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A simple mathematical model for genetic effects in pneumococcal carriage and transmission

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ABSTRACT

Streptococcus pneumoniae (*S. pneumoniae*) is a bacterium commonly found in the throat of young children. Pneumococcal serotypes can cause a variety of invasive and non-invasive diseases such as meningitis and pneumonia. In 2000 a vaccine was introduced in the USA that not only prevents vaccine type disease but has also been shown to eliminate carriage of the vaccine serotypes. One key problem with the vaccine is that it has been observed that the same sequence types (genetic material found in the serotypes) are able to manifest in more than one serotype. This is a potential problem if sequence types associated with invasive disease may express themselves in multiple serotypes.

We present a basic differential equation mathematical model for exploring the relationship between sequence types and serotypes where a sequence type is able to manifest itself in one vaccine serotype and one non-vaccine serotype. An expression for the effective reproduction number is found and an equilibrium and then a global stability analysis carried out. We illustrate our analytical results by using simulations with realistic parameter values.

1. Introduction

Streptococcus pneumoniae, or pneumococcus, is a bacterium which was discovered simultaneously and independently in the late nineteenth century by the American physician George Miller Sternberg and the French chemist Louis Pasteur. Since then approximately 90 serotypes have been identified, although the majority of pneumococcal infection and disease is associated with a much smaller number. The serotype is the polysaccharide capsule that surrounds pneumococcal sequence types. There are hundreds of known pneumococcal sequence types. Pneumococcal serotypes and sequence types have been observed to be highly correlated, with the most invasive sequence types corresponding to the most invasive serotypes.

Pneumococcus is commonly carried in the nasopharynx (the area of the upper throat that lies behind the nose) of children less than two years of age, predominantly causing no infection. However, pneumococcus can cause various infections such as otitis media (an ear infection, common in infants), sinusitis and pneumonia, and invasive diseases such as meningitis and septicaemia. It may be passed from person to person through direct contact and respiratory droplets (e.g. coughs and sneezes) of an infected person.

In the past antibiotics were primarily used to treat pneumococcal infections and disease. However this led to an increase in the number of antibiotic-resistant pneumococcal strains. Therefore, in an effort to prevent the development of pneumococcal infection and disease, vaccines have been developed. The two vaccines currently in use in the UK are the 23-valent polysaccharide vaccine and the 7-valent conjugate vaccine. The 23-valent polysaccharide vaccine contains purified capsular polysaccharide from 23 different pneumococcal serotypes whilst the 7-valent conjugate vaccine consists of purified capsular polysaccharide from 7 different pneumococcal serotypes conjugated to protein.

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The 23-valent polysaccharide vaccine was introduced in the UK in 2003 and is recommended for adults aged 65 years and over and anyone over the age of five years who is at increased risk of developing pneumococcal infection (e.g. those who are immunocompromised). This vaccine is not effective in children under two years old as their immune systems are not sufficiently well developed.

However more recently the 7-valent conjugate vaccine has been developed. This vaccine is effective in preventing pneumococcal infection for those under two years old. This vaccine was introduced to the immunisation schedule of children under two years old in the UK in September 2006.

The 23-valent polysaccharide vaccine is 60%–70% effective against preventing invasive disease from the 23 vaccine serotypes which account for approximately 85%–90% of the circulating pneumococcal strains. On the other hand, the conjugate vaccine is effective against preventing invasive disease from much fewer serotypes, but it has been shown to have almost 100% efficacy in preventing vaccine type invasive disease. One of the other advantages of the conjugate vaccine is that it has been shown to prevent carriage of these serotypes, allowing for the possibility of herd immunity. This occurs when immunising selected individuals in a community protects the whole community. It is thought that, since the conjugate vaccine reduces the carriage of the seven vaccine serotypes in children less than two years old, the overall carriage of these serotypes will reduce. Children under two years old are the primary carriers of pneumococcus. Therefore, it is believed that vaccination of this group may prevent the transmission to adults.

However, there are potential problems associated with the use of these vaccines that may prevent them from having long-term efficacy.

Firstly since these vaccines act only on a limited number of the possible 90 pneumococcal serotypes; there is the potential for serotype replacement where the carriage of non-vaccine serotypes becomes more prevalent, replacing the vaccine serotypes, possibly causing non-vaccine type infection and disease.

The second problem is that it has been observed that the same sequence types are able to manifest themselves in more than one serotype. This is a problem if sequence types associated with invasive disease are able to manifest themselves in non-vaccine type serotypes. We are interested in investigating this.

To emphasise the potential problem we consider data presented in [1]. This shows sequence types with multiple serotypes found in a Scottish study of invasive pneumococcal isolates carried out between January and June 2003. Of most interest in this study was serotype 14 which was reported as having increased invasive disease potential and was discovered to be associated with ten different sequence types. The data show that six of the sequence types associated with serotype 14 are able to manifest themselves in multiple serotypes. Five of these serotypes are not included in the conjugate vaccine. Therefore there is the potential for pneumococcal infection or disease of these non-vaccine serotypes to become more prevalent.

In this study it was also noted that the non-vaccine serotype 8 was the second most common serotype causing invasive disease in Scotland. From the data it can be seen that sequence type 9, the major sequence type of serotype 14, also exists as serotype 8. Therefore, there is the potential for invasive disease of serotype 8 to increase, and not be covered by the vaccine, if all of the sequence type 9 pneumococcal capsules switched to serotype 8.

We are interested in developing simple mathematical models to consider the problem of sequence types being able to manifest themselves in more than one serotype. This is motivated by the work in [2]. Lipsitch considers two serotype models in which he investigates the competition between a vaccine type serotype and a non-vaccine type serotype. However he does not consider sequence types in his model. Therefore to model what happens when sequence types manifest themselves in more than one serotype, a simplified version of Lipsitch's model was altered and classified in terms of sequence type. In Lipsitch's paper the possibility of individuals being simultaneously co-infected with two serotypes was considered. In this paper due to space restrictions we consider a simple mathematical model for the transmission dynamics of the disease where there is one sequence type associated with two serotypes. In future papers we hope to build on this work by considering multiple sequence types and individuals being able to be simultaneously co-infected with multiple serotypes.

In the following section we shall describe the basic mathematical model which we shall use to describe the spread of the pneumococcus. This is followed by an equilibrium analysis. Next we derive the effective reproduction number for this model. This is followed by a global stability analysis. Some simulations and a brief summary conclude the paper.

2. Mathematical model

The model consists of one sequence type associated with two serotypes. This model includes four possible classes of hosts:
those unvaccinated susceptible to carriage of sequence type 1, (X);
those unvaccinated carrying sequence type 1, (T_1);
those vaccinated susceptible to carriage of sequence type 1, (V);
and
those vaccinated carrying sequence type 1, (V_{T_1}).

A proportion f of children receive the vaccine. The sequence type T_1 can express itself as either serotype 1 (Y_1) or serotype 2 (Y_2) with proportions pT_1 or $(1-p)T_1$ respectively. The vaccine is wholly effective against serotype 1 but completely