diluted 1:10 successfully immunizes most vaccinees when administered with a bifurcated needle (10). New vaccine is currently being made by using the same NYCBOH strain on cell cultures (Vero cells and human MRC5 cells). When this vaccine is licensed in late 2003 and added to the approximately 70 million doses of currently available vaccine, the vaccine supply will be more than adequate for the entire U.S. population.

NORMAL VACCINATION RESPONSE

Successful vaccination requires replication of virus at the vaccination site. After vaccinia is successfully introduced into the Malphigian layer of the skin, it multiplies. In fully susceptible persons (primary vaccinees), very little is visible at the site for 3 or 4 days. Then, a papule forms, which matures into a vesicle, and then a pustule, over the next 4 or 5 days. The lesion is largest about 8 days after vaccination. The cardinal signs of inflammation are present from about day 5 to day 10 after vaccination, and mild fever with or without lymphadenopathy is common. Viremia is rare with the NYCBOH strain (11, 12). Neutralizing antibodies and evidence of cellular immunity can be detected starting from about day 8 or 9 after vaccination (3). The lesion then begins to involute and a scab forms, which comes off about 2 weeks after vaccination, leaving a
small scar. Virus can be recovered from the vaccination site and scab during most of this process.

Successful revaccination results in a lesion similar to that of primary vaccination, but the clinical course of the response is milder and accelerated to a varying degree, depending on the amount of residual immunity. If the virus replicates, a central lesion that is surrounded by some degree of inflammation and induration can be seen 6 to 8 days after vaccination; this lesion may be a pustule, ulcer, or scab. Revaccination of a highly immune individual may result in a lesion similar to a positive tuberculin test, with some itching and redness at the site. This lesion resolves fully by about day 3, and nothing is evident 6 to 8 days after vaccination. This type of lesion is the result of 1) high immunity and a good vaccination or 2) modest immunity and poor-quality vaccine or poor vaccination technique. It was once called the “reaction of immunity” but is now called an “equivocal response” (3). Persons with this response, especially those at serious risk for developing smallpox, should be revaccinated with known high-quality vaccine using vigorous technique.

Primary vaccination is a viral infection in a non-immune host and causes rare but significant complications. Most of these occur between 5 and 15 days after vaccination, when the vaccinia virus is actively replicating and the immune system is vigorously responding. Most adverse events occur after primary vaccination because previous immunization with vaccinia protects very well against its own adverse effects. The adverse events associated with revaccination generally occur in older patients who have not been vaccinated for decades or patients who have developed severe cellular immune deficiency with or without a humoral deficit.

CLINICAL FEATURES OF MAJOR ADVERSE EVENTS AFTER VACCINATION

There are three types of rare but potentially fatal adverse events and three common but clinically mild ones. These will be described in the following sections. Photographs of major adverse events (those not associated with the central nervous system) are available at www.bt.cdc.gov/training/smallpoxvaccine/reactions.

Postvaccinial Central Nervous System Disease

Postvaccinial central nervous system (CNS) disease (encephalitis, encephalomyelitis, and encephalopathy) is rare but potentially fatal. Disease usually develops 5 to 15 days after primary vaccination. About 25% of patients die, 25% have residual CNS sequelae, and the remainder recover. The clinical course is similar to that of other postinfectious encephalitides. Patients may present with coma, obtundation, seizures, focal or lateralizing signs, or virtually any CNS symptom. Very few patients have live virus in the brain or cerebrospinal fluid, suggesting that most of these adverse events are immune mediated. The disease is not progressive; the clinical course is complete within about 2 weeks. DeVries distinguished between encephalopathy (edema of the brain without inflammation), which occurred predominantly in children younger than 2 years old, and encephalitis (characterized by perivascular cuffing and pathologic signs similar to those of other postinfectious encephalitides) (13). No known factors increase risk enough to serve as contraindications to vaccination, although the increased rate of postvaccinial encephalitis in infants younger than 1 year of age led to delay of vaccination until the second year of life in the mid-1960s. Supportive care is essentially the only therapy.

Progressive Vaccinia

Progressive vaccinia, also called vaccinia necrosum or vaccinia gangrenosum, can occur after vaccination in patients with severely compromised immune systems. The cardinal signs of inflammation are not seen as part of the vaccination response, and, because of continued viral replication, the lesion continues to enlarge and metastasize beyond the usual time of scab formation (14). Disease may not be diagnosed in these patients until 2 or more weeks after inoculation. Most patients who developed progressive vaccinia in the 1960s had leukemia or agammaglobuline-mia. In today’s environment, we must focus our concern on patients who have severe HIV infection and AIDS, transplantation-related immunosuppression, malignant disorders being treated with chemotherapy, and other iatrogenic immunosuppressive disorders. Vigorous therapy with vaccinia immune globulin (VIG), modern immunoreconstruction, and perhaps modern antiviral agents (such as cidofovir or its analogues) may reduce mortality rates (15).

Eczema Vaccinatum

Eczema vaccinatum is characterized by widespread vaccinial lesions over the body of patients with eczema (true atopic dermatitis) or a history of atopic dermatitis. Patients lose fluid and electrolytes through the skin, similar to patients with severe burns, with the attendant risks for dehydration and organ failure. Modern approaches to burn therapy may help decrease the mortality rate. In the 1960s, death from eczema vaccinatum occurred more frequently in patients who were not vaccinated but who were close contacts of recently vaccinated family members (16). This was probably because of the recognition that patients with obvious eczema should not be immunized. Vigorous therapy with VIG and good supportive care reduced the fatality rate from about 10% in the era before VIG was used to only about 1% (12, 17, 18). Eczema vaccinatum rarely occurred in patients with atopic dermatitis who had been previously vaccinated and who had robust immunity; therefore, after these patients are vaccinated, frequent revaccination is considered appropriate.

Accidental Implantations, Erythematous or Urticarial Rashes, and Generalized Vaccinia

More common but of less concern are accidental implantations, erythematous or urticarial rashes, and “generalized vaccinia.” Accidental implantation occurs when a
Table 1. Frequency of Adverse Events in 1968 after Primary Smallpox Vaccination with New York Board of Health Strain Vaccinia, by Age and Type of Adverse Event*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Age at Vaccination</th>
<th>Adverse Events per Million Primary Vaccinees, n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1 y</td>
<td>1-4 y</td>
</tr>
<tr>
<td>Death (all causes)</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>6-9 y</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>&gt;10 y</td>
<td>1</td>
</tr>
<tr>
<td>Postvaccinial encephalitis</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>7-12 y</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&gt;12 y</td>
<td>4</td>
</tr>
<tr>
<td>Progressive vaccinia</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>2-5 y</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;5 y</td>
<td>7</td>
</tr>
<tr>
<td>Eczema vaccinatum</td>
<td>14</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>6-11 y</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>&gt;11 y</td>
<td>30</td>
</tr>
<tr>
<td>Generalized rashes</td>
<td>400</td>
<td>900</td>
</tr>
<tr>
<td></td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>250</td>
</tr>
</tbody>
</table>

* Adapted from Lane et al. (18), Lane et al. (24), and Neff et al. (25) and reproduced from Lane JM: Smallpox vaccination served great purpose but was not always benign [Editorial]. Infectious Diseases in Children. 2002;15:11, with permission.

Patient touches the vaccination site and then touches an eye, the anus or genitals, or areas of abraded skin (such as the lesions of poison ivy). The result is a vaccinia lesion distant from the intended vaccination site. When vaccinia infects the eye, an ophthalmologist should be consulted to examine for keratitis. About 6% of patients with vaccinia in the eye develop vaccinial keratitis (19). Vaccinia immune globulin is contraindicated in these patients; experimental data in rabbits showed that antigen–antibody precipitates occur in the cornea and cause scaring (20).

Widespread blotchy macular rashes, often with dramatic erythema or urticaria, are very common, especially in toddlers. Affected patients are generally not ill and do very well without therapy. Rarely, a true Stevens–Johnson syndrome rash occurs, which requires more vigorous medical intervention. There is a blurry spectrum of these rashes, many of which are labeled “generalized vaccinia.” This term implies that the vaccinia virus has become bloodborne and has spread throughout the body. With erythematous or urticarial rashes, virus does not replicate in peripheral lesions; true generalized spread of the virus with virus-containing peripheral pustules is uncommon.

Fetal Vaccinia

Pregnancy is a relative contraindication to vaccination because of the accepted practice of avoiding live virus vaccines during pregnancy. Limited data do not show that vaccinia is teratogenic or that it leads to increased fetal wastage. A very small number of cases of fetal vaccinia (usually presenting with scars or pock marks or both) have been reported, but this is exceedingly rare. Pregnant women exposed to smallpox should be vaccinated. In pregnant women, smallpox has been associated with very high rates of mortality (almost 90% in some series) and fetal wastage (almost 100%).

Treatment of Adverse Events after Smallpox Vaccination

Treatment of adverse events after vaccination is not standardized (21). Clinical trials have not been conducted because the frequency of serious problems was low. Vaccinia immune globulin was introduced by Kempe (12) in 1959 and became a standard therapy for progressive vaccinia and eczema vaccinatum. It clearly contributed to the decline in mortality from these conditions. Vaccinia immune globulin is made from the blood of highly immune, recently vaccinated donors and is administered by intramuscular injection in large doses. Currently, supplies are limited and could be exhausted by treatment of several patients with progressive vaccinia or eczema vaccinatum (22). Efforts are under way to increase the supply of VIG (22, 23), but its scarcity should be considered when vaccination policy is being formulated.

In the 1960s, Marboran (N-methylisatin β-thiosemiacarbazone), an early antiviral agent, was used to treat patients with progressive vaccinia and was believed to contribute to the decline in mortality rates. Because Marboran is currently unavailable, lacks FDA approval, and is not supported by good clinical trials, clinicians today would probably use cidofovir (which has in vitro activity against vaccinia) or one of its more bioavailable and perhaps less toxic analogues (15, 23). At present, cidofovir is recommended only for the treatment of cytomegalovirus retinitis and would be used to treat severe adverse events after vaccination under an Investigational New Drug protocol.

Rates of Adverse Events after Smallpox Vaccination

Table 1 presents the frequency of adverse events in primary vaccinees who were vaccinated with the NYCBOH strain of vaccinia. These rates are based on studies conducted in 1968. The rates for death, postvaccinial encephalitis, and progressive vaccinia are taken from national surveillance data (18). The rates for the common but less important adverse events are from studies in 10 small states that actively searched for cases (24). The high rate of erythematous rashes in toddlers comes from a cohort study in a Johns Hopkins University comprehensive care clinic (25). Frey and colleagues (10) found a similar high rate of rashes in 680 adult primary vaccinees.

The overall death rates presented in Table 1 do not fully reflect the risks associated with vaccination because the deaths from eczema vaccinatum in contacts of vaccinated patients (rather than those who were directly vaccinated) cannot be assigned to a denominator of either primary or revaccinates. During the 1960s, when 5 to 6 million primary vaccinations were performed each year in the United States, one or two contacts each year died of eczema vaccinatum (16). Transmission of vaccinia is rare and requires close contact. Transmission from health care...
workers to patients is very rare but has been documented (26).

Table 2 presents the analogous data for revaccinates. The rates are considerably lower because vaccinia is such a good vaccine against itself. Most adverse events occurred in patients vaccinated many years previously, in whom immunity had presumably waned considerably. The rate for progressive vaccinia does not differ greatly from the rate in primary vaccinates because acquisition of an immune deficit negates most of the benefit from previous vaccination.

**Adverse Events after the "New" Smallpox Vaccination**

Growing vaccinia on live cows presents problems with bacterial contamination. Vaccinia grows readily on many tissue culture cell lines, and the vigorous work on recombinant vaccinia strains in the past two decades has contributed to the technology of growing and harvesting the virus (27). The new vaccine that is becoming available consists of seed virus of the NYCBOH strain, grown on either Vero cells or the MRC5 cell line (23). There is no way to predict whether this change in substrate will alter any of the characteristics of the virus. Presumably, a small number of passages on human cells will have little effect, but it is premature to guarantee that the rates of adverse effects found associated with NYCBOH calf vaccine in 1968 will be identical to those found now.

Existing further attenuated strains and inactivated vaccines do not reliably produce cellular and humoral immunity. They have not been shown to protect against smallpox, and some have interfered with development of antibody after challenge with full-strength vaccinia (27–30).

**Estimated Number of Deaths from Widespread Vaccination in 21st-Century United States**

About 120 million (42%) of the 282 million persons in the current U.S. population were born after 1972 and have never been vaccinated. Virtually all of the other 162 million have not been vaccinated for at least 30 years. Se-

**Table 2. Frequency of Adverse Events in 1968 after Smallpox Revaccination with New York Board of Health Strain Vaccinia, by Age and Type of Adverse Event**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Adverse Events per Million Revaccinates, n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age at Revaccination</td>
</tr>
<tr>
<td>Death (all causes)</td>
<td></td>
</tr>
<tr>
<td>Postvaccinial encephalitis</td>
<td></td>
</tr>
<tr>
<td>Progressive vaccinia</td>
<td></td>
</tr>
<tr>
<td>Eczema vaccinatum</td>
<td></td>
</tr>
<tr>
<td>Generalized rashes</td>
<td></td>
</tr>
<tr>
<td>Accidental implantation</td>
<td></td>
</tr>
</tbody>
</table>

* Adapted from Lane et al. (18) and Lane et al. (24).

Table 3. Conservative Estimate of Deaths from Smallpox Vaccination after Implementation of a Policy of Indiscriminate Widespread Vaccination

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Population in Millions</th>
<th>Deaths from Primary Vaccination*</th>
<th>Deaths from Revaccination†</th>
<th>Total Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>125</td>
<td>–</td>
<td>–</td>
<td>125</td>
</tr>
<tr>
<td>5–14</td>
<td>75</td>
<td>37</td>
<td>–</td>
<td>76</td>
</tr>
<tr>
<td>15–19</td>
<td>40</td>
<td>39</td>
<td>–</td>
<td>39</td>
</tr>
<tr>
<td>20–29</td>
<td>167</td>
<td>–</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>≥30</td>
<td>100</td>
<td>–</td>
<td>125</td>
<td>125</td>
</tr>
<tr>
<td>Total</td>
<td>282</td>
<td>76</td>
<td>49</td>
<td>125</td>
</tr>
</tbody>
</table>

* Age-specific death rates are from Table 1.
† Age-specific death rates are from Table 2.

*rologic and epidemiologic data suggest that some residual immunity persists for as long as 30 years (31–33). A considerable, if unknown, proportion of this older population may have so little residual immunity that they react to the vaccine like primary vaccinates, with the risks associated with a “naïve” state of immunity.

Table 3 presents a conservative estimate of the number of deaths that could be expected from widespread attempts to immunize the entire U.S. population. We should expect a minimum of 125 deaths. This assumes resumption of the late 1960s policy of not vaccinating infants younger than 1 year of age and a vigorous and successful effort to screen out and protect immunosuppressed patients from contact with vaccinates. This estimate also does not consider patients dying of eczema vaccinatum acquired by contact, despite the increased prevalence of serious atopic dermatitis today as compared with the 1960s (34).

The number of deaths after smallpox vaccination in the 21st century might be considerably higher than the number in the late 1960s. The rate of progressive vaccinia in adults and the resultant vaccination-related mortality would be higher because of the greatly increased prevalence of severe immunodeficiency—acquired or induced by therapeutic interventions—in our society today. Transient but severe immunosuppression as a result of the use of high-dose steroid therapy in patients with asthma or autoimmune syndromes may also predispose patients to serious adverse consequences after vaccination. We estimate that about 100 000 patients are immunosuppressed after transplantation, 100 000 patients with HIV have low T-cell counts, and about 120 000 patients with various malignant disorders are immunosuppressed after receiving chemotherapy or radiation therapy. Because true atopic dermatitis is more prevalent today than in the 1960s, deaths from eczema vaccinatum might increase (33). If panic resulting from a terrorist attack led to widespread vaccination, death rates could be much higher than in 1968. Two methods can reduce deaths and serious adverse events from vaccination. First is prudent screening of potential vaccinates. Second is handling outbreaks by isolating patients and vaccinating their contacts, the surveillance and containment method used to eradicate smallpox.
DYNAMICS OF SMALLPOX TRANSMISSION

Smallpox does not spread rapidly under natural conditions. Well-conducted studies of variola major in the Asian subcontinent in the late 1960s showed that each case of smallpox gave rise to about three new cases during the seasonal upswing of the disease and less than one case during the seasonal downswing (35–39). In European importation outbreaks after World War II, the spread was often more limited, unless nosocomial spread occurred in hospitals (2). The largest European outbreak, which occurred in Yugoslavia in 1972, included two “hyper spreaders.” One patient with hemorrhagic smallpox had been misdiagnosed as having a severe allergic reaction to penicillin; many hospital staff saw this patient. Smallpox spread from this one patient to 38 people, all but 1 of whom were hospital contacts. Another person with smallpox spread the disease to at least 16 and perhaps 23 contacts. Ultimately, there were cases of smallpox in Belgrade, 5 towns outside Belgrade and Kosovo province, and 18 villages in Kosovo. Despite this impressive spread, the outbreak was rapidly terminated once it was recognized (40). Analysis of epidemics in the prevaccination era supports the leisurely spread of the disease (41).

Careful mathematical modeling of the natural spread of smallpox shows that a reasonable mix of judicious vaccination of close contacts and effective isolation of patients can readily stop outbreaks within two infective generations (about 4 weeks) after recognition of the initial cases (42, 43).

The draft plan from the CDC for handling a smallpox bioterrorism event concludes that rigorous patient isolation, with vaccination of contacts and their contacts, would be preferable to mass vaccination in the event of a terrorist attack (44). Smallpox is spread only from sick persons, many of whom would be prostrate and immobile. Spread from patients does not occur during the incubation period. Smallpox usually occurs in persons who have had close, prolonged contact (not casual or distant contact) with a sick person. Vaccination in the first two or three days after contact generally aborts or greatly alleviates the disease. This method of containment, which led to the ultimate eradication of smallpox, requires relatively few vaccinations for the contacts of each actual case.

Because smallpox is spread through respiratory secretions, isolation and simple properly fitting N95 respirator masks (45) prevent disease propagation. Patients should wear these masks and should be kept in negative-pressure hospital rooms. True small-droplet aerosol spread, although rare, has been documented; a single patient spread smallpox to 17 people in a hospital in Germany (46).

RISKS AND BENEFITS OF VARIOUS VACCINATION STRATEGIES

Any policy that increases vaccinations will lead to an increase in morbidity and mortality associated with vaccinaria. We could resume routine vaccination of the entire U.S. population to reduce the chance of a major outbreak after a terrorist attack. Since no current credible threat exists and such a policy might cost between 125 and 500 lives, this seems unwise.

We could vaccinate first responders who might be involved in caring for or investigating patients with suspected smallpox and their contacts. This strategy might protect those most likely to initially bear the risk for acquiring smallpox. A major problem might be that some of these persons have frequent daily contact with patients with HIV infection or patients who are immunosuppressed as a result of cancer therapy or transplantation. The turnover rate of such personnel is considerable, and such a policy might have to be continuous until intelligence discounts any possible risk for a smallpox attack. At present, there is no way to predict how long such a policy might have to continue.

We might allow citizens to make individual choices about obtaining vaccination after they have been given information about the risks associated with vaccination and potential threat of smallpox (5, 6). Public health authorities would thus cede decisions on a policy with considerable technical ramifications to persons with widely varying abilities to comprehend and weigh the risks and benefits. The media and the medical profession would have to communicate an accurate portrayal of the data and options. In the absence of a known threat of smallpox exposure, this option would be dangerous to many potential vaccinees, their contacts, and the public health initiative. It would subject the population to a known risk for severe adverse events. The publicity about such complications might subsequently keep some persons from accepting vaccination if the need actually arises.

We could continue to pursue the current policy of avoiding mass vaccination while vaccinating small numbers of first responders and personnel who might be involved in the investigation and control of possible smallpox outbreaks. This should be and is being accompanied by an effort to build vaccine supplies, institutionalize vaccine production capacity, develop and expand laboratory expertise, and train public health authorities and first-response clinicians. While these options should be revisited periodically as new information comes to light, at present it seems prudent to continue the present policy and to initiate only modest increases in vaccination of first responders.

From Atlanta, Georgia, and Morrow, Georgia.

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Requests for Single Reprints: J. Michael Lane, MD, MPH, 869 Clifton Road NE, Atlanta, GA 30307-1223.
References

Current Author Addresses: Dr. Lane: 869 Clifton Road NE, Atlanta, GA 30307-1223.
Dr. Goldstein: The Children's Clinic, 1000 Corporate Center Drive, Morrow, GA 30260.