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ADVISORY COMMITTEE ON DANGEROUS PATHOGENS

Categorisation of *Neisseria meningitidis* B – paper from the Health Protection Agency

Summary

1. We recognise that *Neisseria meningitidis* infection presents a serious risk to laboratory workers and we fully understand and support ACDP's desire to minimise these risks.

2. All work which involves handling specimens or cultures of containing *N.meningitidis* should be risk assessed. This has been done for all procedures carried out in HPA clinical, reference and research laboratories and it has been possible to devise safe working practices at containment level (CL) 2, using safety cabinets when appropriate. A requirement for all work with the organism to be contained at CL3 would create considerable practical difficulties for the HPA and all other clinical and research laboratories with respect to disease diagnosis and vaccine research. Specifically:

   a. It could compromise the effectiveness of diagnostic microbiology services. The majority of clinical microbiology laboratories would be overwhelmed if all clinical samples that potentially contained meningococci had to be processed at CL3. This could affect the timely diagnosis and effective management of a variety of infectious diseases not just those caused by meningococci.

   b. It could hinder the development and testing of meningitis B vaccines. The HPA currently plays a critical international role in the rapid assessment of new candidates. The only internationally accepted correlate of protection is by demonstration of serum bactericidal antibody (SBA). Assays to support clinical trials have been devised to ensure that procedures which could cause aerosol release are performed in safety cabinets. The scale of this work is such that automation is essential for the final counting step A requirement for it to be conducted under CL3 containment conditions would be difficult to implement and would at the very least create major delays. The meningitis B vaccine development field is at a very exciting stage, and so this could directly impact on the timeline for licensure of the vaccine.

3. Our understanding is that all documented laboratory-acquired meningococcal infections have resulted from the generation of aerosols while scientists were working on the open bench. Use of an appropriate BSC cabinet in a CL2 laboratory would therefore likely have prevented these accidents. Conversely working in CL3 without using a safety cabinet would not provide a safety improvement

Background Information

Neisseria meningitidis is an organism whose only natural ecological niche is human beings. It is found in the nasopharynx of 5-10% of the overall population however there is considerable variation in this rate depending on age with teenagers and young adults cited as having between 25-40% carriage in surveys.

Meningococci are usually transmitted from person to person by mobilisation of aerosolised secretions from the nasopharynx. Other routes such as intimate kissing and sharing of drinking vessels have been implicated. In clinical laboratories they are most frequently isolated from throat, mouth and pharyngeal swabs and also from cervical and urethral cultures taken to investigate genitourinary infection.

Additionally there have been descriptions of meningococcal disease cases where there is a strong likelihood that transmission and infection has occurred in microbiology laboratories and also to clinicians delivering healthcare to infected individuals.

Clinical presentations

Meningococcal carriage is common, asymptomatic and is probably important in establishing immunity during young childhood years in most individuals. Clinical infection is relatively uncommon but can result in severe illness including septicaemia, meningitis and death.

Circumstances which result in clinical infection are contributed to by organism and host factors. The reasons for some individuals having life threatening infection while most others encountering the same organism experience only a short period of asymptomatic carriage are poorly understood. Population genetic studies of the human immune response is offering insights but at the moment is not capable of indicating which individuals are likely to suffer a poor outcome.

Nearly all disease is caused by organisms that have a polysaccharide capsule. Antibody against capsular components is protective and is the basis for development of effective vaccines against serogroup A,C Y and W135 meningococci. This approach has not been possible for serogroup B which currently causes the great majority of meningococcal infections in the UK. A number of promising candidate vaccines utilising other targets have been developed and are currently undergoing clinical trials.

Meningococci in the microbiology laboratory

Specimens (usually throat and nasopharyngeal swabs) from which *N. meningitidis* is grown are encountered daily in clinical microbiology laboratories. A paper from 1936 reports probable laboratory acquired infection but most descriptions in the literature date since 1990.

An important factor predisposing to the increase appears to be a move away from performing fermentation identification tests on solid media incorporating sugars by inoculation with organisms transferred directly from plated colonies using a loop or wire. Since the 1990s the use of prefabricated strip assays which require a heavy suspension of organisms to be pipetted into galleries containing a range of sugar and chemical substrates has become widespread. Creating the suspension can cause aerosol formation with the potential for organisms to establish nasopharyngeal colonisation from which invasive infection can occur.

Recognition of this risk has resulted in publishing of guidelines recommending that laboratory examination procedures should mandate that any manipulation of organisms, cultures and potentially infected specimens which could result in generating infected aerosols is performed in a biological safety cabinet (BSC).

Documented instances of probable laboratory acquired infections in the UK identified since this guideline was published have occurred when the recommendation had not yet been adopted and this was a factor in case reports from Sweden and USA published in 2007.

There have been several instances of serious untoward incident reports when organisms which subsequently turn out to be *N. meningitidis* have initially been manipulated outside BSCs because the organism has been from an 'atypical' site – most frequently genitourinary – or otherwise unsuspected. None of these resulted in clinical infection however those identified as having been potentially exposed were offered chemoprophylaxis.

Role of vaccination

The changed epidemiology of meningococcal disease means that currently only about 10% of UK clinical infections are caused by strains preventable by the currently available licenced vaccine. Duration of protection is limited and there is a potential for inducing immune hyporesponsiveness by repeated administration so it is of limited utility for general microbiology laboratory staff. This would need to be reviewed when a quadrivalent conjugate vaccine becomes available.

Staff in reference and research laboratories may have greater risks of exposure depending on specific work schedules so appropriate arrangements for vaccination need to be considered on a case by case basis. For serogroup B meningococci this should include early access to formulations showing beneficial effect in clinical trial studies – possibly within 18 months.

Risk mitigation

The most important measure in preventing laboratory acquired infection by meningococci is obviating exposure to aerosolised organisms by handling all liquid cultures and performing mobilisation of organisms from culture plates in BSCs. It is possible to house these in either biological safety containment level (BSCL) 2 or 3 facilities. Such measures are generally in place in laboratories performing reference and research work on meningococci.

It would be appropriate for clinical laboratories to review workload and identify specimens which may yield meningococci (and indeed other pathogens transmitted by the airborne route) so that these cultures are examined in a way which obviates exposure of staff to infected aerosols. Masks would not provide any additional benefit in these circumstances. Any newly introduced manipulation such as trying to secure plate lids with tape would be an added hazard, increasing risk of an untoward incident.

Moving to the use of BSCs for examination and manipulation of cultures from specimens which have a 'possible' rather than a 'strong' likelihood of isolating meningococci could result in risk reduction for laboratory staff but would only be feasible if sited in BSCL2 laboratories. This would facilitate the adoption of best practice models such as performing all manipulation and work on positive blood

cultures and cultures from GUM specimens in BSCs. The workload represented by specimens from which strains may be grown could not be accommodated in the BSCL3 facilities of most clinical laboratories.

Our understanding is that there is a strong international consensus that *N. meningitidis* should remain classified as a biosafety level 2 organism but handled in BSCs when being manipulated in situations where risk of aerosol generation is present.

HPA
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