The Changing Epidemiology of Diphtheria in the Vaccine Era

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The epidemic of diphtheria in the Newly Independent States (NIS) of the former Soviet Union has drawn attention to our incomplete understanding of the epidemiology of diphtheria. Many unanswered questions remain concerning the reasons for a resurgence of diphtheria and for the shift in the age of patients and concerning the mechanisms for acquisition of immunity in adults through natural infection under unfavorable living conditions. Other unanswered questions relate to the precise role of socioeconomic factors and hygiene conditions in the initiation, buildup, and spread of the epidemic. Important characteristics of the NIS epidemic can be used to help predict the spread of future diphtheria epidemics. These characteristics include a high proportion of infected adults, a progressive spread of disease from urban centers to rural areas, and transition from initial amplification of disease in groups with high rates of close contacts in focalized, well-distinguished outbreaks to a more generalized epidemic.

At the beginning of the 1980s, many countries in the world were progressing toward the elimination of diphtheria. Diphtheria incidence rates reached their lowest levels, and there was optimism that elimination of indigenous respiratory diphtheria could be achieved in the European Region by 1990 by maintaining and strengthening immunization services [1].

However, a striking resurgence of epidemic diphtheria in the Newly Independent States (NIS) of the former Soviet Union has drawn attention to our lack of a full understanding of the epidemiology of the disease. The epidemic began in the Russian Federation at the end of the 1980s and had affected all 15 NIS countries by the end of 1994 [2–4]. Since 1992, some of the diphtheria cases reported from other parts of Europe have been linked to transmission from the NIS epidemic: in Belgium (3/3 cases), in England and Wales (1/19 cases), in Finland (10/10 cases), in Germany (8/23 cases), and in Greece (1/3 cases) [5]. In Poland, 19 of 25 persons diagnosed with diphtheria in 1992–1995 had traveled to Russia, Ukraine, or Belarus or had had contact with visitors from these countries [6]. Importation of diphtheria cases to European countries and Mongolia and diphtheria cases among US citizens traveling or residing in the NIS [7] gave rise to the fear that the NIS epidemic might spread over a wider area. As late as 1997, as the epidemic was waning, the NIS countries reported ~40% of the diphtheria cases worldwide (table 1).

Herein, I discuss how observations made during the recent epidemic in the former Soviet Union and information collected previously changed our knowledge of the epidemiology of diphtheria. The impact of routine immunization on the immunity profiles in various age groups and the subsequent changes in the age distribution of diphtheria patients will be discussed, and unanswered questions will be raised.

Patterns of Spread

The diphtheria epidemic in NIS provided important information. First, there was a high proportion of cases among adolescents and adults, especially in Belarus, Russia, Ukraine, and in Baltic States (Estonia, Latvia, and Lithuania), and a lower proportion of cases in these age groups in the southern republics of the Caucasus area and Central Asia. Second, the epidemic began as an urban epidemic, with a progressive transition to include rural areas over time. Third, the epidemic initially amplified in groups with high rates of close contacts (e.g., hospitals, military troops, kindergartens, schools), and later, it made a transition to a more generalized epidemic involving socioeconomically disadvantaged groups (e.g., alcoholics).

The Soviet armed forces may have played a role in the introduction and spread of toxigenic *Corynebacterium diphtheriae,* and several diphtheria outbreaks were reported in Russia among military staff [9–11]. Military recruits were not routinely vaccinated against diphtheria until 1990 [11]. The first cases of diphtheria in Moscow in 1990 were among paramilitary construction workers [12, 13]. From May 1988 to February 1989, the demobilization of 100,000 Soviet troops who had served in Afghanistan, where endemic diphtheria was reported, may have contributed to the introduction and spread of toxigenic strains of *C. diphtheriae* [13].

Changes in Immunity Patterns by Age

Changes in the age-wise distribution of the immunity patterns usually have been explained by the argument that immunization led to a marked decrease in the incidence of the disease and to a subsequent reduction of the reservoir of toxigenic *C. diphtheriae* organisms. In the prevaccine era, exposure to toxigenic

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Table 1. Countries reporting more than 10 cases of diphtheria to the World Health Organization in 1997, according to [8].

	No. of cases reported		
Country	11–99	100–999	1000–9999
Algeria	30		
Armenia	12		
Azerbaijan	27		
Bangladesh	96		
Belarus	96		
Brazil	32		
Dominican Republic	25		
Ecuador	19		
Georgia		286	
India			1326
Indonesia			4355
Iran	30		
Iraq		290	
Kazakhstan		160	
Kyrgyzstan		292	
Latvia	42		
Madagascar		154[a]	
Moldova			
Mongolia	46		
Nepal	69		
Niger		726	
Nigeria	31		2016[a]
Pakistan			
Philippines	26	138	
Russian Federation			4057
Sudan			
Syrian Arab Republic	15		
Tajikistan	59		
Thailand		723	
Turkmenistan	38		
Ukraine	38		
Uzbekistan		399	
Vietnam	34	152	

[a] For 1996.

strains of diphtheria organisms was common, and this provided natural boosts to the development and maintenance of immunity against diphtheria. Children were susceptible, and most adults remained immune to the disease. However, after immunization of children became widespread, diphtheria became rare, so exposure to these bacteria (and the concomitant natural boost of immunity) become uncommon. If adults do not have natural exposure to diphtheria-causing organisms or receive booster doses of diphtheria toxoid, their immunity induced by childhood immunization wanes, and they become susceptible to the disease [6, 14, 15].

A large body of evidence has documented changes in the immunity levels of various age groups in the pre- and postvaccine eras. In the prevaccine era, when the circulation of *C. diphtheriae* organisms was common and the prevalence of diphtheria cases was high, natural immunity was acquired by overt or subclinical infection. Most newborn infants passively acquired antibodies from their mothers via the placenta. In 1914 in Vienna [16] and in 1923 in New York City [17], ~80% of newborns showed evidence of diphtheria immunity (figure 1). During the first several months of life, this passive immunity waned and was gradually replaced by active immunity, which was acquired through increasing exposure to natural infection. By 15 years of age, 80% of the children had acquired natural immunity against diphtheria. The rate of acquisition of natural immunity, however, differs from country to country, probably due to differences in the intensity of early contact with diphtheria organisms, overcrowding, sanitation, and hygiene [15].

Available data suggest that the pattern of acquiring diphtheria immunity in developing countries in the 1960s and 1970s resembled the pattern observed in Europe and the United States before the introduction of childhood immunization programs (figure 1). Infections of skin lesions with *C. diphtheriae* organisms seem to play a role in the rapid development of natural immunity in developing countries.

In areas where diphtheria has been controlled through immunization programs, the immune status of the population has changed considerably: Children have high levels of diphtheria immunity as a result of childhood immunization. The level of immunity declines in late childhood and adolescence, depending on the schedule of immunization and the remaining reservoir of *C. diphtheriae* in the population. Without the periodic administration of booster doses of diphtheria toxoid or repeated exposure to toxigenic strains of *C. diphtheriae,* adults become susceptible to diphtheria. The likelihood of having protective antibody levels decreases with age, and in some industrialized countries, >50% of adults are susceptible to diphtheria (figure 2). Although the design and laboratory methods used in different serosurveys conducted in different countries and at different times varied considerably, the results of the serosurveys suggested a clear shift in the immunity distribution in different age groups. This gap of immunity among adults exists in many industrialized countries: France [37], Germany [38], Norway [28], and Italy [39]. In Germany, newborns and persons >50 years of age constituted the least protected groups [34].

In the early 1980s, the lowest levels of diphtheria antibodies in various areas of the Soviet Union were found in persons 20–40 years old [40–42], and at present, this least protected group has shifted to persons 30–40 years old. In other countries, low-level protection was found in persons 40–50 years old in Australia [43], England [44], Germany [45], and Poland [32, 33] and in persons >50 years old in Denmark [46], Finland [29], Sweden [47], and the United States [26]. A lower percentage of adults, especially men, in the northwestern areas of Russia have protective levels of diphtheria antitoxin compared with adults in northern Norway [28].

Thus, a high proportion of the adult population in industrialized countries lacks immunity and remains susceptible to diphtheria. A large pool of susceptible adults constitutes the potential for an epidemic, especially if this pool is coupled with the presence of susceptible children.

Changes in the Age Distribution of Diphtheria Cases

When diphtheria was a common disease, it most frequently affected children: At least 40% of diphtheria cases were among children <5 years of age, and some 70% of the cases were among

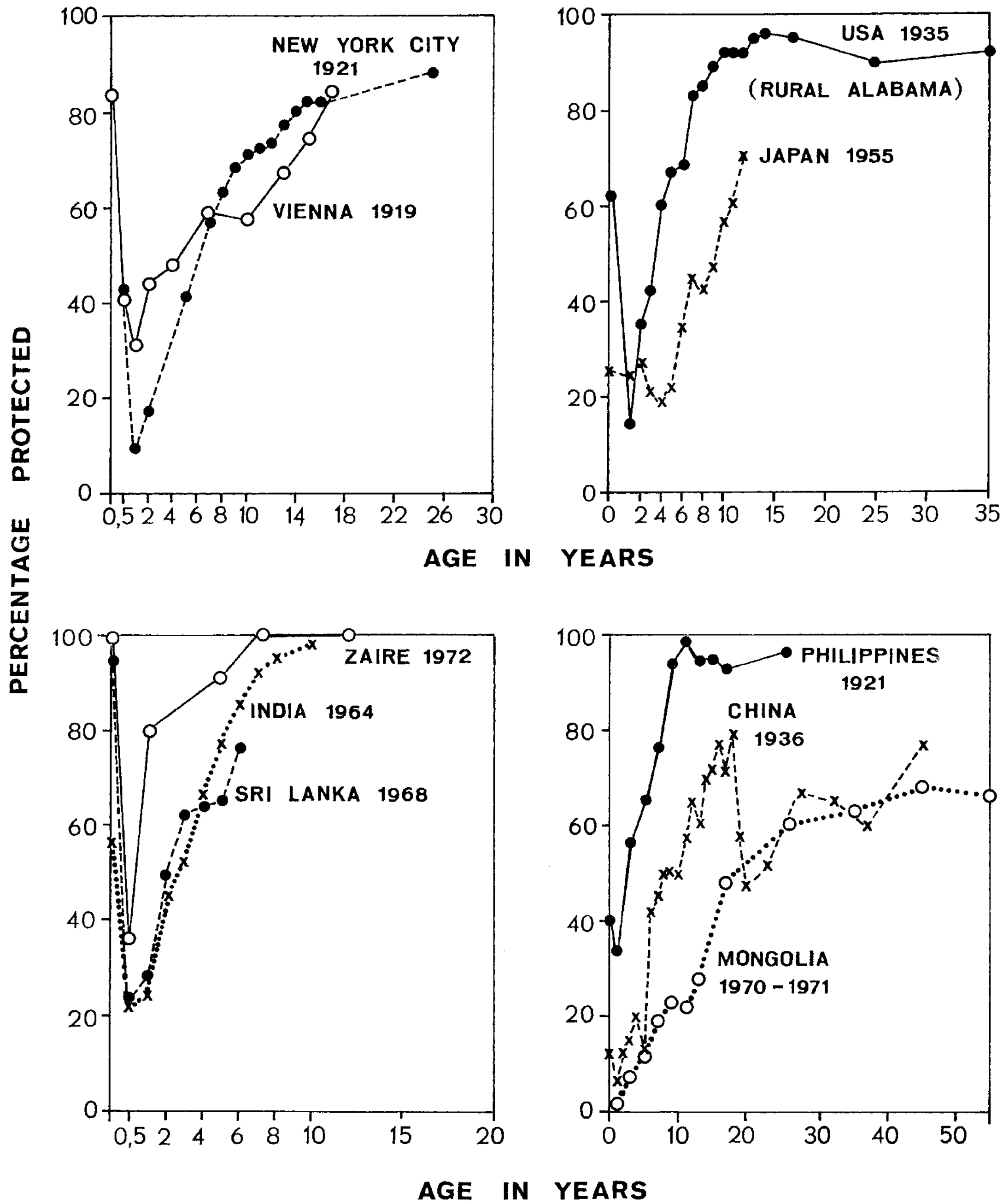

Figure 1. % of population with immunity against diphtheria (negative Schick test results) in New York, 1921; Vienna, 1919; Alabama (United States), 1935; Japan, 1955; and several developing countries, 1921–1972. Data are according to [16] for Vienna, [17] for New York City, [18] for India, [19] for Japan, [20] for Zaire, [21] for India, [22] for Sri Lanka, [23] for Philippines, [24] for China, and [25] for Mongolia.

children <15 years of age. This classic pattern of diphtheria cases was seen in many countries, including the United States in 1908–1934 [48], Germany in 1929–1931 [49], and England and Wales in 1936–1937 [50].

Shifts in the age distribution of diphtheria cases has usually been explained by the impact of immunization. However, historical data show that a shift of the disease to older ages began before mass immunization was introduced. In Cracow, Poland, children <5 years of age accounted for 76% of diphtheria cases in 1889–1909 but only 43% in 1930–1932, without any immunization program [51].

Many European countries experienced diphtheria outbreaks during World War II [2] (table 2), and it was estimated that in 1943 alone, there were a million cases of diphtheria in Europe, with ~50,000 deaths [53]. Changes in the age distribution have been observed in many countries. In The Netherlands [54, 55],

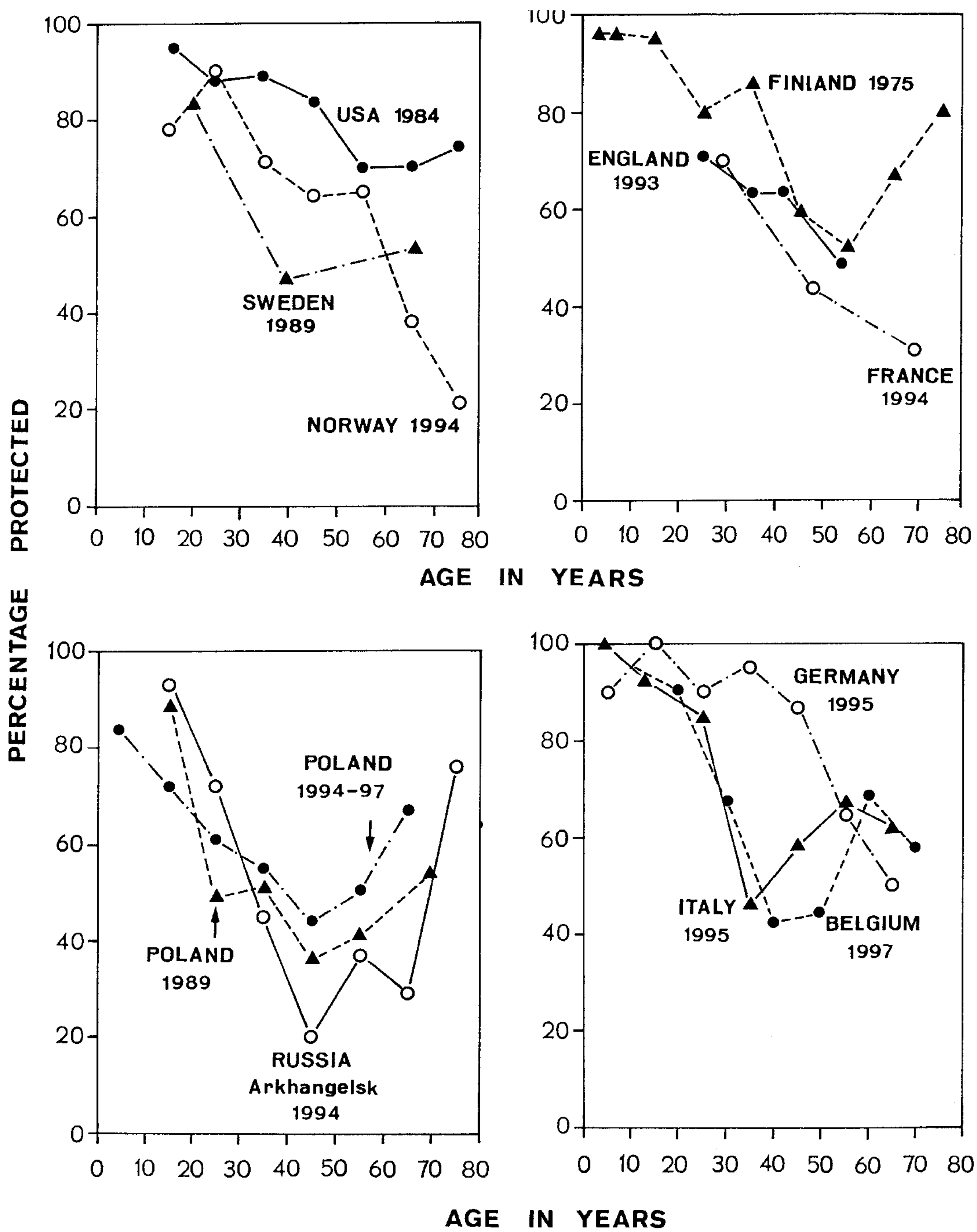

Figure 2. Immunity against diphtheria by age in several European countries and United States, 1975–1997. Data are according to [26] for USA, [27] for Sweden, [28] for Norway and Russia, [29] for Finland, [30] for England and Wales, [31] for France, [32] and [33] for Poland, [34] for Germany, [35] for Italy, and [36] for Belgium.

Norway [56], and Denmark [57], a sharp shift toward infection in older persons was seen in the 1940s. In The Netherlands, the proportion of diphtheria cases in persons >18 years of age rose from 6% in 1930 to 37% in 1944 [54].

In 1944, an epidemic of diphtheria started in Copenhagen. Of 2200 cases, 1500 (68%) were among adults. This outbreak may have been the result of a documented fall in immunity to diphtheria in adults in Copenhagen during the late 1930s, which was thought to have been due to a period when the incidence of diphtheria was low [57].

The most interesting changes occurred in Germany, where diphtheria was endemic before World War II and where an

Table 2. Number of reported diphtheria cases in several European countries, 1937–1945, according to [52].

Year	Denmark	France	Germany	The Netherlands	Norway	Sweden
1937	1348	19,187	146,733	1068	417	299
1938	870	16,800	149,490	1272	190	107
1939	1106	14,019	143,585	1273	71	188
1940	860	13,568	138,397	1730	149	290
1941	917	20,018	173,161	5437	2609	252
1942	1661	31,466	237,037	19,407	8349	1285
1943	2527	46,539	238,409	56,790	22,787	2496
1944	3333	40,230	—	60,226	—	4520
1945	—	—	—	49,730	—	—

alarming rise in the incidence of diphtheria was seen beginning in 1941 (table 2). Frequent references were made to the spread of malignant diphtheria in Germany in the early 1940s, the course of which was so rapid that serum therapy, even at a very early stage of disease development, had no effect [53, 58]. Unexpectedly, the proportion of adult patients rose concomitantly with the overall rise in diphtheria incidence (table 3). In 1943, more than half of the diphtheria cases reported were among adults [59–61]. This was a clear change in the age distribution of diphtheria patients in Germany from the beginning of the twentieth century, when only 1%–2.5% of diphtheria cases were among adults. Furthermore, among all diphtheria deaths reported, those involving adults also increased (from 12% in 1939 to 48% in 1943) [60].

As pointed out by Stowman [53], diphtheria was also an important cause of death in the German army, particularly as a complication of chest wounds and typhus. Stowman did not try to explain the reason(s) for the age shift among diphtheria cases, although data were given as evidence for the efficacy of prophylactic vaccination in childhood. However, the data did not support the conclusions because the total number of diphtheria cases in children increased considerably [60, 61]. In addition, the extent of vaccination against diphtheria during World War II was probably too small to change the age distribution of cases.

All these observations suggest that changes in the age distribution of diphtheria cases resulted from factors other than vaccination. Socioeconomic factors, such as a general increase in the standard of living, smaller families, and less overcrowding, created an environment in which children were not subjected to the same intensity of infection in their preschool years as they had been previously. On the other hand, increasing enrollment in schools, summer camps, and meetings of children, adolescents, and adults from different neighborhoods and social backgrounds probably contributed to wider circulation of *C. diphtheriae* within these age groups. Likewise, migration and displacement of many people during World War II probably enhanced the circulation of diphtheria organisms and contributed to the shift toward more adult cases [15]. In many areas of Germany late in World War II, conditions were far from normal. People were at work during the day and in overcrowded bomb shelters at night. They were under constant stress, which was reinforced by shortages of food, water, and electricity. Some of these conditions enhanced the transmission of infection.

Recent outbreaks of diphtheria in Europe and the United States have occurred in poor, socioeconomically disadvantaged groups living in crowded conditions. Crowding and poor personal hygiene may contribute to transmission and an increase in diphtheria infections. Between 1984 and 1986, socioeconomic factors played an important role in a Swedish epidemic, which mainly affected users of drugs and alcohol [62, 63]. An epidemic of diphtheria that occurred in the United States in the early 1970s mainly affected adults from low socioeconomic groups who were heavy alcohol users [64]. The role of cutaneous diphtheria has been emphasized by several diphtheria outbreaks in the United States among homeless alcoholic men and impoverished groups [65, 66].

Changes in the Epidemiology of Diphtheria in Developing Countries

Changes in the epidemiology of diphtheria are also occurring in developing countries. In such countries, a high rate of skin infections caused by *C. diphtheriae* creates a primary reservoir of diphtheria organisms, and the circulation of *C. diphtheriae* organisms still appears to be an important factor in the early development of natural immunity against diphtheria. However, the epidemiologic patterns of diphtheria may be changed by (1) successful immunization programs (in operation for >1 decade) among children, (2) socioeconomic changes (including migration from rural to urban areas and sociocultural changes with improving hygiene), and (3) changing lifestyles. With these changes, diphtheria can emerge as an epidemic disease, with more serious forms of the disease attacking older children, adolescents, or adults. As an example, diphtheria outbreaks in developing countries in the last 2 decades document a shift in age distribution similar to the shift witnessed in industrialized countries 30–40 years ago. The shift to older age groups seems to occur in two stages: In the first stage, the disease mainly attacks schoolchildren (Jordan 1977–1978, Algeria 1993–1996), and in later stages, the age distribution shifts to adolescents and young adults (Jordan 1982–1983, Lesotho 1989, China 1988–1989). These outbreaks have been characterized by high case fatality rates, a large proportion of patients with compli-

Table 3. Percentage of diphtheria cases in persons >15 years old in select German cities, 1938–1943.

	% of cases in			
Year	Frankfurt men [58]	Berlin [59]	Potsdam [60]	Wilhelmshaven [61]
1938	6.0	—	—	26.7
1939	—	18.3	32.0	—
1940	21.0	20.8	34.0	—
1941	—	25.0	31.0	48.8
1942	30.0	31.6	39.0	59.9
1943	—	54.0	61.0	—

Table 4. Age distribution (in %) of diphtheria cases in recent diphtheria outbreaks in developing countries.

Age (years) group	Country: Yemen, 1981–1982	Jordan 1977–1978	Jordan 1982–1983	Sudan 1978	Sudan 1988	Lesotho, 1989	China, 1988–1989
0–4	67	44	9	50	19	6	10[a]
5–9	28	37	11	39	52	9	
10–14	3	15	14	11	25	38	12[a]
15–19	1	—	17	—	3	27	9[a]
20–29	—	4	31	—	—	10	35
30–39	—	—	14	—	—	10	29
>40	—	—	3	—	—	—	6
Total no. of cases	149	27	36	107	209	68	103
Case fatality rate (%)	14	29	6	21	3	22	2

NOTE. Data according to [67] for Yemen, [68] and [69] for Jordan, [70] for Sudan, [71] for Lesotho, and [72] for China.
[a] Age groups 0–7, 8–15, 16–20.

cations, and the occurrence of the disease in both young and older age groups [15]. A high-incidence outbreak (118/1000 population) reported in preschool children in Yemen (table 4) and diphtheria outbreaks in Jordan and Sudan demonstrated these changing age patterns. Outbreaks in Lesotho and Algeria occurred after periods of high immunization coverage. In a province of China, after a period of low incidence (3 years with no diphtheria cases), an outbreak occurred with 70% of cases in persons >20 years of age (table 4).

In a diphtheria epidemic in Algeria [73] and in Ecuador [74], most cases were reported among older children, adolescents, and young adults.

Unanswered Questions

There are many unanswered questions with respect to the causes of the resurgence of diphtheria epidemics, the shift in the age of patients, and the mechanisms of acquiring immunity through natural infection in adults.

In Copenhagen, diphtheria was a rare disease between 1937 and 1941, but in 1943, a severe diphtheria epidemic occurred among adults. A comparison of immunity levels among adults in 1937 and 1944 did not show marked differences [75], which means that 1 year after a severe outbreak of diphtheria, natural immunity among adults in Copenhagen did not increase significantly.

Similar observations were made in Bergen, Norway, where a diphtheria epidemic occurred at the end of 1941 (apparently introduced by occupying German troops who arrived in April 1940). The epidemic reached its peak in 1943–1944, when the incidence ranged between 4.77 and 4.94 per 1000 inhabitants. Other features of the epidemic included a shift from the mitis to the gravis type of *C. diphtheriae,* an increase in the case fatality ratio (from 2.4% to 5.8%), and a shift of the age distribution of diphtheria cases toward older children [56].

Three to 4 years after the epidemic's peak, the proportion of immune persons was low, and data from 3 groups (nonvaccinated healthy persons, nonvaccinated persons who had had diphtheria, and vaccinated healthy persons) suggest that the process of acquiring natural immunity through contact with *C. diphtheriae* was much less effective than immunization (table 5).

The question also arises as to why adults in Germany did not acquire natural immunity, despite an apparently dense circulation of *C. diphtheriae.* A similar question can be posed concerning why the percentage of immune persons remained low in Norway and Denmark a few years after a severe epidemic of diphtheria. The issue of diphtheria immunity is usually looked upon as mainly a serologic problem. However, other factors may play a role in the process of acquiring natural immunity against diphtheria, including unfavorable conditions for the growth of invading diphtheria organisms on the mucosa of the upper respiratory tract (e.g., an antagonism of existing bacterial flora with diphtheria organisms). Many of these questions remain unanswered.

While incompletely understood, the reasons for the recent diphtheria epidemic in the NIS are likely to have included decreasing immunization coverage among infants and children, a large gap of immunity among adults, the delay of aggressive antiepidemic measures, large population movements, and the lack of adequate supplies for prevention and treatment in most affected countries [2–4, 6].

Why has not diphtheria spread to other countries given that similar immunity gaps exist among adults? The recent epidemics

Table 5. Percentage of persons, by age, with protective levels of diphtheria antibody just after diphtheria epidemic, Bergen, Norway, 1947–1949, according to [56].

Age (years)	% of persons with diphtheria antibody >0.01 IU/mL: Healthy persons, unvaccinated	Persons with history of diphtheria, unvaccinated	Healthy persons, vaccinated
<30	22.1	61.9	95.5
30–50	34.3	52.5	88.6
50–70	56.6	55.5	88.2

seem to confirm the importance of children in the epidemic process: In countries with high vaccination coverage among children, an imported source of infection usually produces an index case of diphtheria without any further spread of the disease [76].

Different modes of infection may have applied in the NIS. Massive migration and large numbers of homeless people facilitated the spread of diphtheria organisms. Many adult patients were alcohol users and belonged to low socioeconomic groups. The stress and anxiety that followed the collapse of the Soviet Union and difficulties in day-to-day life may have contributed to the development and maintenance of the diphtheria epidemic.

Conclusion

The recent epidemic in Russia and other NIS countries reminds us that diphtheria is still a dangerous disease and that there is still much to learn about its epidemiology. Characteristics of the NIS epidemic can be used to predict how future diphtheria epidemics might spread: (1) There was a high proportion of infected adults, (2) the disease initially involved persons in urban centers and progressively spread to rural areas, and (3) there was a transition from an initial amplification of disease within groups with high rates of close contacts in focalized, clearly distinguished outbreaks to a more generalized epidemic. The history of the NIS epidemic provides an important message on the importance of quick and adequate control measures and the need for maintaining immunity in adults. However, many questions, remain unanswered about the role of socioeconomic factors and hygiene conditions in the initialization, buildup, and spread of the epidemic and about the mode of acquiring natural and artificial immunity under unfavorable living conditions.

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