Successful Control of Epidemic Diphtheria in the States of the Former Union of Soviet Socialist Republics: Lessons Learned

Sieghart Dittmann,1 Melinda Wharton,1 Charles Vitek,3 Massimo Ciotti,4 Artur Galazka,5,6 Translated by Stephane Guichard,7 Iain Hardy,11a Umit Kartoglu,7 Saori Koyama,8 Joachim Kreysler,5 Bruno Martin,6 David Mercer,9 Tove Rønne,2 Colette Roure,1 Robert Steinglass,10 Peter Strebel,3 Roland Sutter,3, and Murray Trostle11

Epidemic diphtheria reemerged in the Russian Federation in 1990 and spread to all Newly Independent States (NIS) and Baltic States by the end of 1994. Factors contributing to the epidemic included increased susceptibility of both children and adults, socioeconomic instability, population movement, deteriorating health infrastructure, initial shortages of vaccine, and delays in implementing control measures. In 1995, aggressive control strategies were implemented, and since then, all affected countries have reported decreases of diphtheria; however, continued efforts by national health authorities and international assistance are still needed. The legacy of this epidemic includes a reexamination of the global diphtheria control strategy, new laboratory techniques for diphtheria diagnosis and analysis, and a model for future public health emergencies in the successful collaboration of multiple international partners. The reemergence of diphtheria warns of an immediate threat of other epidemics in the NIS and Baltic States and a longer-term potential for the reemergence of vaccine-preventable diseases elsewhere. Continued investment in improved vaccines, control strategies, training, and laboratory techniques is needed.

Background

In the prevaccine era, diphtheria was a leading childhood killer worldwide. During the 1940s–1950s, the introduction of universal childhood immunization with diphtheria toxoid nearly eliminated diphtheria in most industrialized countries. In developing countries, high levels of vaccination of infants with three doses of diphtheria-tetanus toxoids–pertussis vaccine (DTP) have been achieved following implementation of the Expanded Program on Immunization of the World Health Organization (WHO) in the 1970s. A large proportion of adults in many developed countries and an increasing proportion of adults in some developing countries are now susceptible to diphtheria because vaccine-induced immunity wanes over time unless periodic boosters are given or unless exposure to toxigenic Corynebacterium diphtheriae occurs.

In the 1980s and early 1990s, small outbreaks of diphtheria were reported in both industrialized (Sweden, Germany, and Portugal) and developing (Algeria, China, Ecuador, Jordan, Lesotho, Sudan, and Thailand) countries, including some in which diphtheria immunization coverage had been high for as long as 30 years [1]. Although many of the cases were among adults, the limited scope of these outbreaks did not appear to threaten the rapid progress toward global control and possible elimination of diphtheria [2].

In 1990, epidemic diphtheria reemerged in the Russian Federation, with most cases among adults [3]. During 1991–1993, the epidemic spread rapidly, and by the end of 1994, all of the Newly Independent States (NIS) and the Baltic States of the former Union of Soviet Socialist Republics (USSR) were involved [4]. The epidemic peaked in 1994–1995, with an average annual incidence of 17 cases/100,000 population and a peak incidence of 73 cases/100,000 population in Tajikistan in 1995 (table 1, figure 1). From 1990 through 1998, >157,000 cases and 5000 deaths were reported by the countries of the former Soviet Union, representing >80% of diphtheria cases reported worldwide. Three-quarters of the cases were reported from the Russian Federation. This was the largest diphtheria epidemic since the 1950s, the beginning of the era of widespread diphtheria immunization.

The massive epidemic in the former Soviet Union in the 1990s, which is highlighted in this supplement, has proved a...
## Table 1. Diphtheria incidence in the Newly Independent States (NIS) and the Baltic States of the former Soviet Union, 1990–1998.

<table>
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<tr>
<td>Russia</td>
<td>147.37</td>
<td>1211</td>
<td>1876</td>
<td>3897</td>
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<td>39,582</td>
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<td>230</td>
<td>322</td>
<td>179</td>
<td>102</td>
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<tr>
<td>Ukraine</td>
<td>51.47</td>
<td>109</td>
<td>1103</td>
<td>1553</td>
<td>2982</td>
<td>2990</td>
<td>5280</td>
<td>3156</td>
<td>1364</td>
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</tr>
<tr>
<td>Subtotal</td>
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<td>1342</td>
<td>3005</td>
<td>5516</td>
<td>18,311</td>
<td>42,802</td>
<td>41,254</td>
<td>16,939</td>
<td>5523</td>
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<tr>
<td>Estonia</td>
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<td>7</td>
<td>3</td>
<td>11</td>
<td>7</td>
<td>19</td>
<td>14</td>
<td>3</td>
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<tr>
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<td>5</td>
<td>8</td>
<td>12</td>
<td>250</td>
<td>369</td>
<td>112</td>
<td>42</td>
<td>67</td>
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<td>1</td>
<td>9</td>
<td>8</td>
<td>38</td>
<td>43</td>
<td>11</td>
<td>2</td>
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<tr>
<td>Subtotal</td>
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<td>5</td>
<td>13</td>
<td>20</td>
<td>31</td>
<td>295</td>
<td>431</td>
<td>137</td>
<td>47</td>
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<tr>
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<td>0</td>
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<td>36</td>
<td>29</td>
<td>11</td>
<td>10</td>
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<td>Azerbaijan</td>
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<td>66</td>
<td>72</td>
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<td>841</td>
<td>883</td>
<td>114</td>
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<td>87</td>
<td>97</td>
<td>224</td>
<td>1547</td>
<td>1749</td>
<td>568</td>
<td>378</td>
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<td>Kazakhstan</td>
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<td>28</td>
<td>30</td>
<td>45</td>
<td>82</td>
<td>489</td>
<td>1106</td>
<td>455</td>
<td>162</td>
<td>79</td>
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<tr>
<td>Kyrgyzstan</td>
<td>4.67</td>
<td>6</td>
<td>10</td>
<td>4</td>
<td>18</td>
<td>304</td>
<td>704</td>
<td>412</td>
<td>291</td>
<td>138</td>
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<tr>
<td>Tajikistan</td>
<td>5.93</td>
<td>11</td>
<td>5</td>
<td>16</td>
<td>678</td>
<td>1907</td>
<td>4455</td>
<td>1464</td>
<td>723</td>
<td>158</td>
</tr>
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<td>Turkmenistan</td>
<td>4.01</td>
<td>4</td>
<td>4</td>
<td>22</td>
<td>3</td>
<td>43</td>
<td>87</td>
<td>80</td>
<td>38</td>
<td>19</td>
</tr>
<tr>
<td>Uzbekistan</td>
<td>22.35</td>
<td>12</td>
<td>13</td>
<td>29</td>
<td>137</td>
<td>232</td>
<td>639</td>
<td>160</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Subtotal</td>
<td>53.99</td>
<td>61</td>
<td>62</td>
<td>116</td>
<td>918</td>
<td>2975</td>
<td>6991</td>
<td>2571</td>
<td>1249</td>
<td>420</td>
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<tr>
<td><strong>Total NIS and Baltics</strong></td>
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<td>291.70</td>
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*NOTE.* Data are no. of cases (incidence/100,000 population).

<sup>a</sup> Mid-year population (data source: United Nations Population Division).
watershed event in the vaccine era. This review article briefly summarizes the background and development of the epidemic, the development and implementation of the control strategies, and lessons that have been learned.

Diphtheria Control in the Soviet Union

Vaccination with diphtheria toxoid began in some Soviet cities in the late 1920s, but implementation of vaccination programs was hampered by World War II and post-war reconstruction. Severe epidemics of diphtheria continued to afflict the Soviet Union into the 1950s despite effective childhood immunization programs in many areas. In 1958–1959, near-universal childhood immunization with diphtheria toxoid began throughout the Soviet Union, and by 1963, the incidence of diphtheria had decreased by >90%. The incidence continued to gradually decline through the mid-1970s, with only 198 cases (0.08/100,000 population) reported from throughout the entire Soviet Union in 1976. The remaining cases were disproportionately reported from the Central Asian Republics, and most cases continued to occur among children <15 years of age. An upsurge in diphtheria cases, primarily among adults, began in the late 1970s and peaked in 1984 with 1609 cases (0.65/100,000 population). Reported cases gradually declined to 839 (0.34/100,000 population) in 1989. An intensified surveillance program was implemented, and the diphtheria situation was considered to be under control [5, 6].

Immunization coverage and schedules among children.

Among children in the Soviet Union, the reported coverage with diphtheria vaccine was consistently ≥90% from the 1960s until the beginning of the 1980s. However, during the 1980s, changes in immunization policy, medical practice, and public acceptance of immunization led to less intensive immunization of children. Beginning in 1980, Soviet immunization recommendations allowed the use of an alternative primary immunization schedule against diphtheria (table 2). This schedule recommended three doses of an adult-formulation adsorbed tetanus-diphtheria toxoids (Td) preparation with 5 limits of flocculation (Lf) diphtheria toxoid per dose instead of four doses of vaccine with 15 Lf diphtheria toxoid per dose. The lower-potency vaccine, Td, is similar to the adult formulation of tetanus-diphtheria toxoids vaccine used in Western countries; this vaccine was used extensively for the primary immunization of children in some regions of the Soviet Union, including Moscow and St. Petersburg.

Use of Td was partly driven by overestimation among Soviet
physicians of the risk of pertussis vaccine complications. Physicians’ fears of other adverse events from vaccination led to delays in initiating immunization beyond the first year of life due to an extensive list of contraindications to immunization that was expanded in 1980 far beyond internationally accepted conditions [7]. In the 1986 immunization schedule, the school-entry booster dose was dropped, resulting in an increase in the interval between booster doses. Support for immunization programs slipped in the 1980s due to an altered public perception of the risks and benefits of immunization. While many previously feared childhood diseases had been nearly eliminated, the perception of risk had increased, fanned by an anti-immunization movement that emerged after the political liberalization of 1985. As a result of these trends, coverage of infants with a primary series of diphtheria toxoid-containing vaccines dropped to between 60% and 80% in various republics of the USSR for most of the decade; coverage was even lower in some areas (figure 2).

**Immunity among adults.** Routine adult booster immunization was not recommended in the former USSR. However, in response to the mid-1980s increase in diphtheria cases, adult immunization began on a small scale in 1986 for members of certain occupational risk groups believed to be at higher risk of exposure to diphtheria. Serologic studies during the 1980s documented high rates (19%–66%) of diphtheria susceptibility among adults ≥20 years of age. The most susceptible age group was 30- to 39-year-old adults (40–49 years old in the 1990s) [8]. This age-cohort was born in the late 1940s and 1950s when the incidence of diphtheria was falling in many areas but before vaccination with diphtheria toxoid was universal.

**Diphtheria Epidemic in the Former USSR in the 1990s**

**Geographic development.** In the Russian Federation and the western NIS, epidemic diphtheria spread between the large urban centers (Moscow, 1989–1990; St. Petersburg, 1991; Kiev, 1991) and outwards along major transportation routes, first to other major cities and towns and, finally, to the countryside. The epidemic in the southern Central Asian countries appears to have started with the introduction of toxigenic diphtheria strains from Afghanistan into a refugee population in southern Tajikistan [9]. The source of the epidemics in the Caucasian countries is not firmly established; while spread from Russia is suspected, the initial outbreaks in both Georgia and Azerbaijan were in regions along the southern borders close to Turkey and Iran [10, 11].

In the countries of Central Asia and the Caucasus area, a greater proportion of diphtheria cases occurred in rural areas. This distribution reflects the underlying distribution of the population and the mass displacement of rural populations due to armed conflict in Georgia, Azerbaijan, and Tajikistan.

**The western NIS: Russia, Ukraine, and Belarus.** Although warning signs appeared in 1989, the first clear outbreaks of the epidemic occurred in Moscow in 1990, reportedly among members of a military construction battalion [12, 13]. Moscow City and Oblast reported 541 cases in 1990, 38% of the Soviet total of 1431 cases; only 839 cases had been reported in the entire Soviet Union in 1989. The rest of the Russian Federation reported another 670 cases (47%), and 109 cases (8%) were reported from Ukraine.

In 1991, Russia (1876 cases) and Ukraine (1103 cases) accounted for 94% of the 3167 cases of diphtheria reported from

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**Table 2.** Immunization schedules in the Soviet Union, 1965–1991: diphtheria toxoid-containing vaccines.

<table>
<thead>
<tr>
<th>Age</th>
<th>1965</th>
<th>1980</th>
<th>1983</th>
<th>1987</th>
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<tbody>
<tr>
<td></td>
<td>Alternative A</td>
<td>Alternative B&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Alternative A</td>
<td>Alternative B&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3–18 months</td>
<td>DTP1, 2, and 3</td>
<td>DTP1, 2, and 3</td>
<td>DT1 and 2 or Td1 and 2</td>
<td>DTP1, 2, and 3</td>
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<tr>
<td>18–36 months&lt;sup&gt;b&lt;/sup&gt;</td>
<td>DTP4</td>
<td>DTP4</td>
<td>DT3 or Td3</td>
<td>DTP4</td>
</tr>
<tr>
<td>6 years</td>
<td>DTP5</td>
<td>Td</td>
<td>Td</td>
<td>Td</td>
</tr>
<tr>
<td>9 years</td>
<td>DT</td>
<td>Td</td>
<td>Td</td>
<td>Td</td>
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<tr>
<td>10–11 years</td>
<td>DT</td>
<td>Td</td>
<td>Td</td>
<td>Td</td>
</tr>
<tr>
<td>16 years</td>
<td>DT</td>
<td>Td</td>
<td>Td</td>
<td>Td</td>
</tr>
</tbody>
</table>

**NOTE.** Russian-manufactured vaccines (no. of limit of flocculation units [Lf] diphtheria toxoid per dose): DTP, diphtheria and tetanus toxins plus pertussis (15 Lf); DT, diphtheria and tetanus (30 Lf); Td, tetanus and diphtheria (5 Lf). Nos. following vaccine abbreviations indicate dose no.

<sup>a</sup> Practice of using Td as alternative to DTP or DT for primary series continued until end of 1993.

<sup>b</sup> To be given 12–18 months after last infancy dose.
In 1992, a total of 5749 cases was reported, reflecting extension of the epidemic within Russia and Ukraine and into Belarus. Although these three countries were now experiencing more than three times as many diphtheria cases as at the height of the 1980s resurgence, the primary control measures remained unchanged.

In 1993, diphtheria outbreaks were reported from all the major urban centers of Russia, Ukraine, and Belarus. The NIS and Baltic States reported 19,484 diphtheria cases, >20 times the total cases in 1989, with 15,209 cases (78%) in the Russian Federation and 2982 (15%) in Ukraine. The number of cases reported monthly in Russia rapidly accelerated throughout 1993.

The Baltic States: Estonia, Latvia, Lithuania. In the Baltic States, small increases in cases after 1990 preceded a sharp outbreak in 1994 in Latvia (250 cases) and much smaller increases in Estonia and Lithuania in 1995 and 1996 [14–16]. In the Baltic States, especially Estonia [15], many index cases of diphtheria could be traced back to importation from neighboring Belarus and Russia. The areas of highest incidence in each country included the border areas with Russia and Belarus and the capital cities.

The disparity in incidence rates between the Baltic States is not clearly understood. Although most of the adult Estonian population had received a booster dose of diphtheria vaccine during 1985–1987, serologic studies did not show lower rates of adult susceptibility in Estonia compared with rates in other Baltic States [17]. However, the proportion of ethnic Russians, Ukrainians, and Belarusians was higher in Latvia (42% in 1993) than in Estonia (35%) or Lithuania (10%); increased cross-border introduction is likely to have played a role.

The Caucasus (Armenia, Azerbaijan, and Georgia) and Moldova. Epidemic diphtheria began at the end of 1993 in Azerbaijan and Georgia, and involved Armenia to a lesser extent beginning in 1994 [10, 11, 18]. The epidemic was exacerbated in all three countries by large numbers of displaced persons, severe economic hardship, and energy shortages. In Moldova, the epidemic began to escalate during the second half of 1994 and then spread quickly throughout all regions of the country [19].

Central Asian Republics and Kazakhstan. In 1993, in the aftermath of a civil war, an epidemic began in Tajikistan (678 cases) and rapidly spread, with 1907 cases reported in 1994 (32 cases/100,000 population) and 4455 cases in 1995 (74 cases/100,000 population). The diphtheria incidence rates in Tajikistan were the highest of any country in the NIS. More than half of the cases in Tajikistan occurred in the southern province of Kurgan Tyube, which borders Afghanistan and was the main focus of the 1992–1993 civil war; epidemiologic evidence supports an introduction from Afghanistan [9]. The Tajik epidemic spread into neighboring areas of densely populated Uzbekistan (137 cases in 1993), and in 1994, it extended into Kyrgyzstan [20, 21]. Other areas of high incidence in Central Asia included regions adjacent to Russia in Kazakhstan; molecular analysis of strains from these areas linked them to the epidemic strains of the Russian epidemic [22]. During the diphtheria epidemic, Turkmenistan reported relatively low incidence rates (1–2/100,000 population).

Characteristics of Diphtheria Cases

Age and sex distribution. The defining feature of this epidemic has been the high proportion of cases among adolescents and adults. This was especially true in the countries of the western NIS and in the Baltic States, but elsewhere in the NIS, adults also made up a significant proportion of cases. As a result, adults made up a majority of reported cases during the entire epidemic. In contrast, during the prevaccine era, children were the predominant age group affected by both endemic and epidemic diphtheria. While the proportion of cases among adults increased as the overall number of cases dropped after the introduction of vaccination, only one other large diphtheria epidemic had occurred during the vaccine era. During the massive epidemic that occurred in central and northern European countries during and following World War II, adults were the primary group affected in at least some districts and years [1, 23]. The NIS epidemic demonstrated conclusively the potential susceptibility of adults to epidemic diphtheria in the vaccine era.

In Belarus, Estonia, Latvia, Lithuania, Russia, and Ukraine, the proportion of diphtheria cases in people ≥15 years old ranged from 64% to 82%. Adults 40–49 years old had extremely high incidence and death rates; in some countries, this age group accounted for nearly half of all deaths. Older adults (>50 years of age) had relatively few cases. School-age children and adolescents also had high incidence rates, especially in the Russian Federation; however, these age groups had low death rates, with fatalities primarily occurring among children who had not received a primary vaccination series [12]. In Moldova, the countries of the Caucasus area (Armenia, Azerbaijan, and Georgia), Central Asia (Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan), and Kazakhstan, the proportion of infected adults ranged from 38% to 59%.

Factors that contributed to these differences in age distribution probably included larger average family size, with more children in the southern countries (e.g., in Tajikistan, 40% of the population is <15 years of age, compared with only 22% in Ukraine); greater immunity to diphtheria among young adults in the southern countries due to persistent circulation of toxigenic strains in the 1960s and 1970s; and regional differences in surveillance [24].

In areas where the sex distribution of cases was studied,
women accounted for a majority of adult cases and had sharply higher incidence rates. In Kazakhstan, 63% of adult cases were among females [22]. In three Russian regions in 1994–1996, women 20–49 years of age had a cumulative incidence of diphtheria of 82 cases/100,000 population, compared with 47 cases/100,000 among men of that age [25], and in Moldova, women ≥20 years of age had incidence rates 2- to 3-fold higher than those for men of the same age [19]. A similar pattern was seen in Ukraine [26].

Case fatality ratio (CFR). Due to the lack of diphtheria antitoxin and delayed treatment, the CFR was very high (20%) in some countries at the beginning of the epidemic. In 1994, the CFR (excluding Estonia, from which no deaths were reported among 10 cases) ranged from 2.8% in Russia to 23% in Lithuania and Turkmenistan. Since 1995, the international community has provided antitoxin and antibiotics, and the CFR decreased on average to 5–10%. In Russia, where diphtheria antitoxin was always available, the CFR was ~3% [8]. Variation of CFRs may also be caused by regional differences in surveillance: Less severe cases of illness are more likely to be reported in some countries than in others due to differential availability of laboratory resources and access to medical care [8].

Microbiology. The proportion of reported cases that was microbiologically confirmed by isolation of toxigenic C. diphtheriae ranged from 28% (Georgia) to >89% (Russia) due to variation in the availability of laboratory resources [10, 12]. In Russia, Ukraine, Belarus, the Baltics, and northern Kazakhstan, the predominant strains were biotype gravis; in Uzbekistan, Kyrgyzstan, and southern Kazakhstan, strains of mitis biotype predominated. In Tajikistan, laboratory facilities were extremely limited; however, the testing available suggested that the mitis biotype also predominated (Boltaeva M., personal communication). In Uzbekistan, isolation of intermedius strains were reported, but these accounted for <5% of strains isolated during the period 1993–1995 [20]. The overwhelming majority of strains isolated from diphtheria cases were toxigenic.

A number of molecular typing methods, including ribotyping, pulsed-field gel electrophoresis, and multilocus enzyme electrophoresis, have been developed or adapted to study C. diphtheriae isolates from the diphtheria epidemic in Russia [27]. The emergence of an epidemic clone of toxigenic C. diphtheriae, biotype gravis, was demonstrated in the Russian Federation. Isolates of the epidemic clone were first documented in 1987 and accounted for an increasing proportion of the strains isolated from cases in sentinel areas as the epidemic progressed [28].

Reactions for the Reemergence of Epidemic Diphtheria

The reasons for the reemergence of epidemic diphtheria in countries where immunization programs had nearly eliminated diphtheria in the 1970s are not fully understood but are thought to include the introduction of toxigenic strains into the general population, low coverage with diphtheria toxoid–containing vaccines among children in the 1980s and early 1990s, and a large gap of immunity among adults.

The spread of the epidemic throughout the former Soviet Union was facilitated by six factors:

- Large-scale population movements, including the return to Russia and Ukraine of hundreds of thousands of ethnic Slavs from Central Asian and Caucasian countries, and the flight of refugees from fighting in Georgia, Armenia, Azerbaijan, Tajikistan, and the northern Caucasus
- Socioeconomic instability
- Partial deterioration of the health infrastructure
- Delay in implementing aggressive measures to control the epidemic
- Inadequate information for physicians and the public
- Lack of adequate supplies for prevention and treatment in most of the countries

Introduction of toxigenic strains. The source of the epidemic strains in the Russian Federation remains unclear. Introduction of toxigenic strains from Afghanistan has been postulated due to the coincidence of the initiation of the epidemic in Moscow in 1990 among paramilitary construction workers with the demobilization of at least 100,000 Soviet troops from Afghanistan between May 1988 and February 1989 [8, 13]. Afghanistan was clearly highly endemic for diphtheria; the country reported 13,628 cases of diphtheria to WHO between 1980 and 1989. However, other areas within the Soviet Union also remained endemic for diphtheria during the 1980s, and prior to the demobilization from Afghanistan, strains of the epidemic clone had already been isolated from several sites in Russia despite only limited sampling [28, 29]. Outbreaks of diphtheria among military units, especially those with new recruits, were reported throughout the 1980s in the Soviet Union. New recruits were not routinely revaccinated against diphtheria, and military bases mixed large numbers of individuals, both susceptible and possibly infected, from throughout the Soviet Union in crowded living conditions [30].

Increased susceptibility of children due to less intense immunization. The decreased intensity of childhood vaccination caused increased susceptibility to clinical diphtheria among children. The incidence of diphtheria was higher among unvaccinated persons than among vaccinated persons in Moldova and Russia [19, 31]; in addition, in almost all affected countries, severe disease was more commonly documented among unvaccinated cases than vaccinated cases. A case-control study after the reintroduction of the school-entry booster dose found an interval of >5 years since the last dose to be a risk factor for disease [32]. Some data also suggest that the use of vaccine with a lower antigen content in the primary series increased the risk for children receiving this preparation. In Vladivostok,
a lower level of immunity was found among children who received Td in the primary series compared with those who had received DTP [33]. In a vaccine-effectiveness study performed in Moscow, receipt of four doses (usually reflecting a primary series with DTP) was significantly more effective than three doses (primary series with Td) [34].

Diphtheria cases are much more likely than carriers to transmit the organism [35]. Evidence suggests that a large proportion of the disease among adults may have been transmitted from ill or asymptomatic children and that children played an important role in amplifying the overall epidemic, even in countries where most of the cases were reported among adults. Women had a much higher incidence of diphtheria than men despite no evidence of lower serologic immunity [36]. In a case-control study in Ukraine, the risk among women was not significantly elevated after adjusting for age, vaccination history, and household size and composition, but having ≥2 school-age children in the household was associated with a significant increase in risk [37]. Other evidence includes the progressively increasing proportion of children among cases in the Russian Federation beginning in the late 1970s, which coincided with worsening of diphtheria control among all age groups [24]. Conversely, improved diphtheria control among adults and children was seen in Azerbaijan after initial immunization campaigns targeting only children in 1994–1995 [11]. School and family clusters of multiple cases, especially among adults, and carriers were common during the 1990s epidemic, while clusters of multiple cases and carriers in the workplace were relatively uncommon [19, 25]. A large proportion of adult diphtheria cases was linked with child carriers; schoolchildren may have served as a critical population in transmission and spread, although the most severe clinical disease occurred among their adult contacts.

Increased adult susceptibility. A critical factor in permitting this epidemic was the accumulation of large numbers of susceptible adults as a consequence of the waning of vaccine-induced immunity and the decreased opportunity for naturally acquired immunity [1]. Unlike during the prevaccine era, adults were now susceptible and could both contract and transmit disease. In the NIS epidemic, outbreaks with adult-to-adult transmission occurred in institutional settings characterized by crowding, low levels of hygiene, and high contact rates. These settings included military units, neuropsychiatric hospitals, and concentrations of homeless people [31, 38]. However, clusters of cases were rare in routine work settings, and the carrier rates among adult contacts of cases were usually low.

Other factors besides a high rate of adult susceptibility to diphtheria appear to be needed to produce epidemic diphtheria among adults. Importations of diphtheria to other highly industrially developed countries with high rates of adult susceptibility have not led to significant secondary transmission. In the 1990s, documented cases of diphtheria originating in the NIS were identified in Germany, Finland, and Poland, all of which have very high childhood immunization coverage; spread within these countries did not occur (Germany and Finland) or was limited to small number of secondary cases or small case clusters linked to imported cases (Poland) [39, 40].

Efficacy of Russian-Produced Vaccines

The diphtheria epidemic in the NIS raised concerns about the effectiveness of diphtheria control programs and of the Russian-manufactured diphtheria toxoid used throughout the former Soviet Union. However, case-control studies in Ukraine in 1992 and in Moscow in 1993 demonstrated that receipt of three or more doses of Russian-manufactured diphtheria toxoid was highly effective in preventing disease in children [34, 41]. In these studies, the effectiveness of three doses of any diphtheria toxoid–containing vaccine exceeded 95%. In addition, operational evidence of the effectiveness of both diphtheria control programs and of Russian-produced vaccine comes from the immunization campaigns in the Russian Federation in 1993–1995, in which rapid control of the diphtheria epidemic followed the vaccination of millions of adults and children with Russian-produced vaccine [12]. However, during the Soviet period, the vaccine administered in some areas may have been less effective due to freezing during shipping since vaccine was commonly shipped in uninsulated wooden crates, even in winter [42].

The Control of Epidemic Diphtheria by the NIS and an International Coalition

Russian Federation. In the first years of the epidemic, the public health response relied on the control measures adopted in the 1980s (i.e., improving routine childhood coverage rates and immunizing adults in “high-risk” occupational groups). By the end of 1993, the continued spread of diphtheria led to a directive to vaccinate the >120 million Russian adults. Domestic capacity to produce Td vaccine was limited and could not initially meet the increased demand. This gap was closed when Russian Td vaccine production rapidly increased to nearly 80 million doses during 1994–1995, compared with <6 million in 1992.

Implementation efforts focused on immunizing adults at work sites, followed by intensified efforts, including house-to-house visits, to reach and vaccinate non-working adults. To raise childhood coverage, a shortened list of contraindications was adopted, and full-strength vaccine preparations became the vaccine of choice for the primary series [7]. In October 1994, the school-entry booster dose was reinstituted. Coverage with the primary series at 1 year of age rose to 93% in 1995, compared with 69% in 1991. Adult coverage with one or more doses was estimated at 75% by the end of 1995; between January 1993 and December 1995, nearly 70 million adults were vaccinated in the Russian Federation [12].
Other NIS and Baltic States. Although the Russian Federation was always self-sufficient with regard to necessary vaccines, antitoxin, antibiotics, and diagnostic supplies needed for diphtheria control, other NIS and Baltic States produced few, if any, of these items. Following the dissolution of the Soviet Union, the disruption of vaccine supply was reflected in sharp drops in childhood vaccination rates during 1992–1995 in most NIS outside the Russian Federation.

International efforts to combat diphtheria and the Interagency Immunization Coordinating Committee (IICC). The international community recognized that the dramatic political and socioeconomic changes had compromised the ability of the NIS to carry out disease control and immunization programs and that this would lead to the reemergence of epidemics of vaccine-preventable diseases. Soon after the dissolution of the Soviet Union, various governments and international agencies began a series of assessments of the needs of the NIS and Baltic States in establishing sustainable immunization programs. In 1991, WHO began to provide technical assistance to Russia on the epidemic, and over the next several years, the US Agency for International Development (USAID) and other donor governmental agencies extended the provision of assistance to the Central Asian Republics, Moldova, Ukraine, and the countries in the Caucasus. In 1994, WHO published a strategy document, a field manual, and a laboratory manual for diphtheria diagnosis, prevention, and control in the European Region [43–45].

Also in 1994, USAID and the government of Japan initiated the creation of IICC in Kyoto, Japan. Other members of the IICC were Canada, Denmark, France, Germany, Turkey, the European Union, the International Federation of Red Cross and Red Crescent Societies (IFRC), Rotary International, UNICEF, and WHO. The main objectives of the IICC were to support the NIS and Baltic States in the control of vaccine-preventable diseases (particularly in the control of epidemic diphtheria) and eradication of poliomyelitis and to help ensure primary immunization in children. Although the need for massive direct aid initially was recognized, the ultimate goal was to achieve sustainable immunization programs in the NIS and Baltic States based on vaccine self-reliance via production or procurement.

In June 1995, the IFRC, UNICEF, and WHO launched a public health emergency appeal initiated by the IICC, asking the international donor community for support to control the NIS diphtheria epidemic. In response, more than US $22 million has been provided by the IICC members and other international donors to supply vaccines, antitoxin, antibiotics, syringes, needles, cold-chain equipment, and other commodities.

WHO/UNICEF Strategy to Control Diphtheria

A plan for coordinated action to control epidemic diphtheria in the countries of the former USSR was elaborated in 1995 by WHO and UNICEF in close collaboration with the Centers for Disease Control and Prevention (CDC), the IFRC, USAID, Basic Support for Institutionalizing Child Survival, and the Program for Appropriate Technology in Health; this plan was approved by representatives of the NIS and Baltic States.

The three main components of the strategy follow:

- Initiate mass immunization as rapidly as possible of all age groups in the population with at least one dose of diphtheria toxoid (later modified to include two additional doses for selected age groups, e.g., persons 30–50 years of age).
- Provide early detection and proper management of diphtheria cases.
- Provide early identification and proper management of close contacts of diphtheria cases [46, 47].

While the immunization strategy was primarily developed from review of available data, several immunogenicity studies were also done in the NIS in 1994–1996 to help guide the strategy. The first study was done in Kiev, Ukraine, between March 1994 and June 1995 among 488 workers (18–67 years old), using Russian Td vaccine containing 5 Lf of diphtheria toxoid per dose. This study found that 89% of vaccinees had diphtheria antitoxin titers ≥0.1 IU/mL after one dose, and 92% had titers ≥0.1 IU/mL after two doses administered at a 30-day interval. However, only 71% of persons 40–49 years of age achieved titers ≥0.1 IU/mL after one dose, and 78% achieved such titers after two doses [48]. In Odessa, Ukraine, a study among 341 adults (17–63 years of age) found that the proportion with diphtheria antitoxin titers ≥0.1 IU/mL rose from 57% to 92% after a single dose of Td with 2 Lf diphtheria toxoid per dose (Pasteur-Mérieux-Connaught, Lyon, France) [49]. Only 79% of adults 40–49 years of age had titers ≥0.1 IU/mL. In Georgia, 248 persons (18–59 years of age) were studied following receipt of Td containing ≤5 Lf during late 1995. After one dose, 82% of vaccinees overall but only 66% of vaccinees 40–59 years of age had diphtheria antitoxin titers of ≥0.1 IU/mL [50]. In studies in the Baltic countries in 1996, single doses containing either 3, 6, or 12 Lf were administered to 2315 adults. Overall, 81% of vaccinees had diphtheria antibody levels >0.1 IU/mL after vaccination. No clear differences were seen in the antibody responses to the different doses, but antibody responses were lower overall (15%–69%) among persons 40–49 years of age [17].

Implementation of the Strategy and Results

All of the NIS and Baltic States inherited large networks of primary health care and public health centers staffed by thousands of health care workers from the Soviet Union. Although this network had suffered from underfunding and had been severely disrupted by conflict in Georgia, Azerbaijan, and Tajikistan, it remained relatively intact in most regions. The health personnel were usually well-trained in Soviet methods
of implementing mass disease-control measures; this training had many strengths but lacked both material resources and training in many areas, including cold chain and modern methods of social mobilization.

Implementation of epidemic control measures for all of the NIS and Baltic States, except Russia, required large-scale international assistance to develop and disseminate appropriate strategies and to mobilize material resources. The process required close collaboration between the health authorities of the countries affected and the international agencies. Details of strategy implementation were discussed and developed in many subregional and national workshops that brought together program managers, epidemiologists, clinicians, and microbiologists. Concerted efforts were taken to assist with material supplies, logistics, cold-chain establishment, immunization policy development, campaign planning, and social mobilization. Laboratory kits for diphtheria diagnostics (produced by the Public Health Laboratory Service, London) were provided to the countries where laboratories had lost the most capacity; training in case management and diagnostics was conducted at subregional and national levels.

As in Russia, workplace and school vaccination campaigns were used universally, and house-to-house visits and campaigns in jails, markets, and transportation centers were also conducted in many areas. In several countries, modern social mobilization techniques were used with international collaboration to try to reach groups that had not responded to traditional Soviet social mobilization methods [51].

Some countries of the NIS (Lithuania, Moldova, Tajikistan) were particularly successful in quickly implementing highly successful rapid national mass campaigns and achieving high levels of coverage among the entire population, while other countries have more slowly implemented mass immunization among adults. In countries that quickly achieved high coverage among adults, incidence rates also decreased quickly. For example, in

![Moldova Diphtheria Monthly Incidence Rates, 1993 - December 1998](image)

**Figure 3.** Reported diphtheria incidence by month, Moldova, 1993–1998
the last 30 years had been controlled after causing >157,000 cases and 5000 deaths. It has been estimated that control of the epidemic prevented an additional 560,000 cases and 15,000 deaths.

**Current Needs and Recommendations in the NIS and Baltic States**

The control of epidemic diphtheria in the NIS and Baltic States still requires intensified efforts by the national health authorities, and some countries also require sustained aid from international organizations. The three main principles of the WHO/UNICEF strategy are still valid. Although proper management of cases and contacts is of increasing importance for the consolidation phase of epidemic diphtheria, the most important goal of control measures remains achieving the highest possible immunization coverage for the whole population. Concrete goals for this phase include the following:

- At least 90% of preschool-age children should receive four doses of DTP, starting as early as age 6 weeks of age.
- At least 90% of school-age children should receive a booster dose of Td at school entry and at school exit; a further booster dose could be given in the middle period of school years.
- Adults should receive a booster dose of Td at 10-year intervals.

The international community should continue to assist countries such as Georgia, Ukraine, and some of the Central Asian Republics, where diphtheria incidence is still relatively high and coverage is still inadequate. Additional diagnostic kits or other laboratory support should be supplied to some of these countries due to ongoing severe limitations on basic laboratory capacity.

**Lessons Learned and Future Needs**

The struggle to control epidemic diphtheria in the NIS and Baltic States has taught important lessons in the following areas: diphtheria immunization policy, strategies for diphtheria epidemic control, modern diphtheria laboratory methods, organization of control efforts for international public health emergencies, and the reorientation of health care workers and the public to infectious disease problems.

**Immunization policy.** An important lesson learned from the epidemic of diphtheria in the former USSR is that an immunity gap in adults coupled with large numbers of susceptible children creates the potential for an extensive epidemic. On the basis of this experience, WHO’s European Advisory Group on Immunization made the following recommendations in 1996 with regard to protection against diphtheria:

- Achieving very high coverage (90%–95%) of primary immunization with DTP vaccine is of utmost importance. This series should be completed before 6 months of age. The first booster dose may be given at 16–36 months of age, and booster doses should be given before school entry (diphtheria-tetanus toxoids, adult formulation) and at school exit (Td).

  - In a number of countries, especially those presently experiencing epidemic diphtheria or having recently experienced epidemic diphtheria, a further booster could be given to children in the middle period of school years.
  - Where the risk of diphtheria is considered high, periodic booster doses for adults will be necessary. In other countries, adult diphtheria booster strategies need to be considered in the light of the perceived risk of diphtheria, the opportunities that exist for provision of boosters, and the sensitivity of surveillance.

WHO’s Expanded Program on Immunization is also reconsidering diphtheria immunization policy, particularly the need for booster doses. Currently, they recommend only a primary series consisting of three doses of DTP [1].

**Strategy to control country-wide epidemic diphtheria.** The success of the WHO/UNICEF strategy of “one dose for all” in the NIS and Baltic States demonstrates that successful control strategies must raise immunity among all age groups to high levels. In the early years of the epidemic, investigation and control efforts centered on individual cases failed to control the spread of diphtheria until immunization campaigns closed the population immunity gap. In contrast, an outbreak of diphtheria in Mongolia in 1994–1995, thought to be due to importation from the NIS, was rapidly controlled by mass immunization [52].

In the presence of high rates of susceptibility among adults, achieving high population immunity requires achieving high coverage rapidly with one dose of Td (at least 2 Lf diphtheria toxoid per dose) in virtually the entire population. This rapid one-dose strategy was appropriate in the NIS and will be appropriate in other populations where the majority of the population has been immunologically primed. A rapid one-dose strategy is especially suited for diphtheria epidemics involving large populations (such as the 300 million people of the former Soviet Union) where it is not possible to quickly provide the amount of vaccine needed for a multi-dose strategy.

Certain distinct age groups (e.g., 30- to 50-year-old adults in many of the NIS and Baltic States) are likely to have larger numbers of individuals who have not been immunologically primed against diphtheria due to incomplete initial implementation of immunization programs and decreasing exposure to diphtheria over time. These cohorts can be identified from the epidemiology of the outbreak, supported by serologic studies, if possible. The epidemic control strategy should ensure that these age cohorts receive a full primary series. Additional vaccine to allow administration of a three-dose primary series could be provided later to all other adult age groups.

While a higher susceptibility among rural residents was ob-
served in some parts of the NIS and Baltic States, it did not prove necessary to modify the epidemic control strategy. However, in many rapidly industrializing countries, immunization programs have been less effective in reaching rural areas than was the case in the Soviet Union. Rural-urban differences may have to be considered in future large-scale diphtheria epidemics.

Modern laboratory methods. The European Laboratory Working Group on Diphtheria (ELWGD) [53, 54] was formed at the initiative of the WHO European Office in July 1993 as a result of the epidemic situation in eastern Europe. ELWGD has several objectives: (1) to establish a network of collaborating laboratories to monitor the microbiologic surveillance of diphtheria, (2) to standardize methodologies for laboratory diagnosis in epidemic areas, and (3) to standardize the typing of the causative organism, leading to the establishment of a microbiologic surveillance system for all isolates of C. diphtheriae in the European Region and beyond. These techniques also have proven valuable by demonstrating long-term endemicity within a region in the United States [55].

A global database for molecular typing patterns is centralized in key reference laboratories globally, notably in Paris, London, and Helsinki. This database allows for dissemination of information on C. diphtheriae, specifically on the origin of outbreak strains and their relationship to endemic and epidemic strains worldwide.

A polymerase chain reaction assay also was developed for the rapid detection of strains of C. diphtheriae containing the toxin gene. While this assay will have limited use in most developing countries in the immediate future, it is a valuable adjunct to traditional culture techniques for diphtheria surveillance in developed countries.

Previous studies of virulence and immunogenic factors in C. diphtheriae have been almost exclusively limited to diphtheria toxin; the reemergence of epidemic diphtheria should help spur intensified efforts. A better understanding of the interaction of pathogenic strains of C. diphtheriae and the human host may help to develop improved methods of immunization and treatment and help us understand why certain toxigenic strains have more potential to cause large-scale epidemics.

Lessons for other international epidemic-control efforts. The establishment of an international coalition was critical in developing an effective strategy and mobilizing resources to fight epidemic diphtheria in the NIS; the effective functioning of this coalition required a coordinating committee with adequate staff and funding. Developing a successful joint strategy required the coalition to work in close collaboration with the health authorities and health workers of the epidemic countries. The successful collaboration and coordination of multiple international partners on two continents in controlling an epidemic in 15 different ex-Soviet countries could serve as a model for future public health emergencies.

These emergencies may not be long in coming. Many of the factors thought to be important in producing this epidemic, such as mass population movements and difficult hygienic and economic conditions, remain problems in the NIS and Baltic States and are present in other countries experiencing rapid industrialization or undergoing sociopolitical instability [24]. The current epidemic of tuberculosis in the NIS is a reminder that other infectious agents can and will exploit similar social and political vulnerabilities [56, 57].

Reorientation toward communicable diseases. The diphtheria epidemic forced a new generation of clinicians, laborato-

ries, and epidemiologists worldwide to relearn old lessons and develop new methods in the prevention, control, and treatment of diphtheria. Similarly, a new generation of the public in the NIS and Baltic States needed to relearn the threat of epidemic diphtheria and the benefits of immunization. The human cost of these learning curves shows the need to maintain training of health care professionals in communicable diseases in industrially developed countries and for communication to the public regarding the continuing challenges posed by these diseases. The reemergence and international spread of nearly forgotten diseases, such as diphtheria, reinforce the warning sent by the spread of AIDS—communicable diseases remain a priority health problem for all.

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