



Cutaneous diphtheria among recently arrived refugees and asylum seekers in the EU

30 July 2015

Main conclusions and options for response

There is currently no indication that the cases of cutaneous diphtheria among refugees and asylum seekers reported by Denmark, Germany and Sweden in 2015 represent a significant outbreak of diphtheria among refugees in Europe. However, notification through the health system is unlikely to be a sensitive mechanism for detecting outbreaks of cutaneous diphtheria among refugees as they may have more limited access to health services than other population groups.

Cutaneous diphtheria is a potential risk factor for transmission of diphtheria. Most refugees who arrive in Europe are from endemic countries and have travelled under conditions that increase the risk of acquiring cutaneous diphtheria, and many of them continue to be exposed to over-crowding and poor hygiene once they have arrived in the EU. This may increase the risk of diphtheria.

European travellers may become infected and develop cutaneous diphtheria while travelling or working in endemic countries. ECDC data show that most of the travellers who were diagnosed with cutaneous diphtheria on their return had not received booster vaccinations or had unknown vaccination status.

Limitations in the capacity to confirm toxigenic infections may delay diagnosis, treatment and public health interventions in some EU Member States. Enhanced surveillance, molecular typing and whole genome sequencing of patient isolates have the potential to improve the understanding and monitoring of transmission patterns of cutaneous diphtheria.

Diphtheria caused by toxigenic *Corynebacterium* species is a notifiable disease in the EU.

Options for response include the following:

- Advise travellers to diphtheria-endemic countries to check whether they have completed primary vaccination against diphtheria before departure, and to receive a booster dose of diphtheria toxoid if more than 10 years has passed since the last dose.
- Consider all refugees and asylum seekers who lack evidence of vaccination against diphtheria as unprotected and provide vaccinations with diphtheria-toxoid-containing vaccines in accordance with national guidelines.
- Alert clinicians to the possibility of cutaneous diphtheria among refugees, asylum seekers and travellers returning from endemic areas, provide them with testing algorithms and instructions for how to take samples and how to transport samples to the laboratory.

Suggested citation: European Centre for Disease Prevention and Control. Cutaneous diphtheria among recently arrived refugees and asylum seekers in the EU, 30 July 2015. Stockholm: ECDC; 2015.

Erratum, 2 December 2015: The case numbers for *C. ulcerans* in Table 1 on page 4 were corrected from 15 reported cases in 2014 to 13 cases. Case totals were adjusted accordingly.

- Skin ulcers should be tested for diphtheria especially in returning travellers and in individuals coming from endemic countries. Timely laboratory confirmation of cases is vital for implementing control measures.
- Healthcare providers in EU/EEA countries should be made aware that vaccinated individuals can still be infected by *Corynebacterium diphtheriae* and can become asymptomatic carriers of toxin-producing strains.
- For laboratories and countries that lack capacity for confirming toxigenic diphtheria infections, make provision for them to send samples to the WHO reference laboratory in the UK.
- Address the poor access to diphtheria antitoxin and consider transnational options for securing rapid access to it for all patients in the EU that have suspected or confirmed diphtheria-toxin-induced disease.

Source and date of request

ECDC internal decision, 20 July 2015.

Public health issue

The risks to public health in the EU associated with the recent detection of cases of cutaneous diphtheria among refugees and asylum seekers, the shortage of diphtheria antitoxin (DAT) in the EU, and the recent death of an unvaccinated child from respiratory diphtheria caused by toxigenic *Corynebacterium diphtheriae* in Spain.

Consulted experts

Consulted internal experts (in alphabetical order): Paloma Carrillo-Santisteve, Mike Catchpole, Denis Coulombier, Ida Czumbel, Niklas Danielsson, Birgitta de Jong, Pierluigi Lopalco, Edit Szegedi.

External experts consulted (in alphabetical order): Androulla Efstratiou (Public Health England), Andreas Sing (National Reference Laboratory on Diphtheria, Germany; Bavarian Health and Food Safety Authority), Anders Tegnell (Public Health Agency of Sweden), Karin Tegmark-Wisell (Public Health Agency of Sweden), Ole Wichmann (Infectious Disease Epidemiology, Robert Koch Institute, Germany), Josefa Masa Calles (National Centre for Epidemiology, Spain).

ECDC received declarations of interest from the external experts and found no potential conflict of interest.

Disease background information

Diphtheria is a bacterial infectious disease that can be prevented by vaccination. Humans are the only significant reservoir for *C. diphtheriae* [1]. Transmission is via airborne respiratory droplets, direct contact with respiratory secretions or direct contact with exudate from infected cutaneous lesions [2]. The incubation period ranges from two to five days but can be as long as 10 days.

Symptomatic diphtheria infections present as mild upper respiratory tract infections, as skin infections (cutaneous diphtheria) or as classical pseudomembranous respiratory diphtheria. In highly vaccinated populations, most diphtheria infections are asymptomatic or have a mild clinical course. Such cases are rarely diagnosed unless they are detected during contact tracing, and asymptomatic carriers tend to be underreported. The most common sites of symptomatic as well as asymptomatic infections are the pharynx, larynx, tonsils, nose and skin. The critical diphtheria virulence factor is the production of exotoxin. The gene that encodes the toxin (*tox+*) is carried by a lysogenic beta phage. The presence of the *tox+* phage gene in a *C. diphtheriae* strain does not mean that the gene is always expressed. The proportion of strains that carry the *tox+* phage gene is comparatively low in high-income countries. However, there is a risk that non-toxigenic strains may acquire the phage gene, either in the environment or in a laboratory, and then convert into a toxigenic strain [2,3]. The toxin kills tissue at the site of infection and produces systemic toxin effects including myocarditis, nephritis, polyneuropathy and paralysis when absorbed into the bloodstream.

Respiratory infections with *C. diphtheriae* are most commonly reported in temperate climates, while cutaneous infections dominate in tropical areas and in developing countries [2,4,5]. The cutaneous lesions, which are described as shallow greyish non-healing ulcers, frequently start as insect bites and can occur anywhere on the body. The ulcers are often co-infected with other pathogens such as *Staphylococcus aureus* and *Streptococcus pyogenes*. In developed countries, the cutaneous forms are most frequently reported among returning travellers [6,7] and migrants arriving from endemic countries, [8] and among alcoholics, drug users, the homeless and other disadvantaged populations [9,10].

Cutaneous carriage of *C. diphtheriae* is an important source of person-to-person transmission of the pathogen, particularly in communities where vaccination coverage is low. Transmission from cutaneous lesions can cause both respiratory and cutaneous disease in susceptible contacts [8]. It is extremely unusual for immunised

individuals to develop the systemic toxin-mediated form of disease from cutaneous diphtheria [8]. In a 1975 epidemiological study from a rural community in the US, transmission has been shown to be higher among contacts of patients with cutaneous infections than in those with respiratory tract infections [11]. Several studies highlight the role of cutaneous diphtheria infections in the spread of diphtheria and the relevance of accumulation of carriers as an increased risk for an epidemic [2,8].

Two other species, *Corynebacterium ulcerans* (rarely) and *C. pseudotuberculosis* (very rarely) may cause diphtheria disease. These infections are often zoonotic [2,12]. The diphtheria toxin is 95% homologous to that of *C. diphtheriae* and the biological effect and clinical presentation are similar to the toxin produced by *C. diphtheriae* [2,3].

Treatment

The critical treatment for patients with systemic toxin-induced symptoms is timely administration of purified equine diphtheria antitoxin (DAT) [2,4]. DAT neutralises the circulating toxin and should be given as early as possible to be effective, often on the mere clinical suspicion of diphtheria. DAT treatment initiated later than 48 hours after onset of systemic toxic symptoms has limited impact on the clinical outcome [13].

Treatment of cutaneous diphtheria is either by benzathine penicillin G or a course of oral erythromycin or azithromycin. Close contacts, especially household contacts, should be given prophylactic antibiotic treatment and receive a diphtheria toxoid booster. They should be closely monitored and antitoxin given at the first sign(s) of illness. Carriers identified in the community should receive antimicrobial treatment and be followed until testing negative.

Diphtheria patients should be vaccinated with diphtheria toxoid upon recovery since natural diphtheria infection does not confer long-standing protective immunity.

Diagnostics

Clinical suspicion of cutaneous diphtheria depends on epidemiological circumstances and morphological characteristics of the wound. Skin infections may be manifested by a scaling rash or by ulcers with clearly demarcated edges and membrane, but any chronic skin lesion may harbour *C. diphtheriae* along with other pathogens.

Laboratory confirmation of diphtheria requires isolation of *C. diphtheriae* by culture from a clinical specimen and toxigenicity testing. Procedures for the collection of specimens are available in the WHO *Manual for laboratory diagnosis of diphtheria* [14]. Direct and real-time polymerase chain reaction (PCR) assays can detect the *C. diphtheriae* toxin gene within a few hours, but confirmation of diphtheria toxin expression must be undertaken with Elek's test. Due to low number of isolates in Europe, countries might not stock the required reagents which may delay the diagnosis of diphtheria. Potentially positive samples can be sent for confirmation and further biotyping to the WHO Collaborating Centre for Diphtheria in the United Kingdom*.

Prevention through vaccination

The diphtheria toxoid vaccine effectively protects against the effects of the exotoxin produced by *C. diphtheriae* and probably also against that produced by *C. ulcerans*, and immunisation is the only effective method of preventing the toxin-mediated disease. Vaccinated individuals can still be infected by the bacteria and may become asymptomatic carriers of toxin-producing strains which they can transmit to others. Diphtheria toxoid vaccines are mainly available in combination with one or several antigens including tetanus, pertussis, polio, *Haemophilus influenzae* type b, or hepatitis B, depending on whether the vaccine is for primary immunisation or as booster dose. At least one vaccine producer, Statens Serum Institut in Denmark (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.

Although vaccinations have essentially eliminated clinical diphtheria disease from Europe, there are unresolved issues related to waning immunity and the need for booster doses to adults [15]. WHO recommends booster doses with diphtheria toxoid approximately every 10 years [16] throughout life and that tetanus prophylaxis following injuries should be given as a combination of diphtheria and tetanus toxoid (DT or dT).

Diphtheria epidemiology

Diphtheria is endemic in Haiti and the Dominican Republic and many countries in Asia, the South Pacific region, the Middle East and Eastern Europe. Large outbreaks have occurred in Indonesia, India, Thailand, and Laos since 2011 [1,17,18]. The following countries reported, on average, more than 10 cases annually from 2010 to July 2015: Angola, Bangladesh, Central African Republic, India (accounting now for about two thirds of the cases notified to

* For details, see http://apps.who.int/whocc/Detail.aspx?cc_ref=UNK-194&cc_code=unk

WHO worldwide), Indonesia, Iran, Laos, Myanmar, Nepal, Niger, Pakistan, the Philippines, Somalia, Sudan, Thailand and Vietnam[19]. Ethiopia has not reported on diphtheria since 1999 and Eritrea reported 8 cases in 2012 and no cases in 2013. The globally reported figures are likely to underestimate the true incidence as a result of weak surveillance systems and limited diagnostic capacities.

The Member States of the European Union are expected to report confirmed diphtheria cases in real time [20]. From 2009 to 2014, 142 cases of diphtheria were reported in the EU/EEA of which 79 cases were *C. diphtheriae* infections (Table 1). There has been an increase in the number of *C. diphtheriae* cases reported during the last five years (Table 1). Latvia reported 41 cases during the period and is the only EU Member State with continued indigenous transmission.

Of the 79 *C. diphtheriae* cases, 25 were reported as cutaneous infections. Seven of these 25 were indigenous cases from Latvia and 18 cases were imported. In addition to the 25 cases reported as cutaneous infections, 14 imported cases missed information about the clinical manifestations but are likely to be cutaneous infections. The probable origin of the imported cases were Angola, Afghanistan, Cameroon, Cambodia, Ethiopia, The Gambia, India, Kenya, Madagascar, Mozambique, Pakistan, the Philippines, Sierra Leone, Thailand, the Democratic Republic of the Congo, Sri Lanka and Togo. For all but four cases, the vaccination status was reported as unknown or uncertain. The available surveillance data at European level show a wide age range of cases, with a preponderance in adults and the elderly.

Table 1: Number of cases of *C. diphtheriae* and *C. ulcerans* reported in the EU/EEA, by year and country, 2009–2014

Year	2009	2010	2011	2012	2013	2014	Total
All diphtheria cases	10	14	20	27	31	38	140
<i>C. diphtheriae</i>							
Total	5	3	12	16	19	24	79
Reporting country (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)	AT (2), DE (3), ES (1) FR (1), LV (12), NL(1), NO (2) SE (2)	AT (2), DE (11), ES (1), FR (6), LV (41), NL(2), NO (2) SE (8), UK (6)
Age range (yrs)	11–74	20–68	11–69	3–75	5–75	2–76	2–76
<i>C. ulcerans</i>							
Total	3	11	7	11	12	13	57
Reporting country (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)	DE (6), FR (5), SE(1), UK (1)	BE (2), DE (25), FI (1), FR (18), LV (1), SE (2), UK (8)
Age range (yrs)	30–87	19–89	59–85	10–92	46–85	13–88	10–92
Unknown type							
Reporting country	DE (2)	0	LT (1)	0	0	LV (1)	4
Age range (yrs)	56–62	—	55	—	—	78	55–78

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

In a study conducted during 2007 and 2008 ten European countries each screened between 968 and 8 551 throat swabs (26 821 swabs in total) from patients with upper respiratory tract infections for *C. diphtheriae*. 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 [21].

Event background information

On 16 July 2015, Denmark reported a case of toxigenic cutaneous diphtheria in an asylum seeker from Eritrea through the Early Warning and Response System (EWRS). The patient, who reported having been vaccinated against diphtheria during childhood, arrived in Denmark on 20 June 2015 and presented to health services with a

* New Independent States of the former USSR

traumatic leg wound received in Libya two months earlier. Sampling and biopsy of the wound were carried out on 29 June. On 3 July, culture showed growth of haemolytic *Streptococci* group A and *Staphylococcus aureus*. *Corynebacterium diphtheriae* was detected by Matrix Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS) and was confirmed by PCR. On 6 July, PCR was positive for the toxin gene and on 8 July Elek's test confirmed the diagnosis of toxin-producing cutaneous diphtheria. Seven close contacts among asylum seekers who might have been exposed within the preceding 10 days and healthcare personnel were throat-swabbed, offered prophylactic treatment with azithromycin and given a dT booster unless they had been vaccinated within the last 5 years. The case was treated with antibiotics and was revaccinated. On 13 July, all throat swabs, including those from the index patient, were negative and none of the asylum seekers or healthcare personnel had presented with symptoms.

At the same time, Sweden reported two confirmed cases (MALDI-TOF MS + PCR) of cutaneous diphtheria caused by toxigenic *C. diphtheriae* in asylum seekers from Eritrea. The two refugees, who did not have contact with each other in Sweden, presented with non-healing wounds and scabies. They had similar travel histories to the Danish case. Diagnoses were obtained in mid-June and early July and contacts in Sweden have been followed up and vaccinated. Sweden has also diagnosed two cases of non-toxigenic cutaneous diphtheria in asylum seekers from Eritrea and Ethiopia.

As of 27 July, Germany has reported four cases of cutaneous diphtheria associated with asylum seekers in 2015. All infections were caused by toxigenic *C. diphtheriae* (three of biotype mitis and one of unknown biotype). One was in a refugee from Libya, one in a refugee from Ethiopia, one in a refugee from Eritrea, and one in a patient from Syria (refugee status unknown). In addition, two cutaneous cases caused by *C. diphtheriae* and associated with asylum seekers or foreign visitors were reported to The European Surveillance System in 2014. The first case was a refugee from Somalia and the second case was a child from Angola who had come to Germany for medical care.

In summary, three countries (Denmark, Germany and Sweden) have reported seven cases of toxigenic cutaneous diphtheria and two cases of non-toxigenic cutaneous diphtheria among refugees in 2015, while 13 other EU Member States reported via the Epidemic Intelligence Information System for Vaccine-Preventable Diseases (EPIS-VPD) that they have no notifications of cases of cutaneous diphtheria among refugees in 2015.

ECDC threat assessment for the EU

Cutaneous diphtheria is endemic in tropical countries but is uncommon in Europe. Vaccination is the only effective protection against toxigenic diphtheria and unvaccinated people are at risk of developing potentially life-threatening infection with toxigenic *C. diphtheriae*. The risk is highest when travelling in diphtheria-endemic countries, but does also exist in the EU/EEA Member States as *C. diphtheriae* can circulate undetected. This was recently exemplified by a fatal case of respiratory diphtheria in an unvaccinated child in Spain who had not travelled to an endemic area [22]. The majority of cutaneous diphtheria cases caused by *C. diphtheriae* reported in the EU are EU residents who return from travels to diphtheria-endemic areas.

The nine cases of cutaneous diphtheria among refugees and asylum seekers in 2015 notified by Denmark, Sweden and Germany are not unexpected given that they originated from endemic countries and are likely to have travelled to the EU under difficult and crowded conditions. The information is limited about the vaccination status of these nine cases.

Diphtheria toxoid is included in childhood vaccination schedules across the world and the childhood vaccination uptake among refugees arriving in the EU is likely to reflect the uptake in their respective countries of origin. It may be assumed that most adult refugees have not received booster doses of diphtheria toxoid before leaving their countries.

Thirteen EU Member States have reported through EPIS-VPD that they have not had any cases of cutaneous diphtheria notified in 2015, indicating that the cases that have been reported do not signify that there is a major outbreak of cutaneous diphtheria among refugees and asylum seekers in Europe. However, because access to medical services for refugees and asylum seekers may be limited, notification of cases may not be the optimal source of information for an assessment of the prevalence of diphtheria infections in this group.

It is extremely unusual for immunised individuals with the cutaneous form of infection to develop the toxin-mediated form of the disease. However, transmission from cutaneous lesions can cause both respiratory and cutaneous disease in susceptible contacts. Cutaneous carriage of *C. diphtheriae* is an important source of person-to-person transmission of the pathogen and therefore represents a potential source of exposure and clinical diphtheria in communities where vaccination coverage is low.

A recent inventory of DAT availability in the EU showed that a large proportion of EU Member States do not stockpile it and that many countries have experienced difficulties in sourcing it when they wanted to replace expired stockpiles. The current lack of DAT in the EU is a concern. DAT treatment can be life-saving for patients with toxin-induced systemic symptoms but must be administered early in the clinical course.

Clinicians in the EU may lack first-hand experience of diphtheria and may not consider diphtheria as a differential diagnosis when presented with non-healing ulcers and other skin lesions among refugees and among EU residents

who return from diphtheria-endemic countries. This can potentially delay diagnosis, treatment, contact-tracing and reporting of diphtheria cases.

Conclusions

There is currently no indication that the cases of cutaneous diphtheria among refugees and asylum seekers reported by Denmark, Germany and Sweden in 2015 represent a significant outbreak of diphtheria among refugees in Europe. However, notifications through the health system are unlikely to be a sensitive mechanism for detecting outbreaks of cutaneous diphtheria among refugees as they may have more limited access to health services than other population groups.

Cutaneous diphtheria is a known risk factor for transmission of diphtheria. Most refugees who arrive in Europe are from endemic countries and have travelled under conditions that increase the risk of acquiring cutaneous diphtheria, and many of them continue to be exposed to over-crowding and poor hygiene once they have arrived in the EU. This may increase the risk of diphtheria.

European travellers may become infected and develop cutaneous diphtheria while travelling or working in endemic countries. ECDC data show that most of the travellers who were diagnosed with cutaneous diphtheria on their return had not received booster vaccinations or had unknown vaccination status.

Limitations in the capacity to confirm toxigenic infections may delay diagnosis, treatment and public health interventions in some EU Member States. Enhanced surveillance, molecular typing and whole genome sequencing of patient isolates have the potential to improve the understanding and monitoring of transmission patterns of cutaneous diphtheria.

Diphtheria caused by toxigenic *Corynebacterium* species is a notifiable disease in the EU [20].

Options for reducing the risks associated with cutaneous diphtheria

- Advise travellers to diphtheria-endemic countries to check whether they have completed primary vaccination against diphtheria before departure, and to receive a booster dose of diphtheria toxoid if more than 10 years has passed since the last dose.
- Consider all refugees and asylum seekers who lack evidence of vaccination against diphtheria as unprotected and provide vaccinations with diphtheria-toxoid-containing vaccines in accordance with national guidelines.
- Alert clinicians to the possibility of cutaneous diphtheria among refugees, asylum seekers and travellers returning from endemic areas, provide them with testing algorithms and instructions for how to take samples and how to transport samples to the laboratory.
- Skin ulcers should be tested for diphtheria especially in returning travellers and in individuals coming from endemic countries. Timely laboratory confirmation of cases is vital for implementing control measures.
- Healthcare providers in EU/EEA countries should be made aware that vaccinated individuals can still be infected by *Corynebacterium diphtheriae* and can become asymptomatic carriers of toxin-producing strains.
- For laboratories and countries that lack capacity for confirming toxigenic diphtheria infections, make provision for them to send samples to the WHO reference laboratory in the UK.
- Address the poor access to DAT and consider transnational options for securing rapid access to it for all patients in the EU that have suspected or confirmed diphtheria-toxin-induced disease.

References

1. Centres for Disease Control and Prevention. Health Information for International Travel 2016 ('Yellow Book'). Atlanta: CDC; 2015. Available from: <http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/diphtheria>.
2. Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases. 8th ed. Philadelphia: Elsevier Saunders; 2015.
3. Pappenheimer AM, Jr, Murphy JR. Studies on the molecular epidemiology of diphtheria. Lancet. 1983 Oct 22;2(8356):923-6.
4. Berih A. Cutaneous *Corynebacterium diphtheriae*: A traveller's disease? Can J of Infect Dis. 1995 May;6(3):150-2.
5. Moore LS, Leslie A, Meltzer M, Sandison A, Efstratiou A, Sriskandan S. *Corynebacterium ulcerans* cutaneous diphtheria. Lancet Infect Dis. 2015 Jul 16. [Epub ahead of print]
6. Jakovljevic A, Steinbakk M, Mengshoel AT, Sagvik E, Brugger-Synnes P, Sakshaug T, et al. Imported toxigenic cutaneous diphtheria in a young male returning from Mozambique to Norway, March 2014. Euro Surveill. 2014;19(24):pii=20835. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20835>.
7. Lindhusen-Lindhe E, Dotevall L, Berglund M. Imported laryngeal and cutaneous diphtheria in tourists returning from western Africa to Sweden, March 2012. Euro Surveill. 2012;17(23):pii=20189. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20189>.
8. de Benoist AC, White JM, Efstratiou A, Kelly C, Mann G, Nazareth B, et al. Imported cutaneous diphtheria, United Kingdom. Emerg Infect Dis. 2004 Mar;10(3):511-3.
9. Harnisch JP, Tronca E, Nolan CM, Turck M, Holmes KK. Diphtheria among alcoholic urban adults. A decade of experience in Seattle. Annals of internal medicine. 1989 Jul 1;111(1):71-82.
10. Quick ML, Sutter RW, Kobaidze K, Malakmadze N, Nakashidze R, Murvanidze S, et al. Risk factors for diphtheria: a prospective case-control study in the Republic of Georgia, 1995-1996. J Infect Dis. 2000 Feb;181 Suppl 1:S121-9.
11. Koopman JS, Campbell J. The role of cutaneous diphtheria infections in a diphtheria epidemic. J Infect Dis. 1975 Mar;131(3):239-44.
12. Sing A, Hogardt M, Bierschenk S, Heesemann J. Detection of differences in the nucleotide and amino acid sequences of diphtheria toxin from *Corynebacterium diphtheriae* and *Corynebacterium ulcerans* causing extrapharyngeal infections. J Clin Microbiol. 2003 Oct;41(10):4848-51.
13. Logina I, Donaghy M. Diphtheritic polyneuropathy: a clinical study and comparison with Guillain-Barre syndrome. J Neurol Neurosurg Psychiatry. 1999 Oct;67(4):433-8.
14. World Health Organization Regional Office for Europe. Manual for the Management and Control of Diphtheria in the European Region (ICP/EPI 038(B)). Copenhagen: WHO; 1994.
15. Adler NR, Mahony A, Friedman ND. Diphtheria: forgotten, but not gone. Intern Med J. 2013 Feb;43(2):206-10.
16. World Health Organization. WHO Position paper on diphtheria. Weekly Epidemiological Record. 2006;81th year(3, 20 January 2006):21-32.
17. Hughes GM, A. Husada, D, Irawan, E. Bracebridge, S. Efstratiou, A. Seroprevalence and determinants of immunity to diphtheria for children living in two districts of contrasting incidence in East Java, Indonesia. Pediatr Infect Dis. 2015;In press.
18. Zakikhany K, Efstratiou A. Diphtheria in Europe: current problems and new challenges. Future microbiology. 2012 May;7(5):595-607.
19. World Health Organization. WHO Diphtheria reported cases [Internet]. Geneva: WHO; 2015 [27.07.2015]. Available from: http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tsincidediphtheria.html.
20. European Commission. COMMISSION IMPLEMENTING DECISION of 8 August 2012 amending Decision 2002/253/EC laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Council (notified under document C(2012) 5538)(2012/506/EU) Official Journal of the European Union 2012. Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:262:0001:0057:EN:PDF>.

21. Wagner KS, White JM, Neal S, Crowcroft NS, Kupreviciene N, Paberza R, et al. Screening for *Corynebacterium diphtheriae* and *Corynebacterium ulcerans* in patients with upper respiratory tract infections 2007-2008: a multicentre European study. *Clin Microbiol and Infect.* 2011 Apr;17(4):519-25.
22. European Centre for Disease Prevention and Control. Rapid Risk Assessment: A case of diphtheria in Spain. 15 June 2015. Stockholm: ECDC; 2015. Available from: <http://ecdc.europa.eu/en/publications/Publications/diphtheria-spain-rapid-risk-assessment-june-2015.pdf>.