Diphtheria in Lithuania, 1986–1996

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Diphtheria reappeared in Lithuania in 1986 and rose to epidemic levels by 1992. Between 1991 and 1996, 110 cases of diphtheria were registered, with an incidence of 0.03–1.15/100,000 population. Most cases (84%) and all 17 deaths occurred among persons ≥15 years, most of whom had never been vaccinated. Persons 40–49 years old had the highest average annual age-specific morbidity (1.70/100,000) and mortality (0.53/100,000) rates. Low levels of immunity among individuals 40–49 years old and migration to epidemic areas in Russia and Belarus contributed to the epidemic's occurrence. Between 1991 and 1995, toxigenic Corynebacterium diphtheriae strains were isolated from 84 of all registered patients (76%), and nontoxigenic strains were isolated from 13 (12%). By 1996, two mass vaccination campaigns, which provided one dose of vaccine to individuals 25–30 years old and three doses of vaccine to persons 31–60 years old, helped reduce the number of cases. The first campaign achieved 69% coverage; the second achieved 48% coverage.

Background

Lithuania is a relatively small country on the Baltic Sea that shares borders with Russia, Poland, Belarus, and Latvia. The estimated population in 1998 was 3.7 million people.

Before World War II, morbidity and mortality from diphtheria in Lithuania was high: Between 1930 and 1939, 1000–2500 cases of diphtheria were reported annually. Vaccination against diphtheria was begun in 1- to 8-year-old children in 1946 [1]. Despite the introduction of vaccine, the annual number of diphtheria cases reported still remained above 1100 between 1946 and 1955. In response, a recommended schedule for vaccination against diphtheria was implemented beginning in 1956 (table 1). Three doses of diphtheria-tetanus toxoid–pertussis vaccine (DTP), administered 3–4 weeks apart, were recommended beginning at 5–6 months of age; booster doses were given 6–9 months after the third dose and at 3–4 years of age. Between 1956 and 1965, the annual number of cases of diphtheria dropped from >800 to <30. At the end of this period, the time intervals between primary and booster doses of vaccine were lengthened, and two booster doses were added to the recommended vaccination schedule. During the subsequent 8 years, the number of diphtheria cases declined further to single digits, until no cases were reported in 1973. In that same year, administration of the first and second booster doses of vaccine were delayed, and the fourth booster dose of vaccine was eliminated. In 1980, this booster dose was reintroduced into the recommended vaccination schedule at age 16 years. With the exception of 1976 and 1977, no cases of diphtheria were reported between 1973 and 1985.

Descriptive Epidemiology

Before the breakup of the former Soviet Union, the Sanitary-Epidemiologic Service (SES) of the Ministry of Health operated a well-organized surveillance system for infectious diseases, including diphtheria, and for the assessment of vaccination coverage [2]. After Lithuania declared its independence in 1991, this system essentially remained in place; however, the SES was transformed into the Public Health Centers. These centers are in all county-level districts, and diphtheria reporting remains mandatory from all clinical and laboratory facilities in the state-run medical care system.

Beginning in 1986, cases of diphtheria began to reappear, and with the exception of 1989, have been reported annually since that time (figure 1). The increase in diphtheria cases associated with the beginning of the epidemic in Lithuania began in 1992, when 9 cases were reported. The case count fell slightly in 1993 but rose again in 1994 and peaked in 1995, when 43 cases were reported.

During this time, 14 registered cases (13%) in Lithuania were epidemiologically linked to Newly Independent States (NIS) of the former Soviet Union—7 to Russia, 6 to Belarus, and 1 to Ukraine. Between 1991 and 1996, cases were found primarily in and around Kaunas City, where there is contact with immigrants from the Russian Federation; Vilnius City; Svencioniu and Vilnius districts, both of which border Belarus; and
Throughout the epidemic, most cases and all deaths due to diphtheria occurred among adults. Between 1991 and 1996, 18 cases of diphtheria were reported among children 0–14 years of age. All the cases among children were mild; no children suffered complications from the disease, only 1 child required antitoxin, and no deaths occurred among children [3]. In contrast, 92 cases of diphtheria were reported among individuals ≥15 years of age. The greatest number of cases (45) and deaths (14) occurred among persons 40–49 years old, the group with the highest average annual age-specific morbidity (1.70/100,000 population) and mortality (0.53/100,000 population) rates over the 6-year period. During the same period, 2 deaths occurred among the 22 cases in persons 30–39 years old (9%), and 1 death occurred in the 9 cases among persons ≥50 years old (11%).

The vaccination status of child and adult cases also varied. Among children, the vaccination status was determined from medical records and parental recall. Of the cases that occurred in children, 4 (22%) had never received vaccine, while 14 (79%) had received three or more doses. Within the latter group, disease appeared to develop at ages when the children were due to receive booster doses of vaccine.

Among adults, vaccination status was determined using self-recall, which was known to be unreliable. Nonetheless, it was unlikely that many adults had received booster doses of vaccine because vaccination had not been encouraged for decades. Among cases ≥15 years old, 12% had received three or more doses of vaccine, while 81 (88%) reported never having received any booster doses, and among the latter group, many 40- to 49-year-old people had not received a primary series of vaccinations. Coverage from mass DTP vaccination campaigns initiated in 1956 is unknown.

The standard scheme used for contact management included identification of persons considered to be contacts; evaluation of their vaccination status, including bacteriologic evaluation; vaccination and treatment, as appropriate; and follow-up. During the years of the diphtheria epidemic, >1500 contacts (>14.2/diphtheria case) were identified. In 1995 alone, 588 contacts of case patients were identified, of which 254 (43%) received booster doses of diphtheria toxoid or completed the primary series for vaccination, and 67 (11%) received antibiotic prophylaxis.

### Laboratory Results

Culture samples were obtained from all reported suspected cases of diphtheria. Among the registered cases evaluated between 1991 and 1995, 84 (76%) had toxigenic *Corynebacterium diphtheriae*: 44 (52%) had biotype gravis, and 30 (36%) had biotype mitis. *C. diphtheriae* of an unspecified biotype was identified in 10 patients (12%). The remaining 13 patients had a diagnosis of diphtheria without bacteriologic confirmation.

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**Table 1.** Recommended schedule for diphtheria toxoid vaccination in Lithuania, 1956–1996.

<table>
<thead>
<tr>
<th>Time period, basic vaccinations</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
<th>Fourth</th>
</tr>
</thead>
<tbody>
<tr>
<td>1956–1965, 3 doses, 3–4 weeks apart, at 3–6 months</td>
<td>6–9 months after third dose</td>
<td>3–4 years of age</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1965–1973, 3 doses, 4–6 weeks apart, at 3–6 months</td>
<td>9–12 months after third dose</td>
<td>2–3 years after first booster</td>
<td>6 years of age, ~2 months before school entry</td>
<td>11 years of age (DT)</td>
</tr>
<tr>
<td>1973–1980, 3 doses, 4–6 weeks apart, at 3–6 months</td>
<td>1.5–2 years after third dose</td>
<td>6 years of age</td>
<td>11 years of age (DT)</td>
<td>—</td>
</tr>
<tr>
<td>1980–1987, 3 doses, 4–6 weeks apart, at 3 months</td>
<td>1.5–2 years after third dose</td>
<td>6 years of age</td>
<td>11 years of age (DT)</td>
<td>16 years of age (DT)</td>
</tr>
<tr>
<td>1987–1991, 3 doses, 4–6 weeks apart, at 3 months</td>
<td>1.5–2 years after third dose</td>
<td>9 years of age (DT)</td>
<td>16 years of age (DT)</td>
<td>—</td>
</tr>
<tr>
<td>1991–1996, 3 doses, 4–6 weeks apart, at 5–6 months</td>
<td>1.5–2 years after third dose</td>
<td>9 years of age (DT)</td>
<td>16 years of age (DT)</td>
<td>—</td>
</tr>
<tr>
<td>1996–present, 3 doses, 4–6 weeks apart, at 5–6 months</td>
<td>1.5–2 years after third dose</td>
<td>6 years of age (DT)</td>
<td>16 years of age (DT)</td>
<td>—</td>
</tr>
</tbody>
</table>

* In 1986, use of AKDS-m (reduced-potency diphtheria-tetanus toxoids–pertussis vaccine) and ADS-m (diphtheria-tetanus toxoids vaccine [DT] with reduced levels of diphtheria antigen) were introduced; their use was discontinued in 1991.

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![Figure 1](image-url)  
**Figure 1.** Number of reported diphtheria cases and diphtheria incidence rates per 100,000 population, Lithuania, 1965–1996. No cases were reported between 1978 and 1985.
Molecular typing of the *C. diphtheriae* isolated in Lithuania was not performed; thus, cases could not necessarily be linked to those occurring in other NIS.

**Control measures.** In 1990, Lithuania adopted the vaccination plan and target vaccination goals of the World Health Organization’s (WHO) Expanded Programme on Immunization. In 1991, the Center for Immunoprophylaxis of Lithuania was founded to address issues related to vaccine supply, cold chain stability, assessment of vaccination coverage rates, post-vaccination adverse events, vaccination schedule development and modifications, evaluation of contraindications to vaccination, and education and information dissemination among physicians and the community. The first National Program on Immunization was approved in 1992, and WHO-recommended case definitions of and management practices for cases of diphtheria were translated into Lithuanian and widely distributed to physicians [4]. European recommendations to provide antibiotic treatment to eliminate the diphtheria bacterium and curtail spread of disease were implemented in 1993, and the Lithuanian manual containing WHO definitions and recommendations was prepared and distributed in 1994 [5, 6]. A Memorandum of Understanding (MOU) to provide heightened mass vaccination campaign efforts among the adult population was developed and signed in 1995. In 1996, the Center for Immunoprophylaxis was reorganized and became part of the Center for Communicable Diseases Prevention and Control.

**Vaccination coverage.** Until 1991, vaccination coverage in Lithuania was calculated using guidelines from the Ministry of Health of the former Soviet Union. Beginning in 1991, those guidelines were replaced by standards established by WHO to determine vaccination coverage rates in Lithuania. More specifically, across all clinics, the population of registered newborns served as the number targeted for vaccination, and lists of children who were vaccinated were used to determine the number actually reached. When coverage among children was assessed, only 75% of children had received three doses of DTP by the end of the first year of life, and 76% had received four doses by age 2 years (figure 3).

This situation was considered unsatisfactory. Therefore, in 1992, the first National Program on Immunization was prepared according to WHO standards. The Program instituted the control measures mentioned above and initiated the use of only vaccines meeting international standards of quality. As a result, over the next 4 years, vaccination coverage among 1-year-old children rose, peaking at 97% in 1995. Among 2-year-old children, vaccination coverage for four doses of DTP fell to a low of 62% in 1993 but rose to a high of 98% in 1995. Vaccination coverage of booster doses among school-age and

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**Figure 2.** Cities and districts reporting >5 diphtheria cases and areas of mass vaccination campaigns, Lithuania, 1991–1996

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adolescent populations was not available until 1994, when coverage was 84% for five doses of DT (diphtheria-tetanus toxoids) among 6-year-old children at school entry and 80% for Td (tetanus-diphtheria toxoids with reduced content of diphtheria toxoid) among those leaving school at 16 years of age. In both 1995 and 1996, school-age children and adolescents had vaccination coverage rates ≥90%. It is felt that the achievement and maintenance of relatively high levels of vaccination coverage within the pediatric population was key to preventing the spread of diphtheria in this segment of the population, as evidenced by the low number of cases compared with the number among the adult population.

Mass vaccination campaigns targeted at the adult population in Lithuania began in 1993 and escalated in 1995 when the aforementioned MOU was developed and signed between the Ministry of Health of the Republic of Lithuania, the Center for Immunoprophylaxis, the Lithuanian Red Cross Society, and the International Federation of Red Cross and Red Crescent Societies (IFRC). The vaccination campaign, which was supported through the MOU and by WHO, focused on providing one dose of vaccine for persons 25–30 years old because it was assumed this group had already received a primary series of vaccinations and, thus, only required boosting of their immunity. In contrast, for persons 31–60 years of age, three doses of vaccine (the first and second doses separated by 1–2 months and the second and third doses by 6–12 months) were recommended. This decision was made on the basis of the assumption that this age group had likely never received a primary series of vaccinations (and thus, required three doses for optimal immunity), from the observation that the highest morbidity and mortality from diphtheria was occurring among individuals 40–49 years of age, and from serologic data indicating that this age group had low levels of protective antibodies (Bakasenas V., unpublished data).

The campaign took place in two stages. The first stage occurred in November and December 1995 in the seven southern districts, where the highest morbidity was registered. Among the >1.1 million adults who were registered as living in the Alytus, Jurbarko, Kaunas, Marijampoles, Silute, Utena, and Vilnius districts of Lithuania, 69% had received one dose of vaccine, as determined by review of vaccinee lists from each district (figure 2). The second stage of the campaign was conducted between April and May 1996 and achieved a 48% coverage rate for one dose of vaccine among the >674,000 adults living in five northern districts of Lithuania (Klaipeda, Panevezys, Siauliai, Taurage, and Telsiai), again, as determined by review of district lists. Overall, vaccination coverage for receipt of one dose of vaccine among adults in the targeted age groups reached ~77% between 1993 and 1996.

A serosurvey conducted during the mass vaccination campaigns revealed that immunity against diphtheria within the adult population was also poor. Adults ≥20 years of age were selected from five districts of Lithuania to participate in a serologic survey supported by the IFRC, the European Community, and the Statens Serum Institute of Denmark. Before vaccination, only persons 20–29 years of age had geometric mean (GM) levels of diphtheria antibody that exceeded 0.1 IU/mL, the minimum level believed to provide immunity against clinical disease; the lowest GM levels were among persons 40–49 years old. After vaccination, GM levels among the 780 individuals tested exceeded 0.6 IU/mL; the lowest postvaccination GM levels (0.233 IU/mL) were again among persons 40–49 years old. Routine notification systems, direct telephone contact, and questionnaires used in the serosurvey provided a
means to monitor the occurrence of adverse events following vaccination. No serious events were reported: Among participants in the serosurvey, minor local reactions were reported by 15% and minor febrile episodes by 1% of respondents [7].

The mass vaccination campaigns targeted at the adult population were instrumental in bringing about a large reduction in morbidity in 1996, when only 11 cases were reported. In each of the next 2 years, only 2 cases were reported annually.

Discussion

The reappearance of diphtheria cases, which began 1986, may have occurred due to a number of factors. In general, many of those charged with providing vaccinations supported unfounded contraindications to their use; frequently, vaccinations were postponed without sound reasons. For example, mild respiratory diseases were considered to be sufficient grounds for postponing vaccination for at least 1 month. It was not uncommon for a 3- to 6-month delay in carrying out vaccinations. This common medical practice may have contributed to low vaccination coverage, especially among infants and children.

The reappearance of diphtheria cases coincided with the use of vaccines with lower limit of flocculation units and lower antigen levels than vaccines used in previous years. A study in 1991 revealed that 13% of children vaccinated with Russian-made vaccines did not develop adequate immune responses against diphtheria [1, 8]. As a result, in 1991, use of this vaccine was discontinued.

Other factors that may have contributed to the reappearance of cases was the elimination of the fourth booster dose of vaccine from the recommended vaccination schedule and a delay in the administration of the second and third booster doses to children 9 and 16 years of age beginning in 1987. These changes in policy resulted in children 6–9 years of age and adolescents 13–15 years of age having received their last booster dose of vaccine from 2 to 5 years before the beginning of the epidemic in 1992.

All deaths and severe cases of diphtheria occurred among adults, likely because of poor levels of immunity. Most adults had not received booster doses of vaccine for decades, and many probably did not receive a primary series of vaccinations because mass immunization with DTP in Lithuania began in 1956, a time when coverage rates were unknown but likely low.

The success of the mass vaccination campaigns is in part attributed to effective cooperation between the Lithuanian institutions and foreign organizations. All components of the campaign, including medical and vaccine supplies, widespread promotion of the vaccination campaign among the public, assessment of the segment of the population to target for the campaigns, educational programs to counter misconceptions concerning contraindications to vaccination, and the clinical and serologic surveys undertaken worked to support a strong vaccination campaign.

Conclusions

The epidemic of diphtheria that occurred in Lithuania appeared to be related to low levels of vaccination and immunity, especially among the adult population. Poor-quality vaccines used before 1992 and a system of immunizations that did not effectively reach all of the Lithuanian population were contributing factors. Adjustment of the National Immunization Program to be consistent with WHO standards was important in bringing about control of the disease. Mass vaccination campaigns targeted at the adult population were effective in stopping the outbreak of diphtheria in Lithuania.

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References