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Serious pneumococcal disease outbreak in men exposed to metal fume – detection, response and future prevention through pneumococcal vaccination

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ABSTRACT

Welders and those exposed to metal fume are known to be at increased risk of pneumococcal pneumonia and invasive pneumococcal disease. Current UK guidance recommends that vaccination against pneumococcus be considered in those at risk of frequent or continuous occupational exposure to metal fume, taking into account the exposure control measures in place. We report an outbreak of serious pneumococcal disease that occurred between April and June 2015 among a multinational workforce exposed to metal fumes while working on the refurbishment of an oil rig in a Belfast shipyard. Four confirmed and five probable cases were identified, which occurred despite the use of environmental control measures and the availability of respiratory protective equipment. To provide direct protection to those at risk of pneumococcal disease and to eradicate carriage of pneumococcus and interrupt transmission, pneumococcal polysaccharide vaccine (PPV23) and antibiotic prophylaxis were offered to 680 individuals identified as potentially exposed to metal fume. Low levels of prior pneumococcal vaccination were reported among this target group (<1%). Genomic sequencing indicated a common strain of serotype 4 pneumococcus in two of the confirmed cases and a distinct serotype 4 in one case. The fourth confirmed case was identified as likely serotype 3 using a serotype-specific immunoassay on a urine specimen. Both serotypes 3 and 4 are vaccine-preventable strains covered by the conjugate and polysaccharide pneumococcal vaccines currently available. We propose that consideration should be given to strengthening implementation around pneumococcal vaccination for those exposed to metal fume through their work, even when other control measures are in place, to reduce the risk of future cases and outbreaks of serious pneumococcal disease.

1. Introduction

Pneumococcal disease is caused by the bacterium *Streptococcus pneumoniae (S. pneumoniae)*, an encapsulated Gram-positive diplococcus of which there are currently 92 recognised serotypes [1]. Infection causes a spectrum of disease, from milder illnesses such as otitis media and sinusitis to more severe presentations, collectively described as 'serious pneumococcal disease' [2]. Serious pneumococcal disease includes pneumococcal pneumonia and invasive pneumococcal disease (IPD), defined as pneumococcal infection of any usually sterile site e.g. pneumococcal meningitis and bacteraemia. IPD is associated with a case fatality rate of 12.5% in hospitalised adults [3].

Vaccination with the pneumococcal polysaccharide vaccine (PPV) is recommended for individuals who are aged 65 years or more, or in clinical risk groups [4]. The pneumococcal conjugate vaccine (PCV) has been included in the routine childhood immunisation schedule in the United Kingdom (UK) since 2006. Post-licensure surveillance of PCV in the UK showed a decrease in cases of invasive and non-invasive disease due to vaccine serotypes in both vaccinated and, to a smaller degree, older unvaccinated populations. This herd protection results from reduction in carriage in those who are vaccinated. In 2007, the World Health Organisation (WHO) recommended that all countries should include PCV in their routine immunisation schedule [5]. Despite this, pneumococcal

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vaccine strategies vary internationally, and PCV is not yet part of the routine immunisation schedule in all European countries [6].

It is recognised that welders and those exposed to metal fume are at increased risk of developing serious pneumococcal disease [7,8]. Although not fully understood, this may relate to components of the fume serving as a nutrient to increase adherence of pneumococci to lung tissue, or inhalation of the fume causing damage to the lung's immune defences [9]. UK immunisation guidance recommends that consideration be given to vaccinating those at risk of frequent or continuous occupational exposure to metal fume with PPV, taking into account the exposure control measures in place [4,10].

In Northern Ireland (NI), cases of IPD are reported to the Public Health Agency (PHA) through routine voluntary laboratory reporting arrangements. Isolates are not routinely typed. Between 2010 and 2014 the average annual incidence of IPD in NI was estimated at 6 cases per 100,000 population, with higher rates among the elderly and young children [11]. In May 2015, 4 cases of IPD in men working on an oil rig at a Belfast shipyard were reported to PHA. An outbreak control team (OCT) was convened to investigate and control the outbreak, with reference to national guidance [2]. The preliminary features have been described previously [11]. In this article, we provide updated findings from the completed epidemiological and microbiological investigations and discuss the rationale for and effectiveness of the control measures implemented. The implications for vaccination strategy among those with occupational exposure to metal fume are also considered.

2. Materials and methods

2.1. Setting

The setting of the outbreak was an oil rig which arrived in a Belfast shipyard in January 2015 for major refurbishment. Approximately 3000 individuals were employed on the project, either directly by the shipyard or oil rig owner, or through various contractors. There were up to 700 individuals working on the rig by day and 400 by night, with work taking place across all areas of the rig. There was a significant turnover of staff throughout the project, with workers employed on a variety of longer and short term contracts. Workers lived across Belfast in hotels and private accommodation. Approximately a third of the workers were ordinarily resident in NI, a third came from other parts of the UK and the remaining third from other European countries.

2.2. Epidemiological investigation

2.2.1. Case definitions

Specific case definitions were agreed for the purpose of the outbreak investigation and were defined as follows:

An individual who has worked at the Belfast shipyard since 19th January 2015 AND:

Confirmed case: a clinical diagnosis of IPD or pneumococcal pneumonia AND at least one of the following: pneumococcus isolated from normally sterile site (blood, cerebrospinal fluid (CSF), joint, peritoneum, pleural fluid or other, but not sites such as eye), pneumococcal DNA or antigen detected in fluid from a normally sterile site or pneumococcal antigen detected in urine.
Probable case: a clinical presentation compatible with IPD (conditions such as meningitis or empyema) or pneumonia (supported by radiographic imaging) where serious pneumococcal disease based on available clinical, microbiological and epidemiological evidence is the most likely diagnosis, in the absence of laboratory confirmation.

Relevant clinical information was obtained on confirmed and probable cases from the attending clinicians. The methods for retrospective and prospective case finding have been described previously [11].

2.3. Microbiological investigation

2.3.1. Local laboratory

Hospitalised cases were investigated in line with British Thoracic Society guidelines [12]. Respiratory and blood samples were submitted to the local microbiology laboratory for culture and sensitivity testing. Pneumococcus isolates were forwarded to the Respiratory and Vaccine Preventable Bacteria Reference unit (RVPBRU) of Public Health England for typing. Urine was tested for pneumococcal antigen using Trinity Biotech Uni-Gold™ *S. pneumoniae* immunoassay kit. For cases that tested positive on urinary antigen detection alone, urine samples were forwarded to RVPBRU for further characterisation.

To provide information about current circulating serotypes in the community, pneumococcus isolates from sterile sites submitted to the local microbiology laboratory between March and May 2015 from patients not associated with the outbreak were identified and forwarded for typing.

2.3.2. Reference laboratory

The identification of all referred pneumococcal isolates was confirmed by standard phenotypic methods [13]. DNA was extracted, quantified and sent for whole genome sequencing (WGS) by Illumina sequencing [14]. K-mer identification software was used to confirm species identification and multi-locus sequence typing (MLST) was performed using MOST [15]. Genomic single nucleotide polymorphism (SNP) analysis was undertaken together with 39 unrelated isolates of the same serotype as contextual isolates. Processed reads were mapped using BWA MEM4 to the S. *pneumoniae* reference genome *S. pneumoniae* TIGR4 (NC_003028). Single nucleotide polymorphisms were then called using GATK25 in unified genotyper mode. Core genome positions that had a high quality SNP ($DP \geq 5$, AD ratio ≥ 0.9, $MQ \geq 30$) in at least one strain were extracted. Positions that fulfilled filtering criteria in > 0.9 of the samples were joined to produce a multiple fasta format file. Maximum likelihood trees were constructed from the variable sites using the general time reversible (GTR) evolutionary model in RAxML v7.0.36. 1000 random bootstrap replicates were performed to analyse support for nodes in each tree.

A sensitive and specific Bio-Plex (Luminex technology) bead-based multiplex immunoassay was used to determine serotype-specific antigen from the urine specimen [16,17].

2.4. Environmental investigation

A site visit was undertaken during the outbreak investigation by a team from the health and safety enforcement authority for Northern Ireland. The team included microbiology expertise and had particular experience of welding and ship building environments.

2.5. Control measures

2.5.1. Identification of target population

The target population for prophylaxis was defined as those working on the rig who were exposed to metal fume due to their occupation. This included welders and other employees who worked alongside welders, including supervisors, standby firemen and labourers.