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ADVISORY COMMITTEE ON DANGEROUS PATHOGENS

Categorisation of *Neisseria meningitidis* B – paper from the Health and Safety Executive

Background

2. Reports of cases of laboratory acquired infection caused by *Neisseria meningitidis* have appeared in the literature over a number of years and the ratio of infections among laboratory staff is considered to be higher than those of the general population. The risk factors likely are associated with exposure to droplets or aerosols during laboratory manipulations involving the agent. Although categorised as hazard group 2, the additional hazardous nature of *Neisseria meningitidis* strains is further recognised by their inclusion in Part V, Schedule 3 of COSHH 2002, requiring notification, to HSE, of their use or storage in laboratories.
3. The classification of biological agents in the “Approved List” is made under Section 15 of the Health and Safety at Work etc Act 1974. The Control of Substances Hazardous to Health Regulations 2002 (COSHH), by making reference to this list, imposes requirements which are legally binding. The list also implements the Community Classification of biological agents set out in European Community Directive 2000/54/EC.
4. With certain agents or strains of agents which have an approved classification, the risk of infection may be greater or less than expected. Such agents may be considered as though they were different from the named agent that appears on the approve list and therefore reclassified as if performing a provisional classification. Suitable control and containment measures may then be selected accordingly.

Hazard groups

5. Biological agents are classified into four groups according to their ability to cause infection in healthy humans, the severity of the disease that may result, the risk that infection will spread to the community and the availability of vaccines and effective treatment.

Hazard group 2 - biological agents that can cause human disease and may be a hazard to employees; it is unlikely to spread to the community and there is usually effective prophylaxis or treatment available

Hazard group 3 – biological agents that can cause severe human disease and may be a serious hazard to employees; it may spread to the community, but there is usually effective prophylaxis or treatment available.

Laboratory work

6. In the clinical/diagnostic or research laboratory, *N. meningitidis* may be present in samples of pharyngeal exudates, CSF, blood and subsequently in more concentrated forms, in liquid and solid isolation media. Therefore, risks to laboratory staff from handling or manipulating agents may be derived through a number of routes including; accidental inoculation; exposure of mucous membranes to droplets; inhalation of infectious aerosols. Each of these routes of transmission can be derived from a variety of laboratory procedures and protocols for example; sub culturing isolates from solid or liquid media; aspiration techniques and serogroup identification tests.
7. COSHH requires that at containment level 2 and 3, procedures that may give rise to infectious aerosols must be carried out in a microbiological safety cabinet or other suitable containment. A suitable risk assessment should consider the risk from procedures carried out and apply appropriate control measures.
8. Because the mechanism of natural infection with *Neisseria meningitides* is via droplets or aerosol, manipulations likely to create an aerosol should be carried out inside a microbiological safety cabinet to control any risk from aerosol or splashing. The incidents of laboratory acquired infections with *Neisseria meningitides* strains, according to published literature, appear to have occurred when a variety of manipulations have been undertaken on the open laboratory bench. Information relating to some of the published work can be found in Annex 1

International perspective

9. Strains of *Neisseria meningitidis* are universally categorised as Hazard group 2 across many countries and this is also recognised by WHO. However, most also recommend additional safety precautions when manipulating strains in the laboratory. The general recommendation is for manipulations to be undertaken within a microbiological safety cabinet for those techniques with a high potential for droplet or aerosol formation. Extracts from the US and Canadian National biosafety guidelines together with information published in CDC – MMWR, provide advice for additional measures and can be found in Annex 2. All reinforce the rigorous need to use additional control measures and stipulate the use of safety cabinets to control potential aerosol or droplets formation. It is suggested that the highest risk to laboratory workers involves exposure to isolates of the organism rather than specimens for analysis and that laboratory workers should be offered vaccination as additional control. No reference is made, however, to segregation or application of different control measures between the various serotypes.

Reported instances of laboratory accidents and laboratory acquired infection

Summary:

- Two meningococcal infection fatalities in laboratory workers in USA reported in 1991.
- Two meningococcal infection fatalities in laboratory workers in USA reported in 2002.
- US review in 2005 identified 19 cases worldwide, although this did not capture all those reported elsewhere.
- England and Wales study in 2001 revealed 5 cases (no fatalities).
- Another England and Wales study in 2001 described laboratory practices when handling *N meningitidis* and indicated several cases of accidents.
- US case of infection reported in 2007.
- Three other cases reported not captured by the above

Case study details:

Two fatalities in laboratory workers from meningococcal infection, probably attributable to their work in clinical laboratories, reported in USA in 1991 (1). Both handled patient isolates, in one case there was unconfirmed reference to a laboratory accident.

Two fatalities in laboratory workers from meningococcal infection, probably attributable to their work in clinical laboratories, reported in USA in 2002 (2). One case handled cultures from patient isolates in a laboratory where it was recorded that aspiration of materials from blood culture bottles was performed at the open laboratory bench and that microbiological safety cabinets (MSC), eye protection, or masks were not used routinely for this procedure. The other case handled *N meningitidis* regularly, again on the open bench.

The cases in 2000 (as reported in 2002) prompted a data gathering investigation which was reported by Sejvar *et al* (2005) (3). Submissions yielded previously unreported cases and identified 19 cases worldwide, 16 during the survey period (1985 to 2000) and a further 3 in 2002 between the study period and publication. Of the 16 study cases, 14 were considered previously unreported, the other 2 being the cases that prompted the study. Of the 16, 10 were in USA, plus the further 3 in 2002. Of the 19 cases, 9 were attributed to handling serogroup B, 9 to serogroup C, 1 to serogroup A. Of the last 8 reported chronologically since 1999, 7 were serogroup C and 1 was serogroup A. Infection resulted in fatality in 8 cases, 5 (of 9) from serogroup C and 3 (of 9) from serogroup B.

All cases involved microbiology staff, not haematology, pathology or chemistry. Procedures reported to be carried out leading to infection included handling sources, examining plate cultures, sub culturing isolates and serogroup identification tests. **In all cases work was done on an open bench without the use of an MSC.** Only in two cases was it reported that 'respiratory protection' was employed in the form of a splash guard.

The authors of the report commented that the manipulations did not include those obviously associated with droplet or aerosol generation, only those such as

transferring cultures with an inoculating loop. They recommended the use of MSCs for any work with invasive isolates, especially as the above implies low infectious dose and even the use of splash guards did not prevent infection.

In the UK, a survey of Public Health Laboratories in England and Wales by Boutet *et al* (2001a) (4) revealed 5 probable cases of laboratory acquired infection; 3 in 1992, 1 in 1993 and 1 in 1995. **Note** – as the details of these cases do not match with those reported by Sejvar *et al* (2005), despite them claiming their reported cases were worldwide, these are obviously additional ones. Of these 5 reported in the UK survey, 4 were attributable to serogroup C and 1 to serogroup B. None was fatal, although one required lengthy convalescence. **In all 5 cases, manipulations were being done on the open bench.** The authors correlated the first of the 5 cases in 1992 with the use of a gallery strip test which required inoculation with a heavy cell suspension. This prompted a safety alert by PHLS as was, to use an MSC for such tests, although the second case in 1992 and the third in 1993 were also associated with the use of the test and before extensive implementation of MSC use when handling the test strips. The last 2 cases were not associated with use of the test strips.

Boutet *et al* (2001b) (5) also undertook a survey of 265 clinical microbiology laboratories in England and Wales regarding practices when handling *N meningitidis* for identification tests etc. Of the 186 respondents, they found that 88% (164) always used an MSC for preparing suspensions of the bacteria. Of the 12% that did not always use an MSC, 12 (7% of the total) usually used one, 4 (2% of the total) sometimes and 6 (3% of the total) never used one. It was reported that 16 laboratories had offered chemoprophylaxis to workers following accidents (splash, spillage, breakage or wound contamination) during manipulations performed outside MSCs.

Most recently, Kessler *et al* (2007) (6) reported infection with *N meningitidis* serogroup A in a US temporary student worker. **Again, work was not done in an MSC.**

A further three reports cite laboratory acquired meningococcal infection. Bhatti *et al* (1982) (7) pre-dates the Sejvar review; the paper's authors worked at a Canadian defence establishment therefore it is assumed the case was from Canada. A case reported in France (Christen and Tagan, 2004) (8) was after the Sejvar review. A later case in Canada (Paradis and Grimard, 1994) (9) does not seem to match with dates in the review. No abstracts or reprints are currently available for these papers.

Annex 2

Extract from ‘Biosafety in Microbiological and Biomedical Laboratories; U.S. Department of Health and Human Services Public Health Service; Centers for Disease Control and Prevention and National Institutes of Health Fifth Edition 2007’).

“Specimens for *N. meningitidis* analysis and cultures of *N. meningitidis* not associated with invasive disease may be handled in BSL-2 facilities with rigorous application of BSL-2 standard practices, special practices, and safety equipment. All sterile-site isolates of *N. meningitidis* should be manipulated within a BSC (biological safety cabinet). Isolates of unknown source should be treated as sterile-site isolates. If a BSC is unavailable, manipulation of these isolates should be minimized, primarily focused on serogroup identification using phenolized saline solution while wearing laboratory coat, gloves, and safety glasses or full face splash shield. BSL-3 practices and procedures are indicated for activities with a high potential for droplet or aerosol production and for activities involving production quantities or high concentrations of infectious materials. Animal studies should be performed under ABSL-2 conditions.”

Extract from “CDC MMWR -February 22, 2002 / 51(07);141-4”, Guidelines recommend the use of a biosafety cabinet for mechanical manipulations of samples that have a substantial risk for droplet formation or aerosolization such as centrifuging, grinding, and blending procedures.

“The exclusive occurrence of probable laboratory-acquired cases in microbiologists suggests that exposure to isolates of *N. meningitidis*, and not patient samples, increases the risk for infection. Nearly all the microbiologists in this report were manipulating isolates and performing subplating with an inoculation loop on an open laboratory bench. A recent study indicated that manipulating suspensions of *N. meningitidis* outside a biosafety cabinet is associated with a high risk for contracting disease (3). Isolates obtained from a respiratory source are in general less pathogenic and represent a lower risk for microbiologists.

Extract from Canadian Biosafety guidelines 2004 “additional containment (biosafety level 3) for activities with high potential for aerosol production or activities involving production quantities or concentrations of infectious cultures”.

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