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Epidemiology of epidemic diphtheria in three regions, Russia, 1994–1996*

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Abstract. *Background:* A massive diphtheria epidemic which began in the former Soviet Union in 1990 is the first large-scale diphtheria epidemic in developed countries in more than 30 years and has primarily affected adults. In response, health authorities attempted to maximize vaccination for children and conducted an unprecedented campaign to vaccinate adults. *Methods:* We analyzed diphtheria surveillance data (case report forms and diphtheria vaccine coverage data) from three Russian regions from January 1994 to December 1996 and estimated vaccine effectiveness by the screening method. *Results:* We reviewed records from 2243 (97.2%) of 2307 reported cases. The highest cumulative incidence in the period was among children aged 5 to 9 years (106 cases per 100,000 population); adults aged 40–49 years had the highest adult incidence for disease (88 cases per 100,000) and the highest incidence of any age group of clinically severe disease (29 cases per 100,000) and death (5.1 deaths per 100,000). The incidence among women aged 20–49 years (82 per 100,000 women) was higher than among men (47 per 100,000, $p < 0.01$). The annual incidence decreased from 25.2 cases per 100,000 population in 1994 to 9.4 cases per 100,000 in 1996. The decrease occurred as adult coverage increased from an estimated 25–30% in December 1992 to 88% in December 1995. Vaccine effectiveness was high among both children and adults. *Conclusions:* The Russian diphtheria epidemic primarily affected adults, especially women; this pattern is likely representative of diphtheria epidemics in immunized populations. Raising childhood immunization coverage and mass adult vaccination was effective in controlling the Russian epidemic. An improved understanding of the current epidemiology of diphtheria will be useful to design public health responses to prevent or control modern epidemics.

Key words: Age distribution, Diphtheria (epidemiology), Diphtheria (prevention and control), Disease outbreaks, USSR (epidemiology), World health

Introduction

After almost three decades of good control of diphtheria, a massive diphtheria epidemic began in the Russian Federation in 1990. The epidemic began in Moscow and St. Petersburg, but by the end of 1993 virtually all parts of the Russian Federation were affected; the Russian Federation has reported three-fourths of the more than 145,000 cases and two-thirds of the over 4000 deaths reported from the New Independent States (NIS) of the former Soviet Union during 1990–1996 [1–3].

This is the first large-scale diphtheria epidemic reported in developed countries since epidemics in the Soviet Union in the 1950s; unlike epidemics in the pre-vaccine era, morbidity and mortality in the NIS predominantly occurred among adults. In response, the Russian Ministry of Health (MOH) has instituted multiple measures to raise childhood vaccination coverage and to achieve unprecedented levels of adult immunization. Although the epidemiology of diphtheria in the pre-vaccine era has been well described [4], limited information on the NIS epidemic has been published.

The MOH and the US Centers for Disease Control and Prevention (CDC) collaborated in three sites to better define the modern epidemiology of diphtheria and monitor the impact of control measures. This report summarizes diphtheria cases reported in these areas in 1994–1996.

Methods

Study population

Three study regions were chosen for convenience purposes by the MOH and CDC.

Novgorod City. Novgorod City is located in northwestern European Russia and has a population of 248,000.

Vladimir oblast (state). Vladimir oblast is located in central European Russia and has a population of 1,653,000.

Voronezh oblast. Voronezh oblast is located in south-central European Russia and has a population of 2,495,000.

Diphtheria case surveillance

Surveillance system and case investigation
The MOH maintains an epidemiologic service, called the Sanitary–Epidemiologic Surveillance (SES), that is responsible for infectious disease surveillance and control [5]. Reporting for diphtheria is thought to have been virtually complete, due to integration of clinical and laboratory facilities within a single government-run system and to a well-accepted system of reporting [6]. SES epidemiologists initiated investigations within 24 hours on suspected diphtheria cases using a standardized form. The guidelines for diphtheria surveillance and investigation which were in effect throughout the Russian Federation during the study period had been unchanged since 1983 [7].

Case investigation forms for confirmed diphtheria cases reported between 1 January 1994 and 31 December 1996 were obtained from the Gabrichevsky Institute of Epidemiology and Microbiology, Moscow, and the SES stations in the three regions.

Case definition
We accepted all reported confirmed diphtheria cases as cases. According to national guidelines, pharyngeal and nasopharyngeal specimens for isolation of diphtheria were obtained routinely from all patients with pharyngitis. Patients with pharyngitis and toxigenic *C. diphtheriae* identified were reported as bacteriologically confirmed cases. Patients with pharyngitis and a oropharyngeal pseudomembrane without another identified pathogen, and patients with a clinical course consistent with severe diphtherial disease were reported as clinically confirmed cases even if a toxigenic strain of *C. diphtheriae* was not isolated.

Disease severity classification
In Russia, disease severity was classified using a staging system based on the extent of pseudomembrane and neck edema [8]. For patients without neck edema, cases were classified as localized (pharyngitis with a positive culture only or with a pseudomembrane in one location) or spread (pseudomembrane with extension to another site). For patients with neck edema, cases were classified as subtoxic (edema of cervical lymph nodes), first degree toxicity (edema extending to the mid-neck), second degree toxicity (edema to the clavicle), third degree toxicity (edema below the clavicle) or hypertoxic (neck edema with severe hypotension). We classified patients with localized or local spread of disease as mild and patients with subtoxic or toxic manifestations as severe.

Diphtheria case vaccination status
Vaccination history (including vaccine lot numbers and date administered of each dose) was routinely obtained as part of case investigations from immunization cards maintained at polyclinics for children and from available records for adults; these records do not usually include a history of childhood vaccinations. A small proportion of adult case-patients were reported as vaccinated on the basis of a verbal history; these doses were accepted as valid only if accompanied by a date (month and year) of administration. We classified any adult who had received $\geqslant 1$ dose of diphtheria toxoid within the last 10 years as vaccinated.

Population vaccination coverage data

Clinical health care delivery system
The Soviet-era organization of the primary health care system in the study oblasts facilitated accurate surveillance. Populated areas were divided geographically and each area was served by separate adult and child polyclinics. Within each subarea of a polyclinic's territory, an individual physician was responsible for the clinical care, including vaccination, of all adults or children. The population was registered by periodic census by the physician's nurse and by cross-registration with other government agencies. This registration was nearly complete, especially for children, despite the increased mobility of the post-Soviet period.

Vaccination coverage reporting
Twice yearly, area pediatricians reviewed individual immunization cards and reported age-specific coverage to the SES; children were categorized by vaccination status (e.g. receipt of less than a primary series, a primary series, a first revaccination). Two alternative vaccination schedules were commonly used between 1980 and 1993 (Table 1). The most commonly used schedule required three doses of full strength diphtheria toxoid (primary series) in the first year of life followed by a fourth dose (first booster) in the second year and the other schedule required two doses of reduced-potency diphtheria toxoid (primary series) in the first year of life followed by a third dose (first booster) in the second year; subsequent booster dose recommendations were identical. Thus, the

Table 1. Diphtheria vaccination schedule (Soviet Union 1965–1991, Russian Federation 1991–1997, Ministry of Health, Russian Federation)

Age	Year						
	1965	1980		1986		1994	
		Alternative A	Alternative B[a]	Alternative A	Alternative B[a]	Alternative A	Alternative B
3–18 mos. (infancy)	DTP [3 doses]	DTP [3 doses]	Td (or DT) [2 doses]	DTP [3 doses]	Td (or DT) [2 doses]	DTP [3 doses]	DT [2 doses]
18–36 mos.[b]	DTP	DTP	Td (or DT)	DTP	Td (or DT)	DTP	DT
6 yrs	DTP	Td				Td	
9 yrs				Td			
11–12 yrs	Td	Td				d	
16 yrs		Td (after 1983)		Td		Td	

Antigenic content of Russian-manufactured vaccine. DTP = 15 lf units diphtheria toxoid per dose; DT = 30 lf units diphtheria toxoid per dose; Td = 5 lf units diphtheria toxoid per dose; d = 5 lf units diphtheria toxoid per dose.
[a] Although the alternative schedule containing DT was acceptable, it was rarely used.
[b] To be given 12–18 months after the last dose in infancy.

number of doses of diphtheria toxoid received by two individuals with the same reported vaccination status could vary by one dose.

Before 1994, adult vaccination coverage was not routinely monitored. In 1994, twice yearly reporting was mandated. We reviewed the coverage reports for the period 31 December 1994 to 31 December 1996. For 1993, we estimated coverage using data on the number of doses of diphtheria toxoid administered to adults since 1986.

Epidemic control measures

Childhood immunization

During the 1980s, misperceptions among physicians and the population of the risks and benefits of vaccination led to an extensive official list of contraindications, resulting in decreased vaccination coverage, delays in vaccination, and increased use of the lower potency schedule [3]. In 1986 the booster dose at school entry (6 years of age) was shifted to 9 years of age and a second booster at 11 years of age was eliminated, increasing the intervals between booster doses to 7 years.

In December 1993, the MOH issued new recommendations; contraindications to vaccination were markedly reduced and the use of lower potency vaccine in young children was strenuously discouraged. The first school age booster dose was moved back to 6 years of age and the dropped revaccination was reinstated in November 1994. The MOH mounted large-scale efforts to change the behavior of pediatricians by education, intensive monitoring of vaccination coverage, and incentives based on achieved coverage.

Adult coverage

Routine revaccination of adults every 10 years had been recommended since 1986 but implementation was limited and aimed at groups thought to be at high risk, including child care, public transport, and retail sales workers. Adult coverage nationally was estimated at 25–30% in December 1992 [Ministry of Health, Russian Federation, unpublished data]. In November 1993, universal vaccination of adults with one dose of diphtheria toxoid was recommended. Initial vaccination campaigns at work sites were followed by door-to-door campaigns and supplemental measures to vaccinate hard-to-reach populations. In 1995, three doses were recommended for adults who lacked documentation of a primary series. These recommendations for adult vaccination are consistent with those of WHO in 1994 and 1996, respectively [9, 10].

Vaccine effectiveness

We used the screening method to estimate vaccine effectiveness (VE) [11]; this method is suitable where available surveillance data include the immunization status of cases and good estimates of population coverage. Estimates of VE were derived using the formula $VE = 1 - [PCV/(1 - PCV)]\ [(1 - PPV)/PPV]$, where PPV is the proportion of the population vaccinated and PCV is the proportion of case-patients vaccinated. Separate VE estimates were obtained for six-month periods between 31 December 1994 and 30 June 1996 for adults and for children aged 1–5 years.

The PPV was obtained from the coverage figures reported every six months by the oblasts. Children aged 1–5 years who were reported as having received a primary immunization series or a primary vaccination series and first revaccination would have received 2–4 doses depending on which of the alternative schedules was used for their vaccination. Less than 20% of schoolchildren sampled during other studies in the three oblasts had received the lower potency schedule.

PCV for each six-month period was obtained by analyzing the vaccination history of cases with onset ± 3 months from the coverage report; cases with unknown vaccination history were excluded.

For adults (⩾18 years of age), the effectiveness of ⩾1 doses compared with 0 doses was calculated for each six-month period. For children aged 1–5 years, having received a primary series with or without the first revaccination was compared with receiving less than a primary series.

Results

Epidemic diphtheria affected all three regions beginning in 1993 (Figure 1). In all three areas, incidence rates reached a peak in 1994 and declined in 1995–1996, paralleling trends in the national data. Reported cases decreased from 1108 cases in 1994 to 412 in 1996.

Of the 2307 cases reported for 1994–1996, 2243 (97.2%) case reports were available for analysis (Table 2). The expected seasonal increase in cases was seen in 1994 and 1995, but did not occur in 1996 (Figure 2). In 1994, the highest age-specific incidence rates were in children aged 5–9 years and in adults aged 40–49 years (Figure 3). By 1996, age-specific incidence rates had fallen in all three oblasts, especially among children.

Of the 2243 cases, 380 (16.9%) were clinically severe and 63 cases (2.8%) were fatal (Table 3). Adults (> 18 years) accounted for 63.9% of all cases, 81.8% of severe cases, and 74.6% of fatalities. The case–fatality ratio in both children and adults increased progressively with the increasing severity of illness ranging from 0.1% (3/1683) among cases with localized disease to 46.7% (21/45) among cases with third degree toxicity. Overall, a fatal outcome occurred in 0.7% (13/1863) among cases with mild disease and 13.2% (50/380) among cases with severe disease.

The severity of disease and case–fatality ratio were dependent on vaccination status (Table 2). Among unvaccinated children the proportion of severe cases was fourfold higher and fatal cases tenfold higher than among children who had received ⩾1 dose of vaccine. Among adults, severe disease and death were twofold higher among adults who had no documented doses of vaccine within the last 10 years compared to adults who had received ⩾1 dose of vaccine.

Overall, adults 40–49 years of age had the highest incidence of severe disease (28.6 cases per 100,000 population) and the highest case-fatality ratio (5.7%) of any age group over the three year period and accounted for 42.9% (27 of 63) of all fatalities (Figure 4). The proportion of cases classified as severe among adults 40–49 years of age (37.4% of unvaccinated cases and 25.1% of vaccinated cases) was significantly higher ($p < 0.01$) than those for adults of any other age groups, stratified for vaccination status.

Among adults, a marked difference in incidence rates was noted by gender. During the period 1994–1996, the incidence rate among women 20–49 years of age was 74% higher than that in men (81.5 vs. 46.9 cases per 100,000, $p < 0.01$); the excess cases among women accounted for 23% of all cases among adults ⩾20 years of age. The proportion of cases among women that were mild (78.9%) was not significantly higher than that among men (75.3%, $p = 0.15$) despite a higher proportion of cases among women (52.2%) having been vaccinated than among men (40.2%, $p < 0.01$).

The highest incidence rate for disease over this period was found among children aged 5–9 years (105.9 per 100,000 children) who also had the highest mortality (2.5 per 100,000) among children and adolescents. Of the eight fatal cases in this age group, all had received < 3 doses of diphtheria toxoid while only 12% of the nonfatal cases ($p < 0.01$) had received < 3 doses.

Of the 2243 cases, 2025 (90.3%) were laboratory confirmed including 1731 of the 1863 (92.9%) mild cases and 294 of the 380 (77.4%) severe cases. No difference in the rate of laboratory confirmation was noted between males (89.4%) and females (90.9%). Biotype gravis strains were isolated from 1,701 (84.0%) and biotype mitis strains from 310 (15.3%) of the laboratory confirmed cases. The case–fatality ratio did not differ significantly between cases with gravis strains isolated (2.4%) and those with mitis strains (4.2%, $p = 0.11$).

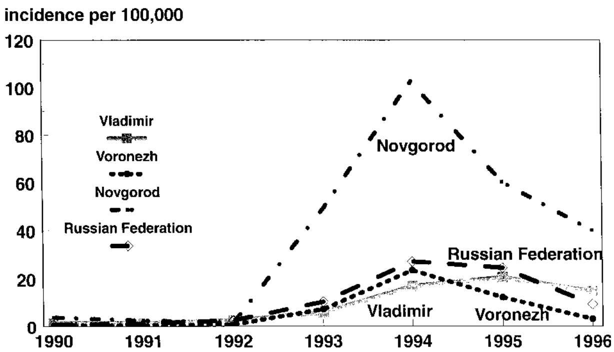

Figure 1. Diphtheria incidence in Vladimir and Voronezh Oblasts, Novgorod City and the Russian Federation: 1990 to 1996.

Immunization coverage data

Adult coverage increased dramatically during the time period of the study. Coverage among adults was estimated at between 40 and 50% in December 1993; reported coverage levels increased from 68% in December 1994 to 88% in December 1996. Although one-dose coverage was high in all three areas,

Table 2. Population and diphtheria case characteristics

	Vladimir oblast	Voronezh oblast	Novgorod city	Total study regions	Russian Federation
Population	1,653,000 (1994)	2,495,000 (1994)	248,000 (1995)	4,396,000	148,000,000 (1993)
% adults (⩾18 years of age)	76%	77%	76%	76%	78%[a]
Case data					
Reported 1994–1996	851	954	502	2307	88,748
Reports 1994–1996 analyzed	848 (99.6%)	900 (94.3%)	495 (98.6%)	2243 (97.2%)	
1994 cases [c,d]	286	520	260	1066	39,582
1995 cases [d]	334	312	137	783	35,652
1996 cases [d]	228	68	98	394	13,604
% adults (⩾18 years)	63.1	68.4	57.0	63.9	66.3[a,e]
% females among					No data
– children and adolescent cases (< 18 years)	54.3	51.8	46.9	51.5	
– adult cases (⩾18 years)	68.2	64.9	63.5	65.9	No data
Laboratory confirmation (%)	96.7	84.0	90.7	90.3	89.9[b]
Gravis strains among laboratory confirmed (%)	79.3	80.3	98.7	84.0	71.8[b]
Proportion of cases classified as severe (%)	12.7	20.6	17.6	16.9	11.4[b]
Fatalities	26	30	7	63	2243
(Case–fatality rate)	(3.1%)	(3.3%)	(1.4%)	(2.8%)	(2.5%)

[a] > 14 years of age.
[b] For 1993.
[c] Includes 11 cases (Vladimir 3, Voronezh 3, Novgorod 5) with onset in late December 1993 but reported in 1994.
[d] For study sites includes cases with onset date during this year, for Russian Federation includes cases with report date during this year.
[e] For 1994–1995.

reported coverage with more than one dose varied considerably.

Childhood vaccination levels were suboptimal in 1992. Coverage with a completed primary series among children in the second year of life was below 90% in all three regions and below 70% in one; coverage with the first booster among children in the third year of life was below 90% in all three regions and below 80% in two. However, by December 1994, both coverage with a primary series among children in the second year of life and coverage with the first booster among children in the third year of life exceeded 90% in all three regions. Timely coverage continued to improve during the study period as measured by an increase in coverage with the first booster among children in the second year of life from 10% in December 1994 to 26% in December 1996; the improvement in timely immunization was largely due to reduced temporary contraindications. In addition, the proportion of children classified as having permanent contraindications to vaccination dropped significantly; in Novgorod, of the 48,000 children ⩽14 years of age, none were classified as having permanent contraindications to diphtheria vaccination in December 1995 as compared with 0.3% in December 1993. Implementation of the

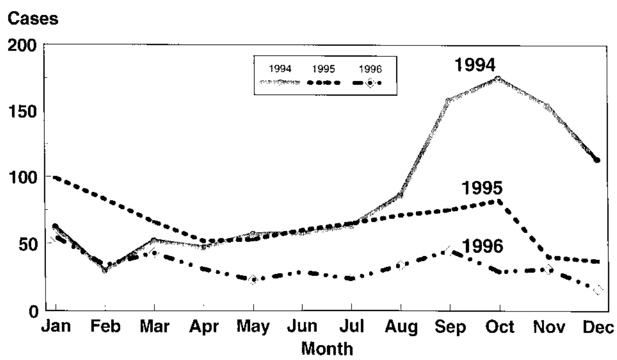

Figure 2. Diphtheria cases by month of onset: Voronezh and Vladimir Oblasts, Novgorod City 1994–1996 (n = 2232).

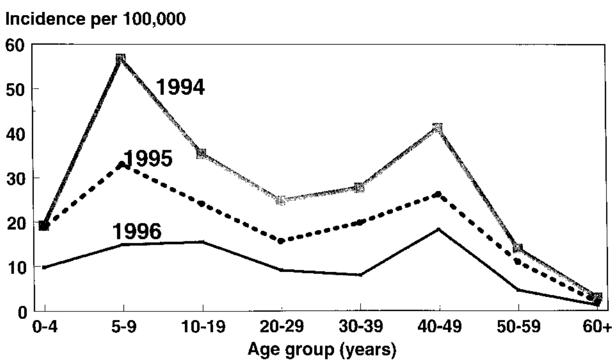

Figure 3. Diphtheria incidence by age group and year, Voronezh and Vladimir Oblasts and Novgorod City, 1994–1996.

Table 3. Vaccination status, severity of disease, and case-fatality rate among children and adults

Cases	Children (< 18 years) 810 Immunization status				Adults (⩾18 years) 1433 Immunization status[a]			Total 2243
	Unknown	0 doses	1–2 doses	3+ doses	Unknown	0 doses	⩾1 dose	
Total cases	34	69	82	625	157	661[b]	615	2243
Severe disease (%)	0	21 (30.4)	18 (22.0)	30 (4.8)	26 (16.6)	187 (28.3)	98 (15.9)	380 (16.9)
Fatalities (%)	0	9 (13.0)	4 (4.9)	3 (0.5)	8 (5.1)	28[c] (4.2)	11[d] (1.8)	63 (2.8)

[a] Data on any childhood diphtheria immunizations were obtained in 103 case investigations (patients aged 18–28 years).
[b] Included 20 cases whose last dose of diphtheria toxoid was > 10 years prior to onset of disease.
[c] Includes one case recorded to have received diphtheria toxoid. This patient had received 6 doses with the last dose 18 years prior to illness.
[d] Includes 8 cases with one dose, 2 with 2 doses, and 1 with three doses of diphtheria toxoid.

reinstated school-entry booster dose was rapid in all three sites, with coverage in June 1996 ranging from 67% in Vladimir oblast to 88% in Novgorod City.

Vaccine effectiveness

Among adults, the proportion of cases who had received ⩾1 dose of diphtheria toxoid within the past 10 years increased from 39% for the six-month period around June 1994 to 70% for the period around June 1996. However, as noted above, coverage in the population increased rapidly during this period as well and point estimates of the vaccine effectiveness of ⩾1 doses remained fairly high, ranging 64–83% for the individual six-month periods.

Ninety-seven cases occurred among children aged 1–5 years during the period analyzed; The number of doses received was zero doses (15 cases), one dose (seven cases), two doses (one case), three doses (38 cases), and four doses (42 cases) and unknown vaccination status (4 doses). Population coverage with at least a primary series was between 94 and 98% among children aged 1–5 years during this period. The estimated vaccine effectiveness of coverage with at least a primary series ranged 86–96%.

Discussion

This is the first large diphtheria epidemic to occur in any country with a longstanding universal childhood immunization program and a majority of cases occurred among adults. The decreased opportunity for naturally-acquired immunity due to the control of diphtheria and the waning of vaccine-induced immunity has created a new population of susceptible adults in the NIS and other developed countries. In the pre-vaccine era, most adults in developed countries were protected by natural immunity acquired in childhood, usually from subclinical infection [12]. After implementation of childhood vaccination programs, an increased diphtheria incidence among older age groups was noted before the near-total disappearance of diphtheria [13]; in the epidemics at the end of World War II in Copenhagen and some parts of Germany, a majority of diphtheria cases were among adults [14, 15].

In the former Soviet Union, widespread childhood vaccination against diphtheria was begun in the late 1950s leading to near elimination of the disease by 1965. Consequently, many adults now in the 40–49 year age group in the Russian Federation never acquired immunity to diphtheria, because they were born at a time when disease incidence was dramatically reduced but never received a primary series of diphtheria toxoid. The lower level of immunity in this age group is supported by serologic studies [16, 17]. These individuals require a full primary series for adequate protection.

The higher incidence among women has not been a widely appreciated feature of diphtheria epidemiology, although an increased risk for diphtheria among women was noted in some series in both the pre-vaccine and early vaccine eras [14, 18, 19]. The factors contributing to the increased risk among women in the present epidemic are not well studied. Increased exposure to children who are cases or carriers is likely to play an important role. Serologic studies have shown equivalent levels of immunity to diphtheria among women and men in the NIS [18, 20] and although military service for males was near-universal in the former USSR, routine diphtheria vaccination for recruits was not introduced until the late 1980s. In our study, female cases are more, not less, likely to have documented vaccinations than male cases. Evaluation of the protection afforded to women by the current recommendations for adult vaccination is warranted.

Although disease incidence was high among children, severe disease and death were infrequent due to high vaccination levels. The very high rate of disease among 5–9 year old children is presumably related to high contact rates among children in primary school; peak rates of subclinical and clinical disease were

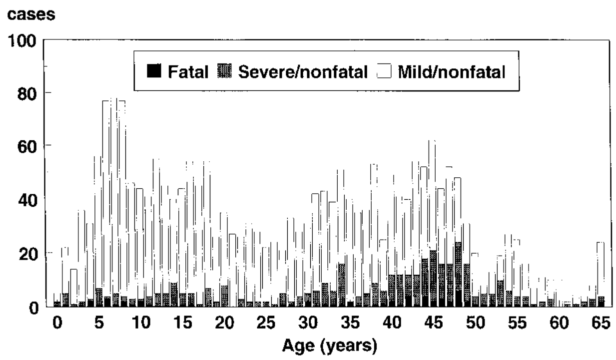

Figure 4. Diphtheria cases by age and disease severity: Voronezh & Vladimir Oblasts, Novgorod City 1994–1996 (n = 2243).

noted in this age group in the pre-vaccine era [21]. Although coverage is very high currently among school-aged children in the Russian Federation, the remaining under-immunized children are at risk. In addition, infected school-aged children may disseminate the disease to adults, especially through contact with care givers.

Molecular typing of *Corynebacterium diphtheriae* strains has demonstrated that the outbreak in the Russian Federation was associated with the emergence of a dominant epidemic clone of closely related gravis strains; 19 strains from 1993 and 1994 from Vladimir oblast were included in one study and 18 strains belonged to this clone [22]. Our surveillance data shows a similar predominance of gravis strains in all three locations. However, the 297 cases with mitis strains reported in the three year period between 1994 and 1996 in these three regions represent a twofold increase over the number of cases reported due to both gravis *and* mitis organisms between 1990 and 1992 in these regions. The coexistence of epidemics of both mitis and gravis strains supports an important role for population factors in permitting the epidemic to occur, in addition to any pathogen-specific factors.

Our estimates of vaccine effectiveness by the screening method supports the high efficacy of Russian-produced diphtheria vaccine among both children and adults. Vaccination with a primary series of three doses of full potency diphtheria toxoid produces antibody levels exceeding the accepted minimal protective level in 94–100% of infants [23]. A case control study in Moscow in 1993 found a VE of $>96\%$ for three doses in children 0–5 years of age [24]. The response to booster doses in adults depends primarily on the recipient's immune status due to previous vaccination or disease; a study in the Ukraine found 89% of the adults aged 18–67 years had antibody levels exceeding the accepted minimal protective level one month after revaccination with a single dose of Russian-produced vaccine although only 70% of the 40–49 year olds had protective antibody levels [18].

It had previously been thought that immunity among 70% of the childhood population would be sufficient to interrupt transmission of diphtheria [25]; these assumptions were developed when immunity from natural disease was still high among adults. The experience of the current epidemic demonstrates that high levels of vaccination among both adults and children are necessary to interrupt a modern epidemic; failure to rapidly implement these measures early in the epidemic contributed to the spread and severity of the epidemic. From 1990 to 1993, the emphasis was on improved implementation of the existing recommendations which focused on achieving very high childhood and limited adult coverage; these measures had been sufficient to control an upsurge of diphtheria in the early 1980s but did not prove effective in the 1990s. The policy changes since 1993 have emphasized universal vaccination of children and adults; implementation of these changes has achieved very high rates of coverage in the entire population correlated with a rapid decrease in the incidence of diphtheria among all age groups. For example, one-dose coverage among adults of $>70\%$ was associated with a declining adult incidence in the study oblasts while among children 5–9 years of age, achieving high coverage with the school-entry booster dose was associated with a rapid decline in incidence. Maintaining herd immunity to prevent future outbreaks will require adult vaccination although maintaining immunity among children will continue to be critical due to their high contact rates in schools and day care centers.

The three regions described in this paper probably provide a representative picture of diphtheria cases in the Russian Federation; the distribution by age and severity of illness of reported cases in our 1994 data is similar to that reported in an analysis of national surveillance data from 1993 [26]. Although the Russian surveillance system effectively collects remarkably complete data [6] our analysis was limited to the quality and quantity of data routinely collected in case investigations and population coverage reports. Recorded vaccination status of cases was sometimes limited to the most recent booster dose for adolescents and, for adults, was limited by the inaccessibility of records of childhood vaccinations and adult vaccinations at workplaces that had closed. Thus, vaccination histories among adolescents and adults were likely to be incomplete. Population coverage data for children do not include, which of the two alternative primary vaccination schedules was received and for adults age-group specific coverage data are unavailable. The lack of these data limits the precision of our vaccine effectiveness estimations.

A proportion of the mild cases reported by the Russian surveillance system may have escaped detection or been classified as carriers under less-stringent surveillance. Russian policy instructed physicians to culture all cases of pharyngitis for diphtheria and all symptomatic patients with a positive diphtheria culture were classified as diphtheria cases, regardless of the presence of a membrane or copathogens. This case classification policy differs from the WHO diphtheria case definition which requires the presence of a pseudomembrane and helps to explain the relatively low case–fatality rate compared to historical averages (5–10%). The proportion of cases in our study with pharyngitis but without a membrane is difficult to estimate without additional clinical data. Data from case series in St. Petersburg found that the proportion of cases with bacteriologic confirmation but lacking typical clinical features was 57% among vaccinated children and 68% among adults [27, 28]. However, the proportion of severe disease among cases in St. Petersburg was two- to threefold lower than in our study, suggesting a lower rate of overdiagnosis of carriers as cases in our study regions. Additionally, some variations in the case-severity and case–fatality ratio were observed between oblasts, raising the possibility of differences in diagnostic standards.

The introduction of effective childhood vaccination has affected the balance between the human population and toxigenic *C. diphtheriae*, decreasing the circulation of the organism and allowing the accumulation of populations of adults who lack immunity due to lack of exposure to the organism and the waning of vaccine-induced immunity in the absence of periodic booster doses. Currently the childhood vaccination schedules recommended by the WHO Expanded Programme on Immunization and by many national health authorities for several diphtheria endemic countries lack recommendations for booster doses after primary immunization against diphtheria. The experience of the Russian outbreak argues for the need to maintain high levels of immunity against diphtheria among all age groups of the population through booster doses in older children, adolescents, and adults.

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