EU Diphtheria Case Definition: Position Paper

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Background

Good surveillance is fundamental to every vaccination programme. The responsibility of public health authorities is to demonstrate that these programmes are effective, particularly in view of the susceptibility to diphtheria amongst adult populations in Europe and the demonstrated potential for diphtheria to re-emerge rapidly if vaccination coverage or efficacy falls[1]. Maintaining confidence by demonstrating safety and effectiveness is critical. However, the quality of diphtheria surveillance varies greatly between countries both at laboratory and public health levels, and standards need to be agreed and set, and methodologies harmonised across Europe. Furthermore, the standards need to be higher than for other diseases due to specific programmatic targets to demonstrate the absence of disease or to ascertain reliably low levels of disease incidence. In this way, vaccine preventable disease surveillance in high coverage countries, and diphtheria surveillance specifically, has particular requirements which may differ from some other European surveillance projects that have focused on high incidence diseases.

Case definition

1. Clinical description

The diphtheria case definition was agreed by the Community Decision of 19th March 2002. This predated establishment of the DG SANCO feasibility study DIPNET 122/SID/2001. An opportunity to discuss the current case definition was created by the first DIPNET steering committee meeting held in January 2002. A further discussion and

agreement on a modified case definition took place between diphtheria experts representing 40 participating countries, including thirteen of the fifteen EU member states, at the 7th International Conference of the European Laboratory Working Group on Diphtheria, in Vienna, June 2002 (Abstract/programme book enclosed).

In highly vaccinated populations it is more appropriate to include a description of the diverse disease manifestations. This maximises capture of cases, which may be less severe and manifest in a milder form but which nevertheless, may be as infectious as others. These clinical presentations occur frequently in South East Asia and the Indian Subcontinent. Many of the importations of diphtheria into EU countries, particularly the UK, originate in these regions. Clinicians frequently overlook non-respiratory forms of the disease, including cutaneous diphtheria or diagnosis may be delayed.

2. Laboratory criteria for diagnosis

The laboratory diagnostic criteria have been expanded because the definition proposed by the EU is limited to one species, *Corynebacterium diphtheriae*. However, other species such as *C.ulcerans* may produce diphtheria toxin and clinical manifestations, which are indistinguishable from classical diphtheria. Fatal cases of diphtheria and secondary transmission of these organisms have been documented in recent years.

Diphtheria experts in Europe and beyond do not recognise histopathologic diagnosis of diphtheria as an appropriate diagnostic methodology. Hence this has been excluded in the modified case definition.

3. Case classification

The case classification is essentially the same as that proposed by the Community Decision but now encompasses all recognised toxigenic corynebacteria that may occur in humans.

The note indicates that asymptomatic, non-respiratory and cutaneous cases should be reported because they can be infectious and present a risk of secondary transmission. In

addition, there is a need for vigilance and highly sensitive surveillance of vaccine preventable disease within the EU. In recent decades the capacity for diphtheria to re-emerge has been demonstrated in the European Region, with epidemics in Russia and the Newly Independent States. The capacity of a surveillance system for early detection of epidemics depends upon its sensitivity as well as specificity. For rare diseases the sensitivity of surveillance must be very high, and this depends upon a highly sensitive case definition, which is also specific. We believe that the modified case definition is both highly sensitive and specific.

Conclusions

The DGSANCO DIPNET feasibility study (122/SID/2001) and potential future establishment of DIPNET should exploit surveillance at the public health level, thus leading to harmonisation of methodologies between countries for case definitions, surveillance and laboratory diagnostics, establishment of definitive surveillance and genotype databases between countries for rapid tracking of epidemic strains, external quality assurance schemes to monitor laboratory proficiency, training visits for scientists and workshops and symposia throughout Europe to maintain and increase awareness[2,3].

References

1. Levy-Bruhl D, Pebody R, *et al.* ESEN: a comparison of vaccination programmes – diphtheria. *Eurosurveillance*,1998;3.
2. Efstratiou A, George RC. Laboratory guidelines for the diagnosis of infections caused by *Corynebacterium diphtheriae* and *Corynebacterium ulcerans*. *Communicable Disease and Public Health*, 1999;2:250-257.
3. Lai S, Efstratiou A. Report from the Sixth International Meeting of the European Laboratory Working Group on Diphtheria, Brussels, Belgium, June 2000. *Eurosurveillance*, 2002;7: 8-11.

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EU CASE DEFINITION FOR DIPHTHERIA
Community Decision of 19 March 2002
(under 2119/98/EC)

Clinical Description

Clinical picture compatible with diphtheria, e.g. an upper respiratory tract illness characterised by sore throat, low grade fever, and an adherent membrane of the tonsils, pharynx, and/or nose.

Laboratory criteria for diagnosis

- Isolation of toxin-producing *Corynebacterium diphtheriae* from a clinical specimen.
- (Histopathologic diagnosis of diphtheria.) EXCLUDE

Case classification
Possible: N.A.

Probable: A clinically compatible case that is not laboratory confirmed and does not have an epidemiological link to a laboratory confirmed case.

Confirmed: A clinically compatible case that is either laboratory confirmed or has an epidemiological link.

Note that asymptomatic carriers, cases with non-toxigenic *C.diphtheriae* or cutaneous diphtheria should not be reported.

EU CASE DEFINITION FOR NATIONAL DIPHTHERIA SURVEILLANCE
Community Decision of 19 March 2002
(under 2119/98/EC)
MODIFIED VERSION

Clinical Description

Clinical picture compatible with diphtheria ie: an upper respiratory tract illness characterised by sore throat, low grade fever, and an adherent membrane of the tonsils, pharynx or nose or non-respiratory diphtheria; cutaneous, conjunctival, otic and genital lesions.

Laboratory criteria for diagnosis

- Isolation of diphtheria toxin-producing corynebacteria from a clinical specimen.

Case classification
Possible: N/A

Probable: A clinically compatible case that is not laboratory confirmed and does not have an epidemiological link to a laboratory confirmed case.

Confirmed: A clinically compatible case that is laboratory confirmed with the isolation of a toxigenic strain of *Corynebacterium diphtheriae* or *C.ulcerans* or has an epidemiological link to a laboratory confirmed case

Note: Non-respiratory/cutaneous diphtheria cases with isolation of toxigenic strains should be reported, as should asymptomatic carriers (any anatomical site) with toxigenic strains. Cases with non-toxigenic *C.diphtheriae* or *C.ulcerans* should not be reported.