RAPID RISK ASSESSMENT

A case of diphtheria in Spain

15 June 2015

Main conclusions and options for response

The detection, management and public health response to the first case of diphtheria in Spain in nearly 30 years has highlighted challenges for preparedness against diphtheria in the European Union.

The case is a 6-year-old unvaccinated child. A case of diphtheria in an unvaccinated individual within a highly protected population is not unexpected, because vaccinated people can be asymptomatic carriers of toxigenic *C. diphtheriae.*

The challenges for diphtheria case management, preparedness and public health response experienced in Spain are shared by many EU Member States. The most urgent critical issue is the shortage of diphtheria antitoxin (DAT) for immediate use when clinicians suspect diphtheria. DAT must be given as early as possible to be effective, often on the suspicion of diphtheria before a laboratory confirmation. EU Member States have for a number of years reported difficulties with sourcing and maintaining adequate stockpiles of DAT for emergency use, a problem they share with many countries around the world. EU Member States have on occasion been forced to arrange emergency deliveries of DAT for patients with diphtheria.

Arrangements to ensure access to adequate quantities of DAT for medical management of diphtheria cases should be an integral part of preparedness for diphtheria. There is an urgent need to find solutions that will allow all EU Member States to have immediate access to DAT in case a diphtheria patient is detected.

As with other vaccine-preventable diseases, the detection of unvaccinated clusters and possible obstacles to vaccination uptake, vaccine supply and delivery should be identified in all EU/EEA Member States, and measures should be taken to improve immunisation coverage in under-vaccinated populations. In addition, surveillance systems that allow the early detection and diagnosis of sporadic diphtheria cases and outbreaks are essential.

Source and date of request

ECDC internal decision, 2 June 2015.

Public health issue

Risks to the EU related to a case of diphtheria in Spain and risk related to under-vaccination against diphtheria and shortage of diphtheria antitoxin (DAT) in the EU.

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Consulted experts

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The external experts have submitted declaration of interest statements pertaining to this risk assessment.

Disease background information

Clinical manifestations and treatment

Diphtheria is a transmissible bacterial disease primarily infecting the pharynx, larynx, tonsils and nose. Occasionally, the bacteria affects skin or mucous membranes including conjunctivae and vagina. The causative agents of diphtheria are mainly toxin-producing *Corynebacterium diphtheriae* transmitted via droplets during close contact. No significant reservoirs for *C. diphtheriae* other than humans have been identified. The incubation period for *C. diphtheriae* ranges from two to five days but can be as long as ten days [1]. Other corynebacteria, *C. ulcerans* and very rarely *C. pseudotuberculosis*, may produce diphtheria toxin, although the strains appear to belong to distinct species [2] and have different routes of transmission.

Diphtheria has a gradual onset with development of a sore throat, low-grade fever and mild exudative pharyngitis. Mild cases resemble streptococcal pharyngitis. In severe cases, pseudo-membranes start forming after 2–3 days. Pseudo-membranes are thick greyish membranes that are firmly attached to the underlying mucosa. The critical pathogenic factor for severe diphtheria disease is the exotoxin produced by toxigenic *C. diphteriae* which causes cell destruction. Upon absorption, the toxin has a predilection for the myocardium and the cells of the nervous system. Although not all *C. diphtheriae* bacteria are toxigenic, non-toxigenic strains may also cause severe disease, e.g. endocarditis.

Most infections in highly vaccinated populations are asymptomatic or result in a mild clinical course and therefore may remain undiagnosed and hence underreported. However, severe cases including two deaths have recently been reported in fully vaccinated children in Brazil, where the disease is still endemic [3].

Successful treatment of diphtheria depends on rapid administration of equine diphtheria antitoxin (DAT) in combination with antibiotics. DAT should be administered upon clinical suspicion of diphtheria as it binds to circulating toxin but does not neutralise toxin that has already bound to, or entered into, cells. DAT treatment initiated later than 48 hours after onset of systemic toxic symptoms has limited impact on the clinical outcome although DAT is, when necessary, offered at any stage of the disease [4]. Administration of DAT can cause acute and delayed hypersensitivity reactions. DAT is included in the World Health Organization Essential Medicines List for Children [5].

Antibiotic treatment, in addition to the DAT treatment, is necessary to eliminate the bacteria and prevent further spread to other susceptible individuals. Countries should follow national guidelines on case management. Most guidelines recommend treatment with benzylpenicillin (penicillin G) or a macrolide (erythromycin, azithromycin or clarithromycin) for a period of 14 days. Individuals who continue to harbour the bacteria after treatment should receive an additional course of oral erythromycin and submit a new sample for culture after completion of the course. Antibiotic resistance seems rare but strains with intermediate susceptibility to penicillin G and erythromycin have been reported [3].

Further, patients should receive immunisation with diphtheria toxoid upon recovery since natural diphtheria infection does not always confer protective immunity.

Toxigenic diphtheria is a notifiable disease in the EU [6], and Member States are expected to report new cases to ECDC as soon as they are diagnosed.

Diagnostic tests

There are no commercial tests available for the diagnosis of diphtheria. Laboratory identification and confirmation of diphtheria requires isolation of *C. diphtheriae* by culture from a clinical specimen (nasal swabs, pharyngeal swabs, or swabs from pseudo-membrane, wound or skin lesions) and toxigenicity testing. Direct and real-time polymerase chain reaction (PCR) assays can detect the *C. diptheriae* toxin gene within a few hours, but confirmation of diphtheria toxin expression must be undertaken with the Elek test. Procedures for the collection of specimens are available in the WHO *Manual for laboratory diagnosis of diphtheria* [7]. Potentially positive samples should be sent for confirmation and further biotyping to the WHO Collaborating Centre for Diphtheria in the UK (http://apps.who.int/whocc/Detail.aspx?cc_ref=UNK-194&cc_code=unk).

Outbreak control

Outbreak control calls for prompt:

- recognition, isolation and management of suspected diphtheria cases;
- identification of individuals with close contact to cases;
- assessment, testing, vaccination and monitoring of close contacts for clinical symptoms for at least seven days from possible exposure;
- treatment of contacts with a positive culture or PCR; and
- exclusion from activities likely to pose a high risk of exposure to others, particularly those with increased susceptibility.

Close contacts that have received less than three doses of diphtheria vaccine are usually offered a booster dose followed by the immunisation series recommended in the country of residence. Contacts that have received three doses or more of diphtheria vaccine usually receive a booster dose, unless the last dose was administered in the last twelve months.

Prevention through vaccination

Diphtheria toxoid vaccines were first introduced in Europe in the 1940s. Today, diphtheria toxoid vaccines are mainly available in combination with one or several antigens including tetanus, pertussis, polio, *Haemophilus influenzae* type b, and hepatitis B, depending on if the vaccine is to be used for primary immunisation or as booster doses. At least one vaccine producer (SSI) offers a monovalent vaccine containing diphtheria toxoid only for use in adolescents and adults since use of combination vaccines is limited to the younger age groups.

The vaccine effectively protects against the effects of the exotoxin produced by *C. diphtheria* and *C. ulcerans* but vaccinated individuals can still be infected by the bacteria, become asymptomatic carriers of toxin-producing strains and may transmit these to others.

All children in the EU/EEA are offered primary vaccination against diphtheria in a 2- or 3-dose schedule during the first year of life and subsequent boosters later during childhood and adolescence [8]. The reported vaccination coverage among children in the EU/EEA is > 95%, but with groups of people refraining from vaccination for philosophical or religious reasons. In addition, there are families from under-served population groups, including migrants who may not have been offered vaccination yet.

Diphtheria vaccines are effective and have essentially eliminated clinical diphtheria disease from the European region. There are unresolved issues about waning immunity and the need for booster doses. Limited data on population level immunity published in 2000 reported significant proportions of susceptible individuals particularly among adults and the elderly [9].

If adults do not have natural exposure to diphtheria-causing organisms or receive booster doses of diphtheria toxoid, their immunity induced by childhood immunisation wanes and they become susceptible to the disease [10].

Therefore, WHO recommends [11] booster doses with diphtheria toxoid approximately every 10 years throughout life and that tetanus prophylaxis following injuries should be given as a combination of diphtheria and tetanus toxoid (DT or dT).

Diphtheria epidemiology

The reported number of cases of diphtheria remains low in the EU/EEA. During 2009–2013, 102 cases of diphtheria were reported in the EU/EEA with 55 cases of *C. diphtheriae* (Table 1). There has been an increase in the number of *C. diphtheriae* cases reported at EU level since 2011 (Table 1). Latvia is the only EU Member State that reports indigenous transmission.

Table 1: Number of cases of *C. diphtheriae* and *C. ulcerans* reported in the EU/EEA, by year and country, 2009–2013

Year	2009	2010	2011	2012	2013	Total
Total number of cases reported	10	14	20	27	31	102
C. diphtheriae (n)	DE (2), SE (1), UK (2)	DE (1), LV (1), UK (1)	DE (2), FR (3), LV (6), SE (1)	DE (3), FR (2), LV (8), NL (1), SE (2)	LV (14), SE (2), UK (3)	DE (8), FR (5), LV (29), NL (1), SE (6), UK (6)
C. ulcerans (n)	FR (1), UK (2)	DE (7), FR (2), LV (1), UK (1)	DE (2), FR (2), SE (1), UK (2)	BE (1), DE (6), FI (1), FR (2), UK (1)	BE (1), DE (4), FR (6), UK (1)	BE (2), DE (19), FI (1), FR (13), LV (1), SE (1), UK (7)
Unknown type	2	0	1	0	0	3
Age range (years)	11–87	19–89	11–85	3–92	5–85	3–92

Countries reporting cases: BE–Belgium, DE–Germany, FI–Finland, FR–France, LT–Lithuania, LV–Latvia, NL–Netherlands, NO–Norway, SE–Sweden, UK–United Kingdom

In a recent European study, ten European countries each screened between 968 and 8551 throat swabs from patients with upper respiratory tract infections for *C. diphtheriae* during 2007–2008. Six toxigenic strains of *C. diphtheriae* were identified: two from symptomatic patients in Latvia and four from Lithuania (two cases, two carriers). Among the toxigenic isolates, the Sankt Petersburg epidemic clone that caused large diphtheria outbreaks in Russia and the NIS* countries in the 1990s was still in circulation [12]. Carriage rates among household contacts of a laboratory-confirmed case may be as high as 25% [13].

Event background information

On 31 May 2015, Spain reported a case of toxigenic diphtheria through the Early Warning and Response System (EWRS) and made a call to other EU Member States for support with obtaining DAT for treating the case as none was available in the country.

After Spain's notification through EWRS, the Directorate General for Health and Food Safety (DG SANTE) responded quickly. In addition, several Member States offered to provide DAT. Over the weekend of 7–8 June, DG SANTE was in close contact with Spain to explore the best available options to procure DAT, in close collaboration with other Commission services. Additionally, a request for DAT was sent to the Health Security Committee to explore availability of additional DAT in view of potential additional cases.

The case is a 6-year-old unvaccinated boy who first developed symptoms on 23 May 2015. He visited his general practitioner on 25 May and was prescribed amoxicillin. His condition worsened and he was hospitalised on 28 May. He was found upon admission to have fever, general malaise and pseudo-membranes covering the tonsils. His condition further deteriorated, and on 29 May a throat swab was sent to the National Centre for Microbiology upon clinical suspicion of diphtheria, which was confirmed on 30 May when the sample tested positive for toxigenic diphtheria by PCR. The sample was forwarded to the WHO collaborating laboratory in the UK to confirm the diagnosis with toxigenicity tests (Elek test). This confirmation was sent to Spain on 5 June. Meanwhile, the child was transferred to a tertiary care hospital in Barcelona on 31 May, where he remains in a serious but stable condition. He is being treated with antibiotics and has received DAT on 1 and 2 June. The hospital experienced difficulties in acquiring DAT. It was finally provided by France and Russia, both having stockpiles.

Both the case and his sibling were voluntarily unvaccinated. The investigation conducted has neither identified an epidemiological link to countries with endemic transmission of diphtheria nor an indigenous source of infection. The last indigenous case of diphtheria in Spain was notified in 1986.

Before developing symptoms, the boy attended a local school camp for two days on 19 and 20 May. Fifty-seven children who attended the school camp, and additional school attendees, their families, teachers and healthcare workers attending to the sick child, were identified as contacts and are currently being monitored according to the Spanish national guidelines [14]. Contacts have been vaccinated, and throat swabs for diphtheria diagnostics were obtained. The Catalan Public Health Agency is currently following between 100 and 150 individuals who have been in contact with the sick child. On 8 June, it was made public that PCR tests from eight healthy contacts of the index case harboured diphtheria bacteria expressing the toxigenic gene. Preventive measures have been taken with administration of antibiotics to prevent onset of illness and further transmission in line with national guidelines. The eight children had previously been vaccinated against diphtheria in line with Spanish vaccination recommendations. Vaccinations against diphtheria are offered at two, four and six months of age in Spain, with booster doses at 15–18 months and 13–14 years of age.

* New Independent States of the former USSR

ECDC threat assessment for the EU

The diphtheria case in Spain does not currently represent a serious cross-border threat to health in the EU. Such cases are not unexpected among unvaccinated individuals since exposure to *C. diphtheriae* occurs regularly.

Eight carriers have been identified through contact tracing. All eight children have been in close contact with the index case and were exposed to the pathogen, but did not develop the disease because they were fully vaccinated against diphtheria. They are now receiving appropriate antibiotic treatment.

Absence of vaccination against diphtheria

Even in non-endemic countries, people not vaccinated against diphtheria are at risk for developing the clinical form of diphtheria because *C. diphtheriae* may circulate in healthy vaccinated populations. Diphtheria is a life-threatening condition with a high risk of sequelae among survivors, and the only effective protection is vaccination. Families and individuals who do not vaccinate or are hesitant about vaccinations tend to cluster geographically, creating pockets of unvaccinated communities within otherwise highly vaccinated populations [15,16]. This increases the risk of developing the disease if *C. diphtheriae* would be introduced into this community. In addition, there may be population groups that are under-served and under-vaccinated and they also tend to cluster geographically [17].

Availability of DAT in EU/EEA Member States

Several countries stopped manufacturing DAT following the significant decline in incidence of the disease after the introduction of mass vaccination in Europe [18].

ECDC does not have a clear picture on the availability of DAT in EU/EEA Member States. The most recent information of relevance comes from a study conducted in 2012, which shows the range of DAT stockpiles across countries participating in the study [18].

Countries with possible indigenous cases, such as the Baltic countries, hold a stockpile at national level. However, there are several countries, including some which reported imported cases in the last five years, that do not hold a stock, or hold a stock which is close to expiring, or has expired. Some countries have mainly relied on DAT produced in Croatia, but production has been stopped and vials still available have now largely expired.

Attempts by EU/EEA governments to procure DAT from producers in Russia (www.microgen.ru), India (http://www.indiamart.com/vinsbioproducts) and Brazil (http://www.butantan.gov.br) have encountered difficulties, although occasionally DAT from non-EU suppliers has been imported for emergency use.

ECDC has received information that the Bulgarian company BulBio (http://www.bulbio.com) produces DAT for internal use, although they do not currently have stock to share.

The situation is similar in North America, where no supplier exists. In addition, there is a quality assurance issue for non-licensed pharmaceutical products. Some EU/EEA regulatory agencies work closely by testing and conducting research to analyse DAT concentrations and to assure the quality of the product.

The current lack of DAT is of great concern. DAT is needed to treat cases of diphtheria in the EU/EEA, which are rare, but still occur every year.

The scarcity of DAT stock also emphasises the importance of the maintenance of high vaccine coverage in all countries.

Clinical recognition of diphtheria

Most clinicians in the EU might lack first-hand experience of diphtheria and may not even consider diphtheria in the differential diagnosis of patients unless an outbreak has been declared or it becomes clear that the patient is unvaccinated. Delays in the recognition of symptoms can be compounded by difficulties in accessing diphtheria diagnostics.

Carriage in general EU populations

Carriage of *C. diptheriae* in unvaccinated and vaccinated healthy individuals is documented and will remain an important determinant of the risk of exposure to diphtheria. Knowledge about trends and distribution of carriage rates is important for the risk assessments but can only be obtained through repeated representative surveys [12].

Surveillance of diphtheria immunity levels

Regular determination of diphtheria toxin antibodies is of value in assessing responses to vaccination and immunisation schedule effectiveness, in determining the rates of immunity within broad populations of all age groups, as well as exploring the immune status of individuals who may be at risk of infection (i.e. travellers, physicians, lab personnel, medical risk groups, elderly people, hard-to-reach populations, etc.) [9,19].

Conclusions

This case of diphtheria in Spain has highlighted several important issues with non-vaccination, as well as the diagnosis and the treatment of cases of diphtheria in the EU. Most critical is the longstanding problem with respect to access to DAT in Europe. This problem reflects the situation in Europe as a whole, and is not specific to Spain. Although several EU Member States responded to Spain's call for support with DAT, they could mostly offer expired DAT from their own stockpiles. A similar event occurred in 2008 when it took France four days to secure DAT from Brazil for treating an acutely ill patient [18,20].

There is an urgent need to find a solution to the shortage of DAT in the EU. DAT is a life-saving countermeasure for sporadic cases and during outbreaks of diphtheria, but the window from onset of toxic symptoms to irreversible organ damage is short, which makes rapid administration of DAT essential for the outcome of individual patients. Unless healthcare providers in the EU have immediate access to DAT, there is a risk that treatment in patients with toxigenic diphtheria will be delayed. Thus, adequate quantities of DAT are essential for the medical management of suspected and laboratory-confirmed cases, both at the national and regional levels.

As with other vaccine-preventable diseases, unvaccinated clusters and possible obstacles to vaccination uptake, vaccine supply and delivery should be identified in all EU/EEA Member States. Steps should be taken to improve immunisation coverage in under-vaccinated populations.

In addition, access to appropriate diagnostic services and the maintenance of surveillance systems that allow the early detection of sporadic diphtheria cases and outbreaks are essential.

Options for reducing the risks associated with limited access to DAT in the EU

Short-term options

A range of options need to be considered for resolving the acute shortage of DAT. Decisions need to be informed by an initial assessment of the current stockpiles within the EU.

The development of an inventory of available DAT products in the EU/EEA and worldwide, which could be made available online to EU/EEA Member States, would be beneficial. It was not possible to identify an EU/EEA DAT producer with currently available stocks as part of the investigations undertaken for this risk assessment. However, four non-EU/EEA producers of equine DAT were identified; Microgen in Russia, Kaketsuken in Japan, Biofarma in Indonesia, and ViNs Bioproducts Limited in India.

Options to centrally test identified DAT products for potency and quality to support future procurement should be explored.

The role EU regulators could play in authorisation of DAT products from non-EU/EEA countries should also be explored.

Long-term options

The possibility of authorising one or several identified DAT products in the EU/EEA through the available mechanisms for central or decentralised authorisation procedures may provide a longer-term solution.

The interest of EU/EEA Member States in the joint procurement of DAT for use as an emergency stockpile should be assessed.

The provision of incentives and grants for the development and production of human DAT with a high titre of DAT antibodies or recombinant monoclonal antibodies against diphtheria exotoxin – with the aim to minimise the risk of anaphylaxis when treating patients with DAT – is also a possible option.

Options for reducing the risks associated with non-vaccination against diphtheria

A range of options need to be considered for resolving the issue of non-vaccination against diphtheria in the EU/EEA. These options would support vaccination against all other vaccine-preventable diseases:

- Develop and roll-out training programmes for vaccine providers that will make them better equipped to deal with parents who are hesitant about vaccinating their children.
- Similarly, develop and roll-out information programmes for vaccine receivers to better understand why they are offered vaccination.
- Explore efforts to monitor vaccine coverage using electronic immunisation registries that may facilitate the identification of unvaccinated individuals, who will then receive reminders. Efforts to include all age groups including children, adolescents, adults and elderly in such registries have been successful in several EU/EEA countries and could be explored elsewhere. Such registers also have the potential to offer an appreciated service to individuals and parents who want to keep track of their children's vaccinations.
- Consider the notion of an informed opt-out from childhood vaccination schedules, which implies that parents must actively say no to vaccination and verify that their vaccine provider has informed them about the risks of not vaccinating.
- Enforce controls of vaccination status at certain time points in a child's life, at least at entry to kindergarten and at school start.
- Offer regular boosters Tdap every ten years.

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