

Diphtheria in the south of France, March 2011

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In March 2011, a 40 year-old French man was diagnosed with diphtheria caused by toxigenic *Corynebacterium diphtheriae*. Fifty-three close contacts were identified from whom throat samples were analysed. *C. diphtheriae* was found only in the asymptomatic partner of the index case. The two cases had travelled in Spain during the incubation period of the index case. Investigation around the second case identified 13 new close contacts. None of them was found to be infected.

Case report

On 14 March 2011, the French Institute for Public Health Surveillance (Institut de Veille Sanitaire, InVS) was informed by the Regional Health Agency of Languedoc-Roussillon that *Corynebacterium diphtheriae* had been isolated from a patient with angina and pseudomembranes since 7 March. The patient had no history of vaccination, and no history of recent travel to an endemic area. He had visited his General Practitioner on 8 March, who performed a throat swab and prescribed oral antibiotic treatment with cefuroxime 500 mg daily. On 12 March, *C. diphtheriae* was isolated by a local laboratory from the throat swab. The patient was immediately advised to attend a hospital emergency department. He did not present any signs suggestive of severe disease. Antibiotic treatment was changed to roxithromycin, 300 mg daily for 14 days after receipt of the microbiological results and it was agreed that the patient could stay at home but had to remain in isolation and wear a protective mask in the event of receiving visitors. Diphtheria antitoxin was not given, as the interval between the onset of the disease and the date of availability of the serum was too long, and the case did not have any signs of systemic affection. A laboratory follow-up test six days after the start of treatment with roxithromycin was negative for *C. diphtheriae*.

Contact tracing

Immediately upon receipt of the positive results from the local laboratory, on 12 March, an investigation was conducted by the local health authorities to identify the source of infection, trace contacts and to implement control measures. The investigation followed the

French national guidelines for diphtheria case management [1].

Fifty-three close contacts were identified around the index case. These were close friends or work colleagues (n=2), healthcare workers (n=15) and patients waiting with the case in the same room of the emergency department and not wearing protective masks (n=36). Contacts were contacted and physically examined, and were all offered throat swabs and antibiotic prophylaxis. All close contacts agreed to have their samples taken and all were negative except that of the index case's partner who was identified as an asymptomatic carrier of *C. diphtheriae* from a throat swab taken 11 days after the onset of disease of the index case. This second case had been vaccinated with diphtheria, tetanus, and pertussis (DTP) vaccine in 2006 and received azithromycin 500 mg per day for three consecutive days and one dose of booster vaccine for diphtheria.

Around this second case, 13 co-workers were identified as close contacts. They were also offered testing and prophylaxis and laboratory results were negative for all 13 contacts. Prophylaxis recommended to all persons in close contact with the two cases, was azithromycin 500 mg per day for three consecutive days and one dose of booster vaccine for diphtheria, unless they could document a history of full vaccination (three doses) with a booster within less than five years.

International notification

In the course of the investigation, patient history revealed that, from 3 to 6 March, the two cases had travelled together in Spain. They did not report any specific close contacts during this trip. However, they had both participated in an international gathering (Carnival of Sitges) between 5 and 6 March. The national Spanish Health Authorities were informed by the French Health Authorities about the two diphtheria cases and a notification through the European Union's (EU) Early Warning and Response System (EWRS) was performed on 24 March. No cases of diphtheria have been reported by the local Spanish Health Authorities.

Laboratory investigation at the National Reference Centre

On 9 March, a culture seed, on a Columbia CNA agar + 5% sheep blood plate and two throat samples from the index case were sent to the National Reference Centre (NRC) where they were analysed for toxigenic corynebacteria and where a PCR assay for the detection of diphtheria toxin gene (*tox*) was performed. On 16 March, the NRC confirmed *C. diphtheriae* carrying the *tox* gene in these samples. The sample used for molecular analyses and for seeding a new culture was the first from Columbia CNA agar + 5% sheep blood plate. The throat swabs were kept at -20°C .

Throat samples from identified contacts were sent to the NRC from 16 March onwards where they were processed in a similar fashion than the samples from the index case.

The non-production of diphtheria toxin in the index case and in a second case identified during the contact tracing, as well as the isolates' sensitivity to antibiotics, in particular macrolides, was confirmed only 12 days after the detection of the *C. diphtheriae* *tox* gene because the purification of the isolate from the contaminated culture received was difficult. The two isolates from the two respective cases were *C. diphtheriae* biovar *mitis*. The molecular typing was recently performed by multilocus sequence typing (MLST) and both isolates have the same sequence type (ST), ST (212) which has not been described in the literature so far. The Elek test was negative for both.

Background and epidemiological situation in France

Diphtheria can result in an acute bacterial toxic infection of the upper respiratory tract or in cutaneous lesions. It is caused by toxin-producing *C. diphtheriae*, *C. ulcerans*, and *C. pseudotuberculosis*. The infection is characterised by a sore throat with an adherent pseudomembrane on the tonsils, pharynx or nasal cavity. The severity of the infection is related to obstruction of the upper respiratory tract and the dissemination of diphtheria toxin, which may cause myocardial and neurological lesions. Diphtheria is transmitted by aerosol secretions and/or contact with skin lesions. It can also be transmitted from asymptomatic individuals who may carry the bacteria for several weeks.

Toxigenic diphtheria is a mandatory notifiable disease in France and all cases suspected on clinical grounds (angina with pseudomembranes, or cutaneous lesions with pseudomembranes) must be notified without delay to the Regional Health Agency if a *Corynebacterium* is isolated. Since 2003, the case definition of confirmed cases also includes *C. ulcerans* harbouring the *tox* gene [2]. Due to widespread immunisation, there were less than five cases notified per year in the 1980s (Figure). In addition, 18 indigenous cases of diphtheria *C. ulcerans* harbouring the *tox* gene (*tox*-positive) have been reported in France since the early 2000s. The last

indigenous cases of infection with *C. diphtheriae* were reported in France in 1989. Four imported cases were notified between 2002 and 2010 [3].

Despite a high vaccination coverage in infants (98–99%), immunisation coverage remains insufficient in adults in France especially after fifty years-old [4]. This mainly reflects the fact that booster diphtheria vaccination was only introduced in the immunisation schedule in 2006 [5].

Discussion and conclusion

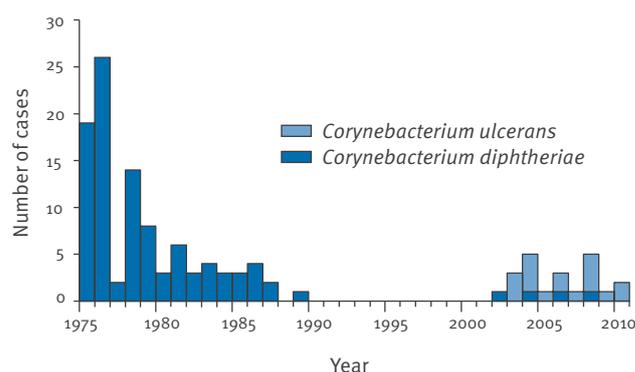
Two epidemiologically linked cases of toxigenic *C. diphtheriae* infections were identified in March 2011 in France. This is the first notification of *C. diphtheriae*, with no travel history to an endemic area, in France since 1989. Among the patients' contacts in France, no additional cases were identified suggesting an absence of local transmission. Both cases had travelled to Spain where they had attended the Carnival of Sitges. Transmission during this international event is possible, especially considering the interval between the event and the onset of disease in the index case, which was within the usual incubation period of diphtheria (2 to 5 days) [6]. The second case may have been infected at the same time, or have been infected by the index case. We can also not rule out that the asymptomatic case was the first infected.

The investigation followed national guidelines [1], identifying all persons in close contact with the cases during the incubation period. The main difficulty was to detect close contacts among the patients who stayed several hours in the same waiting room as the case inside the emergency department. This led to a large number of people being considered as contacts, and this could have been avoided with more appropriate case management. This placed a significant workload on the local hospital, local health authorities, and the NRC, with logistical constraints for collecting and processing samples.

Microbiological investigation was complicated because a contaminated isolate delayed the Elek test. However,

FIGURE

Number of laboratory confirmed cases of toxigenic diphtheria, France, 1975–2010



detection of the *tox* gene was performed the day the sample was received with the identification of the bacteria the next morning, indicating that molecular identifications are very useful to quickly confirm the infection.

Effective cooperation between the different partners involved in the investigation and implementation of control measures allowed the successful management of this event. It reminds us of the need to maintain vigilance regarding the possible diagnosis of diphtheria even in the absence of recent travel in endemic areas. The greatest challenges are retaining and developing clinical awareness, microbiological skills and surveillance systems among EU Member States. It also emphasises the need for a high vaccine coverage in the adult population [7].

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