A case-control study in Ukraine provided the first data on the field effectiveness of Russian-produced vaccine during the 1990 diphtheria resurgence in the former Soviet Union. For each of 262 diphtheria cases <15 years of age who were reported from January through October 1992, 2 controls, matched by age and clinic, were selected. The effectiveness of three doses of diphtheria vaccine was 98.2% (95% confidence interval: 90.3–99.9). Among controls, 84% had received three or more vaccinations by 2 years of age. These results suggest that the following five hypothesized causes of the outbreak appeared unlikely: appearance of a new “mutant” diphtheria strain, low potency of the Russian-produced diphtheria vaccine, inadequate cold chain, poor host immunogenicity due to radiation exposure from Chernobyl, and low routine childhood vaccination coverage. It is concluded that initial priority for scarce resources for controlling this outbreak should be placed on vaccination of persons susceptible to diphtheria (e.g., adults) rather than revaccination of children.

In the late 1980s, aside from rare outbreaks among users of alcohol or drugs [1, 2] and from sporadic importations [3, 4], diphtheria was an all but forgotten disease in most industrialized countries [5–7]. Remarkably, diphtheria, with its greatly feared “death by suffocation,” had ravaged major urban centers in Europe and North America just a century earlier [8]. Case fatality rates of 50%–60% were common [9]. Until antitoxin therapy became available, more than half of all deaths among children in Zurich hospitals since 1883 were due to diphtheria [10]. As recent as 1938, diphtheria was still the number one cause of death for children 5–10 years old and the number three cause of death for children 0–4 and 11–15 years of age in England and Wales [11]. Diphtheria was the communicable disease with the greatest documented increase during World War II [12].

Several notable landmarks in the history of medicine, combined with general improvements in hygiene and social conditions [11], however, had sequentially resulted in improved diagnosis, treatment, and successful prevention of diphtheria until it was close to elimination in the United States and elsewhere by the 1980s [13, 14]. It was recognized, however, that without booster immunizations toxoid-induced immunity can drop below protective levels, and, due to poor compliance with routine adult booster recommendations, an increasing proportion of adults in countries with long-standing immunization programs against diphtheria might be becoming susceptible [5, 15]. However, the need for routine adult boosters in the face of low disease incidence was increasingly disputed [16].

It was extremely alarming, therefore, in 1990, amidst the chaos following dissolution of the former Soviet Union (where diphtheria had previously been well controlled), when reports first reached the West of a large outbreak of diphtheria in Moscow [17] with rapid spread to other regions [13]. These reports led to the first of several travel advisories for Westerners [18]. It was not until 1992 that the first opportunity arose for the Centers for Disease Control and Prevention (CDC) to assist in the investigation of this outbreak. By this time, diphtheria had spread to Ukraine, and the reported incidence had jumped 10-fold, from 0.21/10⁵ in 1990 to 2.27/10⁵. Due to currency exchange and other difficulties [19], Ukraine could no longer be confident of a stable supply of vaccines from its former sources in Russia. In October 1992, the United States Agency for International Development (USAID) received a request from the Ministry of Health (MOH) in Ukraine for 3.8 million doses of diphtheria toxoid-containing vaccines (combined with tetanus toxoid and pertussis [DTP] for children and tetanus toxoid [Td; with a reduced diphtheria toxoid content] for adults, hereafter referred to as diphtheria vaccine). In turn, USAID requested that the CDC assess the status of the outbreak and verify the amount of vaccine needed and the ability of the MOH to efficiently store, distribute, and administer the vaccine [20]. This visit also permitted the first evaluation of the field effectiveness of diphtheria vaccine in this outbreak.

**Methods**

From 28 October to 8 November 1992, assessment visits were made to the Ukraine MOH in Kiev, the Sanitary-Epidemiologic
Service (SES), hospitals in Kiev and Vinnitsa, and rural clinics in Mogilev Podalski County and Sovko Elena County. At each location, assessments were made of the epidemiology of diphtheria (including diagnosis, treatment, and surveillance) and the immunization system (especially of the cold chain; the availability of vaccines, antitoxin, and sterile syringes and needles; contraindications; and vaccine coverage). To assess vaccine effectiveness (VE), a rapid case-control study was conducted. Immunization records were retained in polyclinics until persons were 15 years of age and then discarded; therefore, all 262 diphtheria cases who were <15 years of age and reported between January and October 1992 were identified with the assistance of the MOH. Telegrams were sent to the health districts where the cases occurred, requesting the date of birth and the date and type of vaccine received for the case and 2 controls. The controls were selected from the birth register of the same polyclinic as the matched cases and were the children with the closest birth date (and, if necessary to break ties, the closest place of residence) to the case.

The requested information was returned by telegram and entered into a computer program (Epi Info; USD, Stone Mountain, GA). The percent VE was calculated, using a matched analysis, as \((1 - \text{the odds ratio of diphtheria in vaccinees vs. nonvaccinees}) \times 100\) [21]. The vaccination status of cases and controls was compared for the date 2 weeks before disease onset in the case.

Results

**Epidemiology of diphtheria in Ukraine.** In 1888, the incidence of diphtheria was 444/10^5 population. In 1896, the L. Gromashevsky Institute of Epidemiology and Infectious Disease in Kiev was created, with the production of equine diphtheria antitoxin as one of its key roles. Routine vaccination against diphtheria (in the form of DTP) was introduced in the mid-1950s, with a gradual reduction in the incidence of diphtheria in the following decade. The nadir of 8 cases (0.016/10^5 population) was reached in 1976. A gradual increase in diphtheria incidence was subsequently observed, reaching 109 cases (0.21/10^5) in 1990. In 1991, the incidence jumped 10-fold to 1103 cases (2.21/10^5) and 50 deaths (4.5%). This outbreak continued into 1992 despite attempted control measures, such as vaccination of adults in high-risk groups and efforts at improved early diagnosis of suspected diphtheria cases. At the time of the assessment, 1108 cases and 48 deaths (4.3%) had been reported through 29 October 1992 from all 27 Ukrainian oblasts. Urban areas were hardest hit: Kiev City (251 cases = 9.6/10^5), Odessa (161 cases = 5.9/10^5), and Lviv (120 cases = 4.4/10^5). The outbreak in Odessa had just begun, with only 30 cases reported by the end of May 1992 (vs. 133 for Kiev City and 87 for Lviv at that time). Rates of diphtheria reported from the other regions were generally between 1–2 cases/10^5.

Despite the large increase in the number of diphtheria cases in 1991 and 1992, the relative proportion of cases among children and adults has remained stable since at least 1986 (figure 1); adults constitute 70%–80% of the total reported cases. The high rate of susceptibility to diphtheria among adults in Ukraine is confirmed by annual serosurveys: ~40% of adults >28 years of age have no detectable diphtheria antibodies, as determined by passive hemagglutination assay. This assay has not been calibrated with international standards to allow for the expression and comparison of these results in international units. Adults constitute a larger proportion of total cases; however, the mortality rate is ~3-fold higher for diphtheria cases who are 0–14 years of age (9.6%), compared with 3.4% for older cases. In 1991 and 1992, the rates of diphtheria were also highest among younger age groups: Children 3–6 years old had the highest rate (22 cases/age cohort/year), followed by children 7–14 years old (19 cases/age cohort/year) and children 0–2 years old (13.5 cases/age cohort/year).

**Vaccines and vaccination schedule.** Six different types of Russian-manufactured diphtheria toxoid–containing vaccines have been used, each with a different diphtheria toxoid content (measured in limits of flocculation [Lf]) and indication for use. In Ukraine, the diphtheria vaccination schedule has changed several times since 1974. From 1986 to 1991, three different

![Figure 1. Percent of total reported diphtheria cases by age group—Ukraine, 1986 to 30 September 1992](image-url)
schedules, with decreasing total Lf, were available for use depending on how reactive a child was to previous doses in the series. The most recent change in 1992 includes adult boosters every 10 years. Of note, in contrast to the 15 Lf of diphtheria toxoid in standard DTP vaccine (called AKDS) or diphtheria-tetanus toxoids (DT) vaccine (called ADS), a reduced-potency DTP with 5 Lf of diphtheria toxoid (AKDS-m) was available for use in persons concerned about DTP reactogenicity, and Td vaccine (ADS-m) was available for booster doses in older persons. Since 1991, certain “high-risk” adult groups have been targeted for special vaccination. These include health care workers, public transport employees, sales clerks, teachers, students and workers residing in dormitories, and day care and kindergarten workers. These programs have had mixed success in terms of compliance.

The list of medical contraindications for diphtheria vaccination in Ukraine was much longer and included more mild illnesses than the list in other countries. Data reported to the MOH suggested that ~90% of children had received three doses of diphtheria vaccine by 1 year of age during 1972–1990. In one clinic in Kiev, however, 28% of children had not received three doses of diphtheria vaccine by 1 year of age. Assuming that the controls enrolled in the VE study were representative of the general population, the proportion receiving three or more doses of diphtheria vaccine of any type increased on average from 66% by 1 year of age to 84% by 2 years of age, 89% by 3 years of age, 91% by 4 years of age, and 92% by 5 years of age (figure 2). Of the 15 age cohorts, only 3 had substantially lower levels of diphtheria vaccine coverage for three or more doses when they had reached 1 year of age: 58% in children 7 years of age, 45% in children 10 years of age, and 59% in children 11 years of age. However, all 3 of these cohorts had diphtheria vaccine coverage exceeding 86% for three or more doses by 3 years of age (figure 2).

VE study. Vaccination histories were obtained for 262 cases and 517 matched controls. Only 14 cases (5%) and 28 controls (5%) had received any doses of the reduced-potency DTP. Sixty-five cases (25%) and 4 controls (1%) received no doses of any diphtheria vaccine. The VE of three doses of any diphtheria vaccine was 98.2% (95% confidence interval [CI]: 90.3–99.9), increasing to 99.7% (95% CI: 97.2–100.0) with four doses and to 99.9% (95% CI: 89.7–100.0) with five or more doses (table 1). The VE for one or two doses also exceeded 93%, although the CI was wide. Among children who had received three or more doses of diphtheria vaccine, children 0–7 years of age had a higher vaccine efficacy (98.8% [95% CI: 93.8–99.8]) than children 8–14 years of age (94.1% [95% CI: 53.8–99.3]).

Discussion

When diphtheria reemerged in outbreak form in the former Soviet Union in 1990 after several decades of excellent control, there was substantial initial uncertainty as to whether other industrialized countries with a similar history of diphtheria control and substantial susceptible adult populations might also be at risk. This would especially have been the case, for example, if a new mutant strain of diphtheria had emerged. The outbreak rapidly spread to other Newly Independent States (NIS), like Ukraine, with a mounting disease toll by 1992. Consequently, the need to better understand the cause(s) of the outbreak became more acute so that appropriate control measures could be undertaken. Critical supplies, including diph-

![Figure 2](https://academic.oup.com/jid/article/181/Supplement_1/S178/839838) Percentage, by age in years, of vaccine effectiveness—study controls in 15 age cohorts who received three or more doses of diphtheria vaccine—Ukraine, 1992. Mean coverage among cohorts is shown in black.
Table 1. Effectiveness of diphtheria toxoid vaccine—Ukraine, January to October, 1992.

<table>
<thead>
<tr>
<th>No. of doses received</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>1/odds ratio</th>
<th>Vaccine effectiveness (%)</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>24.8</td>
<td>0.8</td>
<td>Referent group</td>
<td>93.1</td>
<td>31.1–99.3</td>
</tr>
<tr>
<td>1</td>
<td>4.6</td>
<td>1.4</td>
<td>14.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3.8</td>
<td>3.5</td>
<td>20.8</td>
<td></td>
<td>56.0–99.5</td>
</tr>
<tr>
<td>3</td>
<td>11.1</td>
<td>10.4</td>
<td>55.6</td>
<td>98.2</td>
<td>90.3–99.9</td>
</tr>
<tr>
<td>4</td>
<td>21.8</td>
<td>26.9</td>
<td>333.3</td>
<td>99.7</td>
<td>97.2–100</td>
</tr>
<tr>
<td>≥5</td>
<td>34.0</td>
<td>57.0</td>
<td>1286.0</td>
<td>99.9</td>
<td>89.7–100</td>
</tr>
</tbody>
</table>

*Cases compared with matched controls.

Table 2 shows causes that were considered for the diphtheria outbreak [20]. Those causes, each potentially necessitating a different control strategy, included mutation(s) in diphtheria bacteria or toxin, which made the diphtheria vaccine inefficacious; a change in patterns of diphtheria transmission (e.g., due to population crowding and migration accompanying the breakup of the former Soviet Union); and less-than-optimal diphtheria immunity in the population. Reduced immunity could have been due either to (1) low vaccine coverage in children (e.g., due to inappropriate contraindications), (2) excessive use of reduced-potency diphtheria vaccine due to concerns about reactogenicity, (3) high susceptibility in adults (e.g., due to inappropriate contraindications), (2) excessive use of reduced-potency diphtheria vaccine due to concerns about reactogenicity, (3) high susceptibility in adults (e.g., due to inappropriate contraindications), (4) reduced vaccine potency (e.g., due to poor production quality, inadequate cold chain that permitted the vaccine to be frozen in transit, or poor administration technique), (5) reduced immune response of the population (e.g., due to radiation exposure from Chernobyl), or (6) falsification of immunization records to meet ”quotas.”

One urgent question was the field effectiveness of the Russian-produced diphtheria vaccine that the Ukrainian and other former Soviet populations had received. Reduced vaccine potency or reduced immune response were genuine concerns, given the relatively old state of Russian vaccine production facilities, the fact that vaccines were shipped without any insulation during the cold winters in Ukraine (freezing inactivates diphtheria vaccine) [23], the consequences of the Chernobyl nuclear disaster in 1986 [24], and low VE potentially due to change in the organism. Conversely, a high VE would argue against the relative role of these etiologies. There was also uncertainty as to what extent the reduced-potency AKDS-m vaccine, which was commonly used in Moscow, was used in Ukraine [25]. If the VE was low, depending on the specific cause, potentially hundreds of millions of persons in the former Soviet Union would have needed to be immunized (or reimmunized)—a daunting task at best, given the change in the political and economic milieu at the time.

In the VE study that we conducted, it is likely that the relative simplicity of the study design plus the explicit instructions to the polyclinics on control selection minimized any potential biases despite its novelty to Ukraine [26]. The VE after three doses of any diphtheria vaccine in children <15 years of age was 98.2%, increasing to 99.7% and 99.9% with four and five or more doses, respectively. These VE results are only slightly lower than the 100% immunogenicity (defined as ≥0.01 IU) after three doses in clinical trials [27] and are similar to the 92%-97% VE in the most recent study in the United States in 1972 [28]. These results also compare favorably to a VE of 87% after three or more doses of DTP vaccine found during a diph-

Table 2. Possible cause(s) of diphtheria outbreak in Ukraine: existing evidence and proposed evaluation studies.

<table>
<thead>
<tr>
<th>Possible cause</th>
<th>Evidence</th>
<th>Proposed evaluation studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation in <em>Corynebacterium diphtheriae</em> or toxin</td>
<td>Good VE study results</td>
<td>Genetic and other testing of bacteria</td>
</tr>
<tr>
<td>Reduced diphtheria immunity in population</td>
<td>Antibiotics/antitoxin remain effective</td>
<td>Cluster survey for validation of vaccination status and knowledge, attitudes, practices</td>
</tr>
<tr>
<td>Decreased vaccine coverage in children</td>
<td>Coverage in controls of VE case-control study acceptably high</td>
<td>Cluster survey for vaccine-specific coverage</td>
</tr>
<tr>
<td>Increased use of reduced-potency AKDS-m vaccine</td>
<td>Only 5% of cases and controls in VE study had received AKDS-m vaccine</td>
<td></td>
</tr>
<tr>
<td>Poor cold chain</td>
<td>Good VE study results</td>
<td>Cold chain study with temperature monitors</td>
</tr>
<tr>
<td>Poor AKDS potency</td>
<td>Good VE study results</td>
<td>Repeat in other settings using AKDS, potency testing of AKDS vaccine by WHO</td>
</tr>
<tr>
<td>Poor immune response</td>
<td>Good VE study results</td>
<td>ADS-m immunogenicity study in adults</td>
</tr>
<tr>
<td>Falsification of records</td>
<td>Good VE study results</td>
<td>Sero survey</td>
</tr>
<tr>
<td>Change in patterns of diphtheria transmission (e.g., population crowding, migration)</td>
<td>None collected</td>
<td>Case-control study for risk factors</td>
</tr>
</tbody>
</table>

NOTE. VE, vaccine effectiveness; AKDS, 15-limit of flocculation units (Lf) diphtheria toxoid in standard diphtheria-tetanus toxoids–pertussis (DTP) vaccine; AKDS-m, reduced-potency DTP vaccine (with 5 Lf diphtheria toxoid); ADS-m, toxoids vaccine with reduced tetanus-diphtheria toxoid content; WHO, World Health Organization.
theria outbreak in Yemen in 1981 [29]. These findings, confirmed later in a larger case-control study in Moscow [30], suggested that the Russian-produced diphtheria vaccine that was used in Ukraine (and likely elsewhere) remained efficacious against the outbreak diphtheria strain. By extrapolation, diphtheria vaccine produced elsewhere using similar (or improved) technology, which had been available since the 1920s, should have been similarly efficacious in the outbreak if widely applied—as subsequently shown [31].

While our sample size was inadequate to evaluate the VE of the reduced-potency AKDS-m alone, it was reassuring that only 5% of the cases and controls had received this vaccine, suggesting that this was not a major contribution to lower immunity in Ukraine. The vaccine coverage by age group among the controls in our VE case-control study also provided the first independent assessment of up-to-date vaccination status of Ukrainian children. Before the outbreak, coverage with three or more doses of diphtheria vaccine exceeded 80% by 2 years of age and 85% by 3 years of age for almost all age cohorts, compared with 83% by 2 years of age in 1992 in the United States [32]. These results suggest that while efforts to improve the 68% coverage with receipt of three doses by 1 year of age are definitely worthwhile, low childhood vaccine coverage per se was unlikely to be a major cause of the outbreak. Our findings also provided for the first time strong scientific evidence against alternative causes (e.g., toxin mutation and radiation exposure from Chernobyl), which were prevalent considerations early in the confusion of the outbreak [33]: This finding allowed for resources to be directed toward the main culprit—inadequate adult immunity [34].

While the causes of this outbreak are likely to be multifactorial [13, 34, 35], it is interesting that other countries with long-standing routine childhood immunization programs against diphtheria and poor compliance with adult booster policies (and therefore poor adult immunity levels) have not had similar resurgences despite periodic introductions of diphtheria [4, 34]. During World War II, large diphtheria outbreaks occurred in several countries on both sides upon return of large numbers of soldiers from tropical settings (e.g., North Africa and the South Pacific); the cutaneous diphtheria they had contracted transformed to respiratory diphtheria upon return to the more temperate climates [36, 37]. Diphtheria incidence increased sharply in Afghanistan after invasion by the former Soviet Union in 1979. Soviet troops were withdrawn in 1989, and the NIS outbreak was first detected among the military in various locations around this time [13]. Perhaps molecular epidemiology may one day provide insight on whether this was more than a coincidence [38].

This was the first collaborative epidemiologic study on immunization issues between CDC and the Ukraine MOH in the post–Cold War period. As a result of this mission, substantial quantities of diphtheria vaccine were supplied by USAID and other donors to Ukraine. The excellent relationship established also permitted a follow-up adult revaccination immunogenicity trial with diphtheria toxoid in adults to be conducted in Kiev [34]. These results allowed the World Health Organization and UNICEF to define the target age groups and doses needed for optimal protection for the overall outbreak-control strategy. These studies also highlighted the importance of analytical epidemiologic methods, which were novel to the former Soviet Union [26]. Subsequently, several dozen public health professionals from Ukraine and other locations in the former Soviet Union have attended courses in analytical epidemiology at CDC. For the first quarter of 1996 in Ukraine, the number of reported diphtheria cases decreased 37% compared with the first quarter of 1995: This is the first evidence that the tide in the most recent battle against diphtheria may have turned [31, 38].

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