Resurgent diphtheria – are we safe?

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Diphtheria, one of the major causes of morbidity and mortality in the past, seemed nearly eliminated from industrialized countries, thanks to improved hygienic conditions and large scale vaccinations. In 1990, a large epidemic started in Eastern Europe, mainly in Russia and Ukraine, with over 70 000 cases reported within a 5 year period. The main factors leading to the epidemic included low immunization coverage among infants and children, waning immunity to diphtheria among adults, and profound social changes in the former Soviet Union. The possibility of new virulence factors in the epidemic strain has not yet been ruled out. Even though immunity among adults is far from complete in Western Europe, the epidemic did not spread there. The main reason for this might be the good immune status of children and lack of social turbulence favouring the spread of infection. Several countries have also taken preventive measures, which may also have played a role in protection against the potential epidemic.

Diphtheria is caused by Corynebacterium diphtheriae, a Gram-positive bacillus. Man is the only reservoir of the infection, which is usually spread by droplet secretions from the nose and throat. Clinical manifestations vary from asymptomatic carriage and mild cutaneous infection to severe inflammation of the upper respiratory tract. Widespread damage to several organs, including the heart and nervous system, is caused by the potent exotoxin of the organism. Toxigenicity is correlated with infection of C. diphtheriae by a temperate phage, and lysogenization of a nontoxigenic strain with phage carrying the toxin gene will convert it to a toxigenic state. Although non-toxigenic strains are also able to cause invasive infections and small epidemics, they are beyond the scope of this review.

Epidemics of diphtheria have been known for 2500 years. Progress in prevention was achieved when immunity to diphtheria could be induced by the injection of a mixture of diphtheria toxin and antitoxin or, more recently, with diphtheria toxoid vaccine. The success achieved in prevention was so great that a modern textbook of infectious diseases states 'It [diphtheria] has gone from a major health problem to a medical

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... curiosity within recent memory, and stands as a shining example of what can be accomplished with vigorous public health control measures, based on the results of solid scientific investigation. Recent experiences have demonstrated that resurgence of this curiosity can still cause public health problems.

Changes in the occurrence in the 20th Century

Diphtheria used to be one of the major causes of death of children a century ago. Even in the 1920s, the incidence in the US and Canada was approximately 150 cases per 100,000 population, but decreased to 10/100,000 in the 1940s. Following the introduction of immunisation, the yearly number of notified cases shrank to single figures in most Western countries. In the US, a total of 1288 cases were reported during 1971-1981, compared to only 40 cases in 1980-1993. In England and Wales, there were 800,000 notifications of diphtheria during 1920-1934 with 50,000 deaths. The number of cases decreased from over 40,000 in 1940 to 37 in 1957, and during the period of 1970-1994 only 124 cases were identified. In some countries, including Finland and Sweden, decades passed without any cases after implementation of diphtheria vaccinations in the 1950s. Reduction in the number of diphtheria cases has also taken place in the developing world, but the cutaneous forms of the C. diphtheriae infection especially still remain endemic in several tropical countries.

Factors leading to the start of diphtheria epidemics are poorly understood. The last major epidemic in Europe, before the current one, occurred in the 1940s. In 1943, the annual incidences per 100,000 population were as high as 212 in Germany, 760 in Norway and 622 in The Netherlands. It has been estimated that, in 1943, there were 1,000,000 cases and 50,000 deaths due to diphtheria in Europe. Limited epidemics have thereafter been reported both in developing (including China, Tajikistan, Ecuador, Jordan, Lesotho, Sudan, Yemen and Algeria) and industrialized (US, Sweden, Germany) countries. These epidemics have all been local and relatively small; numbers of cases have varied from a few to a few hundred. Carriage rate of C. diphtheriae, even in the proximity of the patients, has been low, and no significant spread of the infection has occurred in the general population.

Recent epidemic in the former Soviet Union

Since 1990, a massive epidemic has prevailed in Eastern Europe, mostly in the Russian Federation, Ukraine and their neighbouring countries. A
smaller epidemic occurred previously in 1983–1985, when the annual number of cases in the Soviet Union exceeded 1400 – being less than 200 in preceding years\(^7\). After a few years of low incidence, rates per 100 000 population started to increase from 0.5 in 1990 to 10.2 in 1993, 26.9 in 1994 and 24.2 in 1995 (Infectious Disease Statistics. The State Committee for Sanitary and Epidemiological Surveillance of the Russian Federation). Especially in large cities, the rates were high (St Petersburg, 52.5/100 000 and Moscow, 47.1/100 000). In some areas the incidence rate even exceeded 100/100 000. Over 63 000 cases were reported from Russia in 1990–1994\(^7\). Thereafter, the epidemic started to decline and, in 1996, the incidence was only 9.2/100 000.

Another country suffering badly from the epidemic is Ukraine. The annual number of diphtheria cases remained below 100 until the end of 1980s, but increased rapidly thereafter. The incidence rates increased from 0.1/100 000 in 1989 to 5.7 both in 1993 and in 1994. The total number of cases in Ukraine between 1990 and 1994 has been estimated at nearly 9,000\(^7\). Reflections of the epidemic can also be seen in other countries close to Russia and Ukraine, although the numbers are smaller. In 1994, Belarus reported 230 cases (incidence: 2.5/100 000), Estonia 7 (0.4), Latvia 250 (9.6), Lithuania 31 (0.3), and Moldova 372 cases (8.6/100 000)\(^1\). Case fatality rates in this epidemic ranged from 3% to 23% in different countries\(^1\).

Features that might be important in understanding the dynamics of the epidemic and its prevention have been studied\(^1\). The most important is the high percentage of adults, 60–77% of cases. This is in contrast with the experience from the prevaccination period, when the corresponding figure used to be below 30%. Certain groups at increased risk were suggested: medical staff, teachers, vendors, transport employees, food handlers, and military personnel\(^7\).

No significant spread has occurred outside the countries of the former Soviet Union. The European Union countries reported only a few cases of diphtheria during the period of this epidemic\(^1\). In 1990–1996, there were 27 cases in Germany, 33 in the UK, 3 in Belgium, 10 in Finland, 3 in Greece, 4 in Italy, 2 in The Netherlands and 3 in Portugal. 23 of the 85 cases in EU countries could be linked epidemiologically to Eastern Europe\(^1\). None of the other EU countries reported cases in this period.

**Molecular epidemiology of *C. diphtheriae***

Exotoxin is considered as the primary virulence factor of *C. diphtheriae*. Besides its association with pathogenicity, no other major virulence factors have thus far been identified. Little is known about differences between strains in their ability to invade or colonise epithelial cell surfaces.
Toxigenic strains seem to have a selective advantage over nontoxigenic strains in unimmunized populations because diphtheria toxin causes local tissue destruction at the site of membrane formation\textsuperscript{17}, which may promote multiplication and transmission of the bacterium. In immunized individuals, toxigenic strains cannot benefit from this, and the metabolic cost of production of toxin may become significant. This could explain why wide use of the toxoid vaccine leads to diminished circulation of toxigenic strains of \textit{C. diphtheriae}\textsuperscript{2}. In addition to disappearance of disease, vaccination also seems to result in diminishing the frequency of carriers.

It has been suggested that naturally occurring variants of \textit{tox} and its regulatory gene (\textit{dtxR}) might be associated with increased or decreased toxin production\textsuperscript{18}. Changes in the \textit{tox} gene might also, in principle, lead to vaccine escape by causing alterations in epitopes recognised by antibodies elicited by vaccination, and could, thus be related to resurgence of diphtheria. Based on this assumption, Nakao et al\textsuperscript{18} analysed toxigenic \textit{C. diphtheriae} strains derived from the Russian epidemic for heterogeneity of the toxin gene and its regulatory element. They observed that these appeared to be highly conserved among the strains, suggesting that the vaccine efficacy should also be sustained.

Several different typing techniques have been used to study the epidemiology of \textit{C. diphtheriae}. Traditional methods include biotyping and phage typing, which both have limitations and disadvantages\textsuperscript{19}. The molecular techniques include restriction enzyme digestion of the \textit{C. diphtheriae} genome and hybridization of Southern blots with different probes: rRNA\textsuperscript{5,6,20}, an insertion element\textsuperscript{21,22}, diphtheria toxin, and corynephage \(\beta\) and its attachment site\textsuperscript{3}, or pulsed field gel electrophoresis\textsuperscript{5,6}. In addition, multilocus enzyme electrophoresis has been evaluated for genotyping purposes\textsuperscript{5,6}.

The application of molecular methods has improved our knowledge of the genetic diversity of circulating diphtheria strains, and has defined certain outbreak strains. Based on recent studies, we know that a distinct clonal group of \textit{C. diphtheriae} emerged in Russia at the onset of the current epidemic. These strains have also been found in surrounding countries as well as among imported cases in Western countries\textsuperscript{23}. During the pre-epidemic period, the diversity of genotypes was much more notable. The Russian epidemic strains are also distinct from strains collected in other recent outbreaks in Sweden, the US and France\textsuperscript{6,22}. The reasons for the emergence of this particular epidemic clone, as well as its pathogenic significance, are unknown. Future molecular studies addressing the potential virulence factors within this strain are thus needed.

**Clinical characteristics**

In order to analyse information about potential changes in the clinical picture of diphtheria, we compared two large, hospital-based archives,
one collected in the 1940s from Los Angeles County Hospital\textsuperscript{24}, the other in the 1990s from Botkin's Hospital in St Petersburg\textsuperscript{25}. The prevailing \textit{C. diphtheriae} strain in both studies was of biotype \textit{gravis}. Possible sources of bias in the comparison relate to the differences in criteria for hospitalization, the use of diphtheria cultures in clinical practice, antimicrobial treatment, and the vaccination status of the population: in St Petersburg vaccine coverage was 70–90\%, but was apparently far lower in the 1940s in Los Angeles. The biggest difference between the cases was in the age distribution: one-third of patients in the US study were adults, whereas in Russia, all patients were above 15 years. The proportion of alcoholics in each study is not known. With all these reservations, diphtheria seems to have preserved its clinical spectrum and outcome during the last 50 years (Table 1). Thus, there is no evidence that changes of the disease itself have contributed significantly to the Russian epidemic.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Percentages of the clinical distribution and outcome of respiratory tract diphtheria in the 1940s in the US\textsuperscript{24} compared with that in the 1990s in Russia\textsuperscript{25}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical type</td>
<td>USA, 1940s</td>
</tr>
<tr>
<td></td>
<td>(n = 1372)</td>
</tr>
<tr>
<td>Anatomical distribution</td>
<td></td>
</tr>
<tr>
<td>Tonsillopharyngeal</td>
<td>71</td>
</tr>
<tr>
<td>Secondary laryngeal or tracheobronchial</td>
<td>19</td>
</tr>
<tr>
<td>Other upper respiratory tract</td>
<td>10</td>
</tr>
<tr>
<td>Toxicity by clinical criteria</td>
<td></td>
</tr>
<tr>
<td>Toxic forms (&quot;bull neck&quot;)</td>
<td>13</td>
</tr>
<tr>
<td>Case fatality rate (CFR)</td>
<td></td>
</tr>
<tr>
<td>Overall CFR</td>
<td>9.6</td>
</tr>
<tr>
<td>Nontoxic forms</td>
<td>6.8</td>
</tr>
<tr>
<td>Toxic forms</td>
<td>32</td>
</tr>
</tbody>
</table>

**Spread in close contacts**

Experience from epidemics in military institutions and schools support the view that diphtheria is spread through droplets from respiratory secretions\textsuperscript{26}, outbreaks among alcoholics have been interpreted to suggest spread also from food or dishes\textsuperscript{27}.

Diphtheria seems, however, not to be a highly contagious disease in modern Western society. Since the epidemic started in Russia, over 3 million trips have been made from Finland to St Petersburg and its surroundings. Among the visitors, only 10 cases of diphtheria have occurred (Table 2). Three of them (cases 1, 8 and 9) have had severe infection, all were middle-aged men with sexual contacts with local people. None of the 10 patients transmitted the infection further in
Table 2 Diphtheria cases in Finland since 1993

<table>
<thead>
<tr>
<th>Case</th>
<th>Date (year/month)</th>
<th>Age/sex of patient</th>
<th>Clinical picture</th>
<th>Treatment</th>
<th>Complications</th>
<th>Strain characteristics (biotype/toxin production/genotype)</th>
<th>Origin of infection in Russia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1993/4</td>
<td>44/M</td>
<td>Severe tonsillitis</td>
<td>ab</td>
<td>Neurological</td>
<td>gravis/tox*/epidemic clone</td>
<td>St Petersburg</td>
</tr>
<tr>
<td>2</td>
<td>1993/4</td>
<td>43/M</td>
<td>Carrier</td>
<td>ab</td>
<td>None</td>
<td>gravis/tox*/epidemic clone</td>
<td>St Petersburg</td>
</tr>
<tr>
<td>3</td>
<td>1993/10</td>
<td>46/M</td>
<td>Tonsillitis</td>
<td>ab</td>
<td>None</td>
<td>gravis/tox*/non-epidemic</td>
<td>St Petersburg</td>
</tr>
<tr>
<td>4</td>
<td>1994/12</td>
<td>42/F</td>
<td>Tonsillitis</td>
<td>ab+at</td>
<td>None</td>
<td>gravis/tox*/non-epidemic</td>
<td>Moscow</td>
</tr>
<tr>
<td>5</td>
<td>1995/1</td>
<td>2/F</td>
<td>Mild tonsillitis</td>
<td>ab</td>
<td>None</td>
<td>gravis/tox*/non-epidemic</td>
<td>Moscow</td>
</tr>
<tr>
<td>6</td>
<td>1995/9</td>
<td>51/M</td>
<td>Tonsillitis</td>
<td>ab+at</td>
<td>None</td>
<td>gravis/tox*/epidemic clone</td>
<td>Sortavala</td>
</tr>
<tr>
<td>7</td>
<td>1995/11</td>
<td>45/M</td>
<td>Carrier</td>
<td>ab</td>
<td>None</td>
<td>gravis/tox*/epidemic clone</td>
<td>St Petersburg</td>
</tr>
<tr>
<td>8</td>
<td>1996/1</td>
<td>57/M</td>
<td>Severe tonsillitis</td>
<td>ab+at</td>
<td>None</td>
<td>gravis/tox*/epidemic clone</td>
<td>Wiborg</td>
</tr>
<tr>
<td>9</td>
<td>1996/9</td>
<td>45/M</td>
<td>Severe tonsillitis</td>
<td>ab+at</td>
<td>Death</td>
<td>gravis/tox*/epidemic clone</td>
<td>Wiborg</td>
</tr>
<tr>
<td>10</td>
<td>1996/11</td>
<td>37/M</td>
<td>Tonsillitis</td>
<td>ab</td>
<td>None</td>
<td>gravis/tox*/epidemic clone</td>
<td>Tver</td>
</tr>
</tbody>
</table>

ab = antimicrobial treatment, at = antitoxin treatment

Finland. The close contacts of the index cases have consistently been culture negative. Altogether, 67 health care workers with exposure to diphtheria patients’ saliva have been investigated in Finland during the Russian epidemic: all have been culture negative.

Immunity to diphtheria in the population

Maternal antibodies provide immunity to diphtheria during the neonatal period, but, in the absence of immunization, decline to nonprotective levels within a few months. Thereafter, the proportion of immune children gradually increases, either as a consequence of natural exposure to C. diphtheriae, or following vaccination. Three doses of the toxoid vaccine induces sufficient amounts of antitoxin antibodies to protect against disease in 94–100% of the vaccinees. One year after the primary vaccination series, 75–97% of children have protective titres of diphtheria antibodies. In Denmark, 22% of those immunized had a titer below the protective level 25–30 years after the primary vaccination series; persistence was longer in people who were immunized when diphtheria was prevalent.

Means of antibody titres might, however, underestimate the immunity of the population. As a protein antigen, diphtheria toxoid induces also immunological memory, which leads to a vigorous antibody response after contact with the antigen. Whether memory plays any significant role in protection, is not known. On the other hand, anecdotal evidence from Russia seems to suggest that the duration of effective immunity may be shorter in individuals intensively exposed to C. diphtheriae.
Resurgent diphtheria

The protective efficacy of diphtheria toxoid vaccination is high, though not 100%. In the current epidemic, efficacy estimates in two retrospective case-control studies were 82% and 96% after three doses of the Russian vaccine\textsuperscript{15}. During an earlier epidemic in the Yemen, the protective efficacy of another vaccine was determined to be 87%\textsuperscript{30}. The disease in previously immunized individuals is milder and less likely to be fatal\textsuperscript{8,31}.

In Russia, infant vaccination coverage decreased from 80% in the 1970s to 68% by 1990, and in many urban areas it fell to below 20%\textsuperscript{15}. The drop was mainly due to negative or negligent attitudes towards vaccination and partly, also, to irregular supplies of vaccines. It should also be noted that in the early 1990s some children received their primary immunizations with diphtheria vaccine that had a reduced amount of diphtheria toxoid (adult Td vaccine was used instead of the DPT vaccine)\textsuperscript{7,14}.

Galazka and Robertson recently reviewed European studies on population immunity\textsuperscript{28}. The overall proportion of adults with antibody titers below the level considered to be protective varied from 23% in Finland, to 26% in Denmark, 38% in the UK, 49% in France, and to 53% in Poland. Understandably, there are subgroups with even lower percentages of protected individuals. The lowest levels of diphtheria antibodies were seen in people aged 20–40 years in Germany, Moldova and Russia, those aged 40–50s year in Poland, and those over 50 years of age in Denmark, England, Finland and Sweden\textsuperscript{28}. Outbreaks may start in subgroups, even though the community as a whole seems to be reasonably well protected.

It was claimed in the medical literature that the spread of diphtheria in the community is prevented if 70–80% or more of the population is immune\textsuperscript{8}. A recent WHO meeting concluded that to achieve the elimination of diphtheria, a minimum immunization coverage rate of 90% in children and 75% in adults is required\textsuperscript{15}. If these figures are true, and population immunity is the only decisive factor in protection against epidemics, Western European countries should be quite vulnerable to diphtheria epidemics.

Social factors

Chen et al\textsuperscript{8} analyzed diphtheria outbreaks in the US in 1971–1981, and concluded that poor socio-economic conditions, incomplete immunization status and high attack rates for American Indians characterized most of them. Sweden experienced 2 small outbreaks in the 1980s: one in Gotenburg with 13 clinical cases\textsuperscript{11}, and another in Stockholm with 8 cases\textsuperscript{27}. A substantial proportion of the patients in these outbreaks were middle-aged homeless men abusing alcohol\textsuperscript{8,11,27,32,33}. 

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Several indicators in Russia suggest that unfavourable changes in society have occurred, parallel to or preceding the epidemic\textsuperscript{34}. Life expectancy for men fell by 6.2 years between 1990 and 1994. In addition, a clear increase in alcohol consumption (to 145 liters per inhabitant), and signs of wide scale alcohol abuse, are clearly seen: mortality rates in alcohol-related diseases increased over 5-fold in 1987–1994\textsuperscript{34}.

In connection with the disruption of the Soviet Union, considerable population migration has occurred, especially into big cities. It is easy to understand that movement of an estimated 1–2 million people leads to temporary housing, crowded living and less than optimal hygienic conditions. Movements of military staff throughout the large country may also have played an important role in spreading the epidemic. The number of cases tended to be high among the military personnel and among the members of paramilitary units, especially in the areas where high numbers of troops were stationed\textsuperscript{35}.

**Discussion**

In spite of the cyclic occurrence and frequent epidemics of diphtheria in past history, the current Eastern European epidemic is exceptional. It is the first major epidemic during the vaccination era, taking place in countries where diphtheria toxoid vaccine has been used successfully for decades, and has spread to a large area very rapidly. The main factors behind the epidemic seem to be low immunization coverage rates among infants and children, waning immunity to diphtheria among adults, and large movements of the population in the Soviet Union\textsuperscript{7}. Whether the epidemic strain has new virulence properties, that have been critical in its spread, remains to be evaluated.

In the prevaccine era, children were susceptible to diphtheria but adults were immune because of exposure to circulating bacteria which provided natural boosting of immunity. Large-scale immunization has resulted in good immunity of children and, subsequently, diminished rates of both symptomatic disease and asymptomatic carriage of *C. diphtheriae*. Before the epidemic, the circulation of diphtheria bacteria in the Russian population was believed to be at a low level, and the majority of the strains circulating were nontoxigenic. This apparent success of the prevention programme might have paradoxically contributed to the spread of the current epidemic. This has led to the situation where the maintenance of immunity is dependent only on vaccination\textsuperscript{28}. In the future, childhood immunization programmes should, therefore, be combined with active attempts to sustain adult immunity by booster vaccinations.
The following actions have been recommended in countries where diphtheria epidemics occur: rapid immunization of groups at risk, prompt diagnosis and proper management of diphtheria patients, and rapid identification and effective management of close contacts\(^{13,15,36-39}\). Mass immunization covering all adolescents and adults should be carried out in areas with diphtheria incidence rates greater than 3.5/100 000. In areas where the rate is lower, immunization could be directed to high-risk groups only\(^{36}\). The countries suffering from the current epidemic have already implemented this action plan, and morbidity figures are now declining.

Why has the epidemic not spread to Western European countries, although significant immunity gaps exist among adults\(^2\). The first major difference is good immunity of the childhood population, due to high vaccination coverages. It may be that contacts between susceptible children are essential for a major epidemic to start, and insufficient immunity among adults is a facilitating factor for its spread. Another major difference between the endemic and nonendemic area is in the social conditions. The turbulence in the former Soviet Union – including massive movements in the population, and increased alcoholism connected often with poor nutritional status – seems to have created ideal conditions for the spread of \textit{C. diphtheriae}\(^{38}\). A third factor is that countries outside the epidemic areas have also had time to increase their preparedness for a possible epidemic. Targeted or mass vaccinations have been implemented, diagnostic capabilities have been updated, and alertness among the medical community for early diagnosis of patients has been increased. Public health workers have a great temptation to think that these actions have had an impact in the prevention of the resurgence of diphtheria.

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