Mathematical model—tell us the future!

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Studying bacterial resistance has direct importance for the antimicrobial treatment of individual patients. In addition, surveillance data pooled from individual diagnostic reports help physicians to choose the most effective drug for empirical therapy. However, this is not the limit of what can be done with the resistance data. There is an increasing need to synthesize the available strands of data in order to construct mathematical models that can be used as tools to predict the likely outcomes of various antibiotic policy options.

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Introduction

Information on resistance can be used to try to understand the influence of different factors on the spread of bacteria resistant to antimicrobial agents. These factors include, perhaps most importantly, the consumption of antimicrobial agents, but also hygiene measures and vaccinations, as is the case with Streptococcus pneumoniae.

How might we control antimicrobial resistance? Reducing and targeting antimicrobial use is important, but how should this be done wisely? Physicians need antimicrobial agents in their daily life. These drugs are the main curative class of drugs in physicians’ treatment arsenal, and physicians’ success is very much dependent on their use. Recommendations to change prescription behaviour need a good scientific basis. Therefore, we should develop tools to predict development of resistance when different antibiotic policies are used.

Mathematical models are important tools that can be used to understand aspects of various processes and to make predictions. During recent decades, huge amounts of resistance surveillance data have been produced. In contrast, over the same period, there has been an almost total lack of antimicrobial consumption data. When we began to study the relationship between bacterial resistance and antimicrobial consumption more than two decades ago, hospital data were easy to obtain. However, it was almost impossible to get figures on antimicrobial consumption from outpatient practice. This information was in the hands of the pharmaceutical industry and, with a few exceptions, they were not interested in sharing data on antibiotic sales. In Finland, the situation changed in the 1990s when the authorities responsible for medicines began releasing all consumption data, even at the community level, for research purposes. In Europe, a cornerstone of progress was negotiation, during which researchers succeeded in buying consumption data from a company responsible for antibiotic consumption data collection. Today, the network for European Surveillance of Antibiotic Consumption is collecting data on antibiotic sales Europe-wide.

Now there is a real opportunity, having both surveillance data of bacterial resistance and consumption of antimicrobial agents, to probe different kinds of mathematical models to try to predict the future of bacterial resistance.

The paper by Magee, in this issue contains delightful philosophical considerations, although the theoretical basis of this model may not be complete. The approach is different from those models published previously. In planning for the future with the assistance of mathematical models, several aspects need to be considered. It is of primary importance to understand that mathematical modelling is a purely theoretical exercise and the results obtained from a model are only as good as the stated assumptions made.

Therefore the first comment on Magee’s model concerns a lack of accurate data on antimicrobial consumption. I miss most a definition of the bacterial species that this theory concerns. Readers want to see how the model applies to the real world. It is reasonable to assume that different bacteria will behave differently. The epidemiology of Streptococcus pneumoniae is different from that of Escherichia coli or Staphylococcus aureus. Most of us have E. coli in our gut, but only a fraction of us are colonized with the pneumococcus or S. aureus. Second, most of the bacteria are epidemic. Even E. coli causing urinary tract infections have been said to be transmissible or of animal origin. Thus, why would only human antibiotic use have an impact on the development of resistance? Methicillin-resistant S. aureus is also very different. Multiresistant clones are spreading despite the level of antibiotic usage. Hygiene measures also have an impact on the spread of bacteria, at least in hospitals, but why not also in the community, especially when most of the bacteria are epidemic?

I have always wondered, why do 80–90% of S. aureus isolates produce penicillinase uniformly all over the world? It has been
suggested that this is caused by nasal lysozyme production that favours penicillinase-producing staphylococci. If this is the case, antibiotic consumption may have had only a minor role in the spread of penicillinase-producing staphylococci. Third, we know that resistance factors in *E. coli* are often in gene cassettes containing resistance genes to several antibiotic classes at the same time. So, reduction of one antibiotic class may not necessarily have any direct influence on the existence of these gene cassettes and the resistance levels may remain unchanged. For instance, it was reasonable to expect that decreased use of sulphonamides would not actually result in decreased resistance to sulphonamides in the UK. The model of Magee predicts a continuous increase of resistance. There are, however, many examples of stable resistance levels despite heavy antibiotic use. Although an exception, *Streptococcus pyogenes* is still completely susceptible to penicillin. In addition, how can this model account for studies that show decreases of resistance of pneumococci in Iceland and group A streptococcus in Finland? In addition, human population density may have a role in the spread of resistant bacteria. Transfer of bacteria is different in urban and remote geographical areas. Seasonal variation in antibiotic use is a common phenomenon, but not for all antimicrobials and not in all communities. Furthermore, adaptation differences of bacteria may cause problems for mathematical models.

Development of bacterial resistance is a complex issue. Thus we need to develop different kinds of models to understand better the spread of bacteria resistant to antimicrobial agents. The article written by Magee is an example of one model. It is now open for discussion and further development. It is to be hoped that development and refinement of current models will one day yield useful tools to predict how different bacteria will behave under different selection pressures caused by antimicrobial agents and many other factors.

**Editorial note**

A reply to the points raised in this article appears in the Correspondence section of this issue.

**Background of this article**

Professor Huovinen was originally invited and agreed to act as a referee for the article by Magee. In his assessment of the article, Professor Huovinen commented that it might be appropriate for Dr Magee’s article to remain more or less unchanged and that his (Professor Huovinen’s) observations be published as an associated article. The Editor discussed this option with both parties and secured their agreement to proceed. We would like to thank Dr Magee and Professor Huovinen for their contributions.

**References**


