Chapter 10
Diphtheria Surveillance

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Abstract Diphtheria is uncommon in developed countries but when cases do arise they are often severe with high mortality. This disease has demonstrated its potential to re-emerge to epidemic proportions in areas where it was previously thought to be under control. Ongoing monitoring and surveillance is therefore essential and in general follows the principles of surveillance utilised for most other vaccine preventable infections, but with some specific adaptations relevant to a disease that is close to elimination. Surveillance across countries and regions is complicated by a number of factors including the use of different case definitions and the variation in laboratory policy and expertise. International networks have been valuable in improving knowledge and skills in this area.

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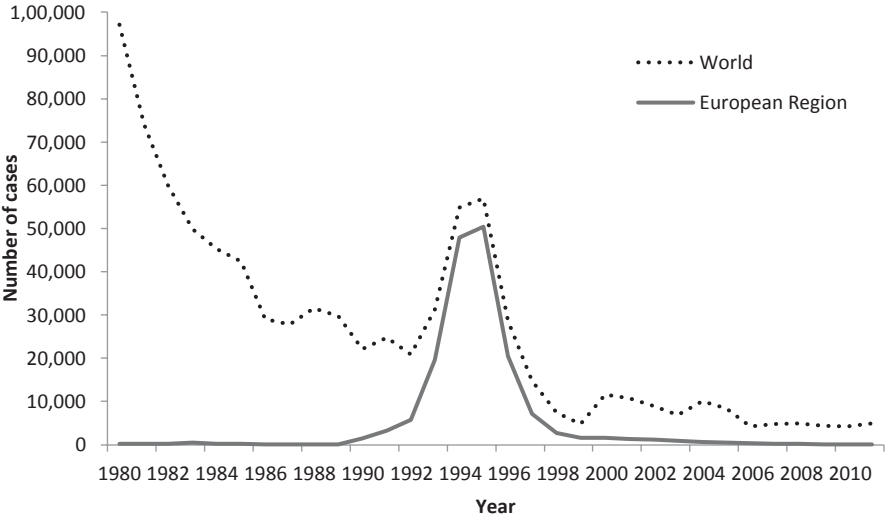

Fig. 10.1 Diphtheria cases reported to the World Health Organization (Data downloaded 24/07/2012), 1980–2011. (Source: WHO 2012)

Keywords Case definitions · Diphtheria · Epidemiology · Monitoring · Surveillance

10.1 Introduction

In the pre-vaccine era, diphtheria was a common cause of morbidity and a leading cause of childhood death. This led to the development of diphtheria antitoxin for treatment, the provision of which was associated with heroic stories such as that of Balto the dog (one of the sleigh dogs who carried antitoxin to an isolated community in Nome, Alaska during an outbreak in 1925) whose statue stands in Central Park, New York. By the middle of the twentieth century, comprehensive routine childhood vaccination schemes were implemented across Europe and North America and marked the beginning of a global decline in incidence (Fitzgerald et al. 1932; Galazka et al. 1995; Vitek and Wharton 1998). Furthermore, in 1974 the Expanded Programme on Immunization (EPI) was established to introduce and improve immunisation coverage in developing countries (Keja et al. 1988). By the beginning of the 1980s in Europe, cases of clinical diphtheria were extremely uncommon and many countries were progressing towards elimination (Galazka and Robertson 2004; Vitek and Wharton 1998). However, by the end of this decade a resurgence of epidemic diphtheria occurred in the Russian Federation, affecting all newly independent states of the former Soviet Union (Vitek and Wharton 1998). Between 1990 and 1998, more than 157,000 cases and 5,000 deaths were reported from the region, accounting for more than 80 % of diphtheria cases reported worldwide (see Fig. 10.1) (Dittmann et al. 2000; Markina et al. 2000; Vitek and Wharton

1998). One of the striking features of this large-scale diphtheria outbreak was the high proportion of adult cases, reported in all affected countries (Dittmann et al. 2000; Galazka 2000; Galazka and Robertson 1995).

Many factors were considered to have contributed to the resurgence, including increased adult susceptibility due to waning immunity, low vaccination coverage among children in the 1980s and early 1990s, disruptions to health service infrastructure and large-scale population movements as a consequence of the break up of the former Soviet Union, as well as the introduction of toxigenic strains (Dittmann et al. 2000). Although now largely under control this epidemic highlighted the continuing danger posed by diphtheria and the need for vigilance and rapid control procedures even in areas where the number of reported cases is usually low.

Although diphtheria is now uncommon in Europe, it is present in every WHO Region (WHO 2012), and there are new and ongoing epidemics (for example in Africa and South East Asia (FluTrackers 2012; WHO 2012), notably India, Indonesia and the Sudan (WHO 2012)) being reported regularly. The risk of importation of *Corynebacterium diphtheriae* from endemic countries, particularly those beyond the European Region, remains. In addition, indigenous infections caused by toxigenic *Corynebacterium ulcerans* (associated with consumption of raw dairy products (Barrett 1986; Bostock et al. 1984), contact with cattle (Hart 1984), and increasingly domestic pets (De Zoysa et al. 2005; Hogg et al. 2009; Lartigue et al. 2005)) further emphasise the need to maintain high levels of vaccination coverage. Only a few countries regularly report toxigenic isolates of *C. ulcerans* (Tiwari et al. 2008; Wagner et al. 2012), however, it is likely that this organism is also circulating in other countries but remains undetected due to a lack of robust surveillance and/or laboratory diagnostics.

10.2 Surveillance

10.2.1 Definition of Surveillance

The purpose of surveillance is to provide sufficient information to enable countries to take timely public health action in the prevention and control of diphtheria. The International Health Regulations 2005 define surveillance as ‘the systematic ongoing collection, collation and analysis of data for public health purposes and the timely dissemination of public health information for assessment and public health response as necessary’ (WHO 2008).

Surveillance practices vary according to the systems, health structures and resources in place within different countries. In addition the level of surveillance needed will depend to a certain extent on the incidence of diphtheria; where the disease is common diagnosis based on symptoms for a proportion of cases may be reliable, but as a country approaches the elimination phase the need for laboratory confirmation and detailed follow-up of all clinically suspected cases becomes essential. In addition to disease surveillance, other important types of surveil-

lance include vaccine coverage and assessment of population immunity, as for all vaccination programmes.

Objectives of Diphtheria Surveillance The World Health Organization (WHO) outlines the rationale for the surveillance of diphtheria as follows (WHO 2003): 'Diphtheria is a widespread severe infectious disease that has the potential for causing epidemics. Surveillance data can be used to monitor levels of coverage and disease as a measure of the impact of control programmes. Recent epidemics have highlighted the need for adequate surveillance and epidemic preparedness.'

The objectives of a diphtheria surveillance system are:

a. To estimate the burden of disease in different populations

In the first instance, a surveillance system should enable timely recognition and response to increases in cases (or individual cases as is most relevant for diphtheria in non-endemic countries) and clusters (clusters may not be detected at local level if they span geographical boundaries) through both early detection and communication of information through appropriate channels such that management and control procedures can be rapidly implemented.

A picture of the overall disease burden in a country will generally be based on data from several sources. Incidence rates for different age groups, geographical areas and time periods can indicate particular risk groups and periods. However, the accuracy of the estimated burden of disease will depend on the sensitivity and specificity of the surveillance systems in place.

b. To assess the public health threat posed by the disease

This is dependent on:

- transmissibility of the organism
- opportunities for spread:
  - living conditions e.g. overcrowding
  - population movements nationally and internationally
  - availability of containment facilities
  - infrastructure, external threats e.g. conflict, breakdown of immunisation programmes
- susceptibility of the population:
  - degree of natural immunity from infection
  - current and historical vaccine coverage
  - vaccine schedule, type of vaccine
  - existence of risk groups e.g. injecting drug users, homeless, alcoholics, immunocompromised individuals, those in contact with animals
- diagnosis and treatment options:
  - awareness of health staff to recognise the disease and enable early diagnosis and treatment
  - laboratory diagnostic facilities
  - health service factors e.g. access to antitoxin/antibiotics/vaccine

c. To identify risk factors for carriage, transmission and complications

Analysis of data collected through enhanced surveillance can give indications of risk factors and provide a starting point for further exploratory studies. For example, recent individual case based data has been used to build up an evidence base for understanding risk factors relating to *C. ulcerans* and its association with domestic animals (for example: Berger et al. 2011; Hatanaka et al. 2003; Hogg et al. 2009; Schuhegger et al. 2009). Where case numbers are low, pooling datasets across several countries is of value. However, this requires standardisation of case definitions and surveillance systems across countries.

d. To monitor the effectiveness of control programmes and inform policy
Reviewing vaccination history on all cases through enhanced surveillance is a valuable means of monitoring the effectiveness of the vaccine. Seroprevalence studies can also be used to assess whether or not the vaccination programme is sufficiently protective, as well as monitoring the degree of waning immunity and the duration of protection (Edmunds et al. 2000; Di Giovine et al. 2012). A high case fatality ratio may indicate problems with late diagnosis, case management, or the availability or quality of antibiotics and/or antitoxin. In addition, a process of review and debrief of incident teams after a case or cluster has occurred enables 'lessons learned' to be identified and can inform guidance.

e. To monitor phenotypic and genotypic changes in the causative organism
The application of molecular epidemiological tools is essential for monitoring the spread of epidemic clones and to allow for distinction between epidemic, endemic and imported cases. This also has major implications for timely and adequate preventative measures. It is facilitated by close partnerships between public health microbiology and epidemiology. Although ribotyping is still used as the 'gold standard' for molecular epidemiological studies, novel typing methods such as MLST (multi locus sequence typing) are being explored with promising results. In addition, standardised protocols have led to more rapid and accurate detection of these 'clones' globally along with the establishment of an online international database for automatic recognition of genotypes. The use of state of the art genome sequencing has also been undertaken and has provided invaluable information on novel targets for rapid typing and information on the pathogenicity of the organisms. Databases for ribotyping and MLST are available within the public domain. The current molecular typing ((http://www.dipnet.org/ribo.public.php, http://pubmlst.org/cdiphtheriae/)) database for diphtheria, which was built using ribotype data from a diverse collection of strains, was imported from Taxotron® to Bionumerics. This has allowed access to laboratories worldwide for *C. diphtheriae* and *C. ulcerans* (via the WHO Collaborating Centre) pattern analysis and has significantly contributed towards the molecular epidemiology of diseases caused by these organisms (De Zoysa et al. 2008; De Zoysa et al. 2005). An EU consensus towards typing at different levels is being developed according to country laboratory capabilities.
f. To disseminate public health information appropriately
Alongside the collection and analysis of data from the sources described above, surveillance includes the need for timely dissemination of information so that front line staff can update their knowledge with respect to the latest findings. Updat-

Table 10.1 Comparison of two case-definitions currently in use within Europe

	1994 WHO case definition for diphtheria (Begg 1994)	2012 EU case definition for diphtheria (European Commission 2012)
Suspected/ possible case	Laryngitis or nasopharyngitis or tonsillitis plus pseudomembrane	Any person meeting the clinical criteria for classical respiratory diphtheria *Classical respiratory diphtheria* An upper respiratory tract illness with laryngitis or nasopharyngitis or tonsillitis AND an adherent membrane/pseudomembrane
Probable case	Suspected case plus one of the following: Recent (<2 weeks) contact with a confirmed case Diphtheria epidemic currently in the area Stridor Swelling/edema of neck Submucosal or skin petechial hemorrhages Toxic circulatory collapse Acute renal insufficiency Myocarditis and/or motor paralysis 1-6 weeks after onset Death	Any person meeting the clinical criteria for diphtheria (classic respiratory diphtheria, mild respiratory diphtheria, cutaneous diphtheria, diphtheria of other sites) with an epidemiological link to a human confirmed case or with an epidemiological link to animal to human transmission Clinical criteria *Classical respiratory diphtheria—see above* *Mild respiratory diphtheria* An upper respiratory tract illness with laryngitis or nasopharyngitis or tonsillitis WITHOUT an adherent membrane/pseudomembrane *Cutaneous diphtheria* Skin lesion *Diphtheria of other sites* Lesion of conjunctiva or mucous membranes Epidemiological criteria At least one of the following epidemiological links Human to human transmission Animal to human transmission

Table 10.1 (continued)

	1994 WHO case definition for diphtheria (Begg 1994)	2012 EU case definition for diphtheria (European Commission 2012)
Confirmed case	Probable case plus isolation of a toxigenic strain of *C. diphtheriae* from a typical site (nose, throat, skin ulcer, wound, conjunctiva, ear, vagina) or fourfold or greater rise in serum antitoxin, but only if both serum samples were obtained before the administration of diphtheria toxoid or antitoxin Confirmed cases should be classified as indigenous or imported (infection acquired abroad) Note: demonstration of toxin production is recommended but not required in typical cases. Microscopic examination of a direct smear of a clinical specimen is not sufficiently accurate to substitute as a culture	Any person meeting the laboratory criteria AND at least one of the clinical forms Laboratory criteria Isolation of toxin-producing *C. diphtheriae, C. ulcerans*, or *C. pseudotuberculosis* from a clinical specimen

ing national and international guidance for clinicians and laboratories allows new recommendations to be clearly communicated. In addition, since cases of diphtheria are uncommon in most European countries, publishing individual case reports in widely read journals can be a valuable means of enabling others to learn from recent experience. The development of surveillance networks which include both epidemiologists and microbiologists allows more direct sharing of information and expertise in a timely manner (see Sect. 10.6).

10.3 Case Definitions

Currently two different case definitions are applied in public health settings across the WHO European region: the 2012 EU case definition, which considers disease caused by *C. diphtheriae, C. ulcerans* and *C. pseudotuberculosis*, and the 1994 WHO case definition, which only considers classical respiratory diphtheria cases caused by *C. diphtheriae* ('epidemic diphtheria'). Both definitions are detailed in Table 10.1 and differences discussed below. In addition, it is standard practice that case definitions may be modified during specific incidents or outbreaks.

The definitions differ with respect to both the clinical presentations and organisms included.

Clinical Presentation Both definitions include classic respiratory diphtheria. The EU case definition also includes alternative presentations such as cutaneous disease and milder respiratory symptoms. The detection of mild cases and unusual presentations can serve as an indicator of a sensitive surveillance system. Loss of laboratory expertise increases the risk of missing mild, subclinical or unusual manifestations. Whilst epidemic diphtheria is associated with respiratory disease, cutaneous infections can be a source of respiratory infection (Koopman and Campbell 1975) so early identification of such presentations can be valuable in assisting with the prevention and control of diphtheria. Information concerning asymptomatic carriers of toxigenic strains, although not included in the case definitions, may be recorded as part of the follow-up of contacts of a case.

Organism Both definitions include toxigenic *C. diphtheriae* infections, the cause of epidemic diphtheria. In addition, the EU definition includes toxigenic *C. ulcerans* infections which can have the same clinical presentations. The reservoirs and transmission routes of *C. ulcerans* are still not fully understood and since only a few cases are reported each year within Europe it is useful to be able to consolidate surveillance data from several countries to try to improve understanding. It has also been suggested that the capability to detect *C. ulcerans* isolates could be interpreted as an indicator for a well functioning surveillance system.

In addition the EU definition includes toxigenic *C. pseudotuberculosis*, a rare infection in humans, typically associated with contact with sheep or goats (Dorella et al. 2006).

Neither of the definitions includes non-toxigenic organisms, which do not require any public health action (antibiotic treatment only). A subset of non-toxigenic *C. diphtheriae* strains are known to carry the *tox* gene (non-toxigenic toxin-bearing [NTTB] or toxin-carrying [NTTC] strains) (Groman 1984; INTAS 2004). During and after the diphtheria epidemic in the former Soviet Union, the circulation of NTTBs was observed (Melnikov et al. 2000), and two NTTBs were detected in Lithuania in a recent screening study (Wagner et al. 2011), but in general the prevalence of NTTB strains is ill-defined. NTTB strains are often isolated alongside other organisms (Berger et al. 2012; Lowe et al. 2011; Reacher et al. 2000). Although the potential of phage conversion to transform NTTBs into toxigenic strains is considered low and rarely observed *in vivo*, circulation of NTTBs may act as a repository for *tox* gene sequences and therefore pose a risk for disease. However, the public health relevance of these strains is yet to be examined and further studies are needed in order to assess the true burden of NTTB strains in Europe and globally.

Sensitivity and Specificity In general, the broader the definition is, the more sensitive the surveillance system will be. However, countries must balance the need for surveillance with financial constraints, and for a rare disease such as diphtheria, it may be sensible to consider broadening the definition once elimination is approaching. With appropriate laboratory expertise the specificity of the surveillance system for diphtheria in a country where the disease is uncommon should be high as all cases would be laboratory confirmed. In countries where diphtheria is more widespread cases may be reported on the basis of symptoms and an epidemiological link only, which is less specific, though this can be reliable when symptoms are typical and the patient has had close contact with another case.

10.4 Sources of Surveillance Data

10.4.1 Case-based Surveillance Data

Early Reporting of Probable Individual Cases to Public Health Authorities on the Basis of Symptoms The frequency of reporting to central level will depend on the incidence of infection (see sect. 10.5). Identification of a probable case of diphtheria necessitates immediate reporting to national level in most countries. It may be sensible to modify the criteria for notifying cases to national level based on the prevalence of disease in a particular country to ensure that the notification system is appropriate and able to give a realistic picture of the current situation. In countries with a high incidence of diphtheria, reports relying on symptoms in the first instance are likely genuine cases, but in countries where diphtheria is rare, cases can typically be notified on the basis of symptoms and later discovered to be due to other cause(s) hence looking at such notifications alone may be misleading.

Laboratory Confirmed Cases Screening policies, laboratory expertise, and also the availability of laboratory reagents differ between countries and will influence the number of cases detected, as well as the ability to characterise strains.

Screening Policies Diagnostics relating to diphtheria are complex and require specialist expertise and media because *C. diphtheriae* and *C.ulcerans* are easily obscured by the normal throat flora. Laboratory guidelines and flow-diagrams have been published to support microbiological identification (Efstratiou et al. 2000; Efstratiou et al. 1998; Efstratiou and George 1999). There are a number of different policy options:

- No screening (where resources and/or expertise are lacking; in many countries there is complacency and screening is not considered to be cost effective).
- Screening only specimens with a specific clinician request and/or risk factor such as a history of travel to an endemic region (this is the practice in many non-endemic countries).
- Sentinel screening of all throat swabs by particular laboratories (undertaken for example in Denmark, Ireland, UK) (Wagner et al. 2011).
- Routine screening of all throat swabs (this practice is no longer undertaken by any countries within Europe).

Laboratory Diagnostics A recent external quality assurance evaluation (EQA) assessing microbiological procedures for diphtheria across the WHO European Region revealed that less than 20% (6/34) of participating international centres were fully capable of diagnosing the specimen correctly (Neal and Efstratiou 2009). This indicated the significant challenges that need to be overcome in terms of developing and maintaining laboratory expertise. Although originally described in the 1940s, the Elek test (Elek 1949; Engler et al. 1997), conventional (24h-48h incubation time) or modified (16h-24h incubation time), is still the gold standard method for the detection of toxigenic strains as it detects expression of the active toxin. In times of austerity and financial constraints, many laboratories do not maintain the laborious laboratory infrastructure or cannot afford to stock the specialised media and diphtheria antitoxin (needed for the Elek test) (Neal and Efstratiou 2009) and therefore, use PCR alone for the detection of the *tox* gene. However, PCR cannot distinguish between toxigenic and non-toxigenic toxin gene-bearing strains (NTTB) and should therefore only be used in combination with the Elek test (Efstratiou et al. 2000; Efstratiou and George 1999).

Strain Characterisation In addition to identifying the organism, specialised reference laboratories also offer procedures for further characterisation; these typing methods allow the identification of clonal groups and (epidemiologically) closely related strains and can provide information on the geographic origin of the strain.

A. Biotyping (C. diphtheriae only) The first stage in characterisation to species level (to distinguish between biovars *gravis, mitis*, *intermedius* and *belfanti*), undertaken by most clinical microbiology laboratories.

B. Ribotyping The currently widely recognised gold standard method for typing of *Corynebacterium spp*. During the diphtheria epidemic in the former Soviet Union in the 1990s ribotyping enabled the differentiation between endemic and epidemic strains (Damian et al. 2002; De Zoysa et al. 1995; Kolodkina et al. 2006; Popovic et al. 1996; Skogen et al. 2002; von Hunolstein et al. 2003). Nowadays ribotyping is used during outbreak investigations for *C. diphtheriae*, and for *C. ulcerans* to identify possible sources of infection and to investigate suspected transmission from domestic animals to humans (Bonmarin et al. 2009; De Zoysa et al. 2005; Lartigue et al. 2005). However, ribotyping is a subjective, band-matching based system using continuous values for classification; it is therefore prone to generate ambiguous data, which, together with a required rigid standardisation procedure, negatively affects reproducibility and portability of the method and no evolutionary information can be collected.

C. MLST (multi locus sequence typing) MLST has been established as a promising successor to ribotyping (Bolt et al. 2010); overcoming problems with ambiguity encountered with ribotyping by indexing nucleotide variations within core metabolic (*housekeeping*) genes. Selected genes are directly sequenced and sequential differences within each gene (allele) provide an allelic profile. The allelic profiles and sequence types are unambiguous, meaning strains can readily be compared between laboratories and numerical values are easily stored in databases, thereby, providing reproducible and portable data appropriate for the epidemiological and evolutionary investigation of diphtheria (Bolt et al. 2010; Maiden et al. 1998). However, the discriminatory power of MLST, and also other sequencing based methods (e.g. VNTR [variable tandem repeat analysis]) which are currently under investigation, is slightly lower compared to ribotyping and not directly comparable; therefore, more systematic studies are required to evaluate and assess the method for the purposes needed.

Enhanced Surveillance This is typically initiated in response to an epidemiological or laboratory report and should involve collaboration with epidemiology and laboratory colleagues to ascertain detailed information regarding at a minimum:

- the patient
  - date of birth, sex, geographical area of residence
- clinical information
  - onset of symptoms
  - description of symptoms
  - duration of illness
  - outcome
- laboratory confirmation
  - organism *(C. diphtheriae, C. ulcerans, C. pseudotuberculosis)*
  - toxigenicity test result
- vaccination history (dates and doses received)
- travel history (for cases of *C. diphtheriae*)
- animal contact (for cases of *C. ulcerans, C. pseudotuberculosis)*

- case management
  - antibiotics (date, name, dose)
  - antitoxin (date, dose)
  - diphtheria vaccine (dates and doses received)
- management of contacts

Hospitalisations Where hospitalisations for diphtheria or symptoms associated with diphtheria recorded in hospital databases may act as a further source of surveillance data for severe cases. However, ideally these cases would have already been reported to relevant authorities via the channels above.

Death Registrations Where diphtheria is recorded as a cause of death provide a further source of data which can be useful in ensuring severe case reports have not been missed. International Classification of Diseases (ICD) coding allows for both the main cause and any underlying causes of death to be recorded, such as a complication from diphtheria in childhood contributing to the death of an adult; therefore full information on any death certification mentioning diphtheria should be sought.

Medical Literature In some instances case reports may be detected in the medical literature that have not been reported through the standard national channels (Wagner et al. 2010).

10.4.2 Population-Level Surveillance Data

Seroprevalence Studies Measurement of population immunity by age group can demonstrate the effectiveness of national immunisation programmes. They can also highlight population groups susceptible to infection, and indicate the need to adapt a country's vaccination schedule. To achieve elimination of diphtheria, a minimum immunity rate of 90 % in children and 75 % in adults is recommended (Begg 1994).

Age-Specific Vaccine Coverage at National and Sub-National Level Reduced vaccination coverage may indicate the need for heightened surveillance in particular age groups or geographical areas, and/or new public health campaigns. The targets proposed by the WHO expert group in 1992 include achieving 95 % coverage of both the primary immunisation series (DTP3) by 2 years of age, and a booster dose in school age children in every district (Begg 1994).

Screening Studies Occasional studies may be of value to detect the presence of toxigenic and non-toxigenic *C. diphtheriae* and/or *C. ulcerans* in throat swabs and can provide reassurance that cases are not being missed. Currently, very few cases of diphtheria are reported within the EU however, results of a recent pan-European screening study revealed that toxigenic organisms are still circulating in Latvia and Lithuania. At least one of the toxigenic organisms circulating in

Lithuania would have not been detected in the absence of this screening study (Wagner et al. 2012).

10.5 Frequency of Reporting

WHO recommended standards for surveillance of diphtheria are as follows (WHO 2003):

- Routine monthly reporting of aggregated data on probable or confirmed cases is recommended from the peripheral level to the intermediate and central levels.
- Designated reporting sites at all levels should report at a specified frequency (e.g. weekly or monthly) even if there are zero cases (often referred to as "zero reporting").
- All outbreaks should be investigated immediately and case-based data should be collected.
- In countries achieving low incidence (usually where coverage is >85-90%[1]), immediate reporting of case-based data of probable or confirmed cases is recommended from the peripheral level to the intermediate and central levels.

10.6 The Need for a Cross-Country Approach to Surveillance: European Surveillance Networks

While national approaches within a country might be advisable for high incidence and high prevalence diseases, a combined European approach to diphtheria surveillance, into which national approaches can feed, allows skills and resources to be shared and increases the ability of a country and its neighbours to detect and respond to epidemics that are small, widespread, and/or at an early stage. With the increase in international travel and migration and the steady increase of the number of countries in the European Union, the benefits of a European-wide surveillance system become even more relevant.

At the peak of the diphtheria epidemic in the former Soviet Union in 1993, the European Laboratory Working Group on Diphtheria (ELWGD) was established as an initiative of the WHO Regional Office for Europe in response to the urgent need to develop laboratory techniques for diphtheria diagnosis and analysis (Efstratiou and Roure 2000). In 2001, and as a response to the epidemic, this approach was taken one step further and the European Commission (EC) (Directorate-General for Health and Consumers (DG SANCO)) funded a feasibility study which led to the

[1] Population coverage of approximately 85% is required for elimination, based on a basic reproductive number (R_0; the average number of secondary cases produced by one primary case in a wholly susceptible population) of 6–7 (Fine 1993).

Diphtheria Surveillance Network (DIPNET). This included both the epidemiological and microbiological aspects of diphtheria and other infections caused by potentially toxigenic corynebacteria. The network was officially recognised in 2006 as an EC Dedicated Surveillance Network, bringing together 25 EU partner countries and 21 collaborating countries from the WHO European Region (Neal and Efstratiou 2007) with the objectives to:

- Harmonise and enhance surveillance of *C. diphtheriae* and *C. ulcerans* within the WHO European Region.
- Determine the disease prevalence and characteristics of toxigenic and non-toxigenic *C. diphtheriae* and *C. ulcerans* in a variety of populations with emphasis upon higher risk countries.
- Expand the DIPNET external quality assurance schemes for laboratory diagnosis to include epidemiological typing and serological immunity (Neal and Efstratiou 2009).
- Develop novel tools for integrated molecular epidemiological characterisation so as to gain a clearer understanding of the spread of epidemic clones throughout the WHO European Region (Efstratiou et al. 2009).
- Undertake serological immunity studies within 'high risk countries' and assessment of serological methodologies across all EU Member States (Di Giovine et al. 2010).

The research findings of DIPNET, which included highlighting a lack of laboratory expertise across Europe (Neal and Efstratiou 2009), identification of toxigenic *C. diphtheriae* during a screening study in a country that had not reported diphtheria in the previous five years (Wagner et al. 2011), and the analysis of aggregated data across member countries (Wagner et al. 2012) emphasised the benefit of a co-ordinated approach, as well as further training and studies to assist with monitoring progress across Europe.

From February 2010 the responsibility for the activities of DIPNET were transferred to the European Centre for Disease Control (ECDC), based in Stockholm, Sweden, in the form of the European Diphtheria Surveillance Network (EDSN) (ECDC 2012). The activities of the EDSN are aimed at integrating the epidemiology and laboratory surveillance of diseases caused by *C. diphtheriae* and *C. ulcerans*.

At the global level, WHO undertakes surveillance in each of its regional units, and together with the United Nations Children's Fund (UNICEF) collates global data at the national level on diphtheria incidence and vaccine coverage (WHO 2012).

10.7 Future Challenges

Remarkable advances have been made since the epidemic of the 1990s with respect to reducing diphtheria case numbers, case management and laboratory diagnostics. However, considerable challenges remain in terms of the surveillance of this disease.

It is vital that cases can be identified and treated in a timely manner. Accurate microbiological and epidemiological surveillance is therefore essential. This entails ensuring that clinicians are aware of the various clinical presentations of diphtheria as well as risk factors for infection including those specific to *C. ulcerans*, and that microbiologists have sufficient skills and resources for microbiological diagnosis. Maintaining this expertise in the face of low prevalence of disease is one of the key challenges for diphtheria surveillance.

Furthermore, as the table included earlier in this chapter demonstrates, consistent case definitions are not currently used across different countries and world regions. This presents challenges when analysing data and limits the ability to pool data across countries, reducing the opportunities to understand risk factors, for example, for *C. ulcerans*.

A further challenge lies in accurately monitoring vaccine coverage in all age groups and maintaining consistently high vaccination coverage across Europe. Owing to the rarity of this disease, the fear of diphtheria and the consequent demand for vaccination is lessened. Furthermore anti-immunisation sentiment may actively discourage vaccination in some countries. Clear public health messages and strong efforts towards achieving the minimum 95 % coverage recommended by the WHO are essential.

Maintaining good inter-country communication, particularly during times of austerity and financial constraints is an additional challenge to overcome as part of a concerted cross-country commitment to achieving and maintaining diphtheria elimination.

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