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The epidemiology of pneumococcal infections—The Swedish experience

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ABSTRACT

Pneumococcal infections are major contributors to morbidity and mortality world-wide and pose a major public health problem. Despite being a devastating pathogen pneumococci are common colonizers of the upper respiratory tract of healthy children. There is a need for more knowledge on the molecular epidemiology, and pathogenesis of pneumococcal infections to be able to find better strategies for prevention and treatment of these common infections. Here we discuss trends in the vaccine era of the epidemiology of pneumococcal carriage, invasive disease and antibiotic resistance development as well as present national epidemiology data from Sweden of invasive pneumococcal infections during 1987–2006.

1. Pneumococcal infections—a major health problem world-wide

Infectious diseases are after cardiovascular diseases the second most common cause of death world-wide, accounting for 26% of the overall mortality. Lower respiratory tract infections are the major infectious cause of mortality with annually 4.2 million deaths globally according to WHO (Fig. 1, adapted from www.int/healthinfo/global_burden_disease). Moreover, pneumonia is a major contributor to mortality among the youngest children below 5 years of age (Fig. 2, adapted from www.int/healthinfo/global_burden_disease). *Streptococcus pneumoniae* (also called pneumococci) is the major cause of community acquired pneumonia, and a major contributor to invasive infections such as septicaemia and meningitis. It also causes milder mucosal respiratory tract infections such as acute otitis media and sinusitis. Even though we have access to antibiotics and intensive care at least in the developed world pneumococcal infections remain responsible for a huge burden of global morbidity and mortality in infectious diseases and it has been estimated that over 1 million children die every year world-wide from a pneumococcal infection [1]. Estimates from the USA show that the fatality rates in pneumococcal pneumonia is about 5%, in combination with septicaemia about 20% and in meningitis as high as 30% [2]. Survivors of pneumococcal meningitis are also at risk to get sequelae such as hearing loss. The risk groups for acquiring pneumococcal infections are the youngest children, the elderly and those that are immuno-compromised for example HIV patients, but also individuals that have been splenectomised. Furthermore, a prior influenza infection predisposes for pneumococcal infections and it has been shown that several of the deaths caused during the 1918 pandemic influenza were caused by superinfections with bacteria, mainly pneumococci [3–5].

Despite being a devastating pathogen pneumococci are also common colonizers of the upper respiratory tract in children. Healthy children attending day-care centres have been shown to carry these bacteria in the nasopharynx in up to 60–70% [6,7]. Carriage rates decrease with age and adult individuals without children at home have a low carriage rate. Still it is not clear why these bacteria sometimes cause disease but usually colonizes harmlessly young children.

2. Molecular epidemiology of pneumococcal infections

Pneumococci can be divided into at least 91 different serotypes depending on differences in their capsular polysaccharides. Virulence has been shown to differ with capsular type and non-encapsulated pneumococci have been regarded as non-virulent. However, non-encapsulated pneumococci may be found in the nasopharynx of children, the major ecological niche for pneumococci. The current pneumococcal vaccines are based on a limited number of pneumococcal capsular polysaccharide types. The polysaccharide based vaccine, including 23 serotypes, has been used for decades but due to the low protective value of the vaccine especially in some of the risk groups, the youngest children under the age of two years, and persons suffering from immunodeficiency,

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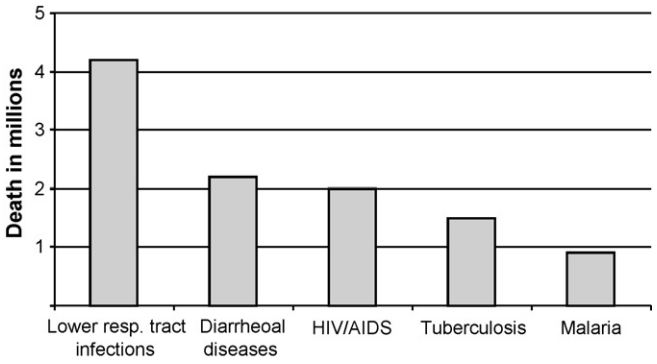

Fig. 1. Deaths in infectious diseases world-wide in 2004. Modified from the WHO home page (Global Burden of Disease Report 2004).

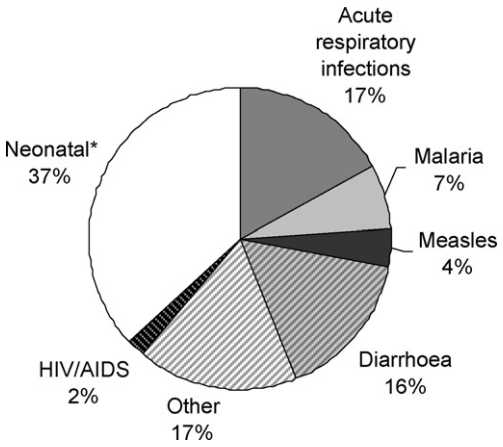

Fig. 2. Deaths world-wide among children below 5 years of age, 2004. Modified from the WHO home page (Global Burden of Disease Report 2004). *Of the neonatal deaths, 25% were caused by infections.

novel so called conjugated vaccines have been developed where the polysaccharide has been coupled to a protein carrier thereby evoking a better immune response. The licensed conjugated vaccines include 7 or 10 different capsular serotypes respectively out of the 91 found so far, chosen to be the most commonly found causing invasive disease mainly in the USA. A 13-valent vaccine has been approved in 2009 in some countries as well.

The 7-valent vaccine was first introduced in the USA in year 2000 and since then it has been introduced into the children vaccination program in many countries. The experiences so far demonstrate a significant decrease of invasive pneumococcal disease and of carriage caused by the vaccine types as well as a herd immunity effect in the adult population. However, an increase of non-vaccine types, especially among antibiotic non-susceptible isolates, has been observed and there is a risk for an expansion of non-vaccine types by serotype replacement or selection of non-vaccine types. The serotype distribution also varies with geographic area and time point studied why the potential coverage rates for these capsular based vaccines may differ. Therefore, efforts are being made to find other approaches for affordable pneumococcal vaccines for example searches for proteins that may be vaccine candidates in a multi-component protein based vaccine. In order to find interesting vaccine candidates and to be able to focus preventive and treatment strategies it is crucial to gain more knowledge about the molecular epidemiology and pathogenesis of pneumococcal infections.

When studying spread and genetic relatedness between pneumococcal isolates, clonality, it is not enough to only perform serotyping, also molecular typing methods have to be used such as PFGE (pulsed field gel electrophoresis, where the bacterial genome is cleaved with a restriction enzyme and the fragments separated depending on charge and size on a pulse field gel) [8], and the sequenced based method MLST (multi locus sequence typing, where 7 different alleles in the pneumococcal genomes are being sequenced and the data obtained are submitted to a database on the internet (www.mlst.net) where a sequence type is assigned that can be compared between different strains) [9]. Other methods used with higher discriminatory power include whole genome based microarrays as well as whole genome sequencing, techniques that recently have become more accessible and affordable. Pneumococci are easily transformed and may incorporate DNA from other bacteria. Hence, pneumococcal isolates may switch capsular types by taking up capsular genes from other pneumococci. Thereby bacteria of different capsular serotypes may carry the same genetic content except for the capsule. The close genetic relatedness in these cases can only be shown by using molecular typing methods.

3. Invasive disease potential differs with capsular serotype

By comparing invasive disease isolates with carriage isolates from the same time point and the same geographic area we and others have found that the invasive disease potential i.e. how prone the bacteria are to cause invasive disease, differs with serotype [10,11]. Furthermore, our recent data show that the invasive disease potential not only differs between pneumococci of different serotypes but potentially also of different clonal types as determined using molecular typing methods. Pneumococci of serotype 1 and 7F were shown to be of high invasive disease potential meaning that they are rarely found causing carriage, while serotypes 3, 6A, 6B, 19F and 23F are common among carriers but can also cause invasive disease [10,12]. However, when studying clinical parameters we found that patients infected with isolates of serotypes with a low invasive disease potential had a higher case fatality rate when they caused invasive disease, than those with a high invasive potential [12]. Also, we found that the proportion of patients with underlying diseases was higher among those infected with pneumococcal isolates belonging to clonal types of low invasive disease potential.

To further study correlations between invasive disease potential and genetic content of the bacteria we performed a genomic comparison using a microarray chip composed of two of the sequenced genomes, R6 and TIGR4. We chose to study pneumococcal isolates belonging to several serotypes and clonal types with different invasive disease potential but could not find one unique pattern distinguishing the most invasive clones from the others, suggesting that there is a considerable redundancy among virulence genes [13]. In addition to the core genome we found that the genome among the 47 clinical isolates studied consisted of 41 variable regions that we called accessory regions. Several of these accessory regions have previously been associated with virulence in *in vitro* and *in vivo* models. One of the accessory regions encode a surface structure, a pilus like structure, on the surface of pneumococci that we have shown to be important for adhesion to lung epithelial cells, as well as for colonization and virulence in mice models [14,15]. The pilus is composed of three structural proteins, RrgA, RrgB and RrgC, and we demonstrated that the minor pilin subunit RrgA is the major adhesin [16]. Homologues to these proteins have been found to encode pilus like structures also in other Gram positive bacteria such as Group A and B streptococci, enterococci and *Corynebacterium diphtheriae*.

4. Antibiotic resistant successful pneumococcal clones spreading globally

Pneumococcal infections have been treated with antibiotics such as penicillin since decades. However, we have witnessed an emerging increase of antibiotic resistance in this pathogen.