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Commentary

# *Streptococcus pneumoniae* controlled human infection models: Opportunities and challenges

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In this article of EBioMedicine, Morton and colleagues [1] evaluated the feasibility of an experimental *Streptococcus pneumoniae* controlled human infection model in Malawi. Building on their experience using this approach in over 1500 adult participants in the UK, the authors have now established this model in a setting with a high pneumococcal carriage burden. This is an important step, since pneumococcal epidemiology and host response to pneumococcal infection and/or vaccination is likely to be different than in high-income countries. In healthy student volunteers, experimental infection with a high dose of pneumococcal serotype 6B (a frequently detected carriage serotype) resulted in carriage being achieved in 4/9 participants (44%) – which was above their pre-defined acceptance criteria of 40% - compared with 3/9 (33%) in the low dose group and 0/9 (0%) participants in the saline group. The feasibility of this carriage model will allow subsequent studies to investigate important questions related to pneumococcal biology and novel prevention strategies.

Pneumococcal carriage is the critical step in the development of serious diseases such as pneumonia, meningitis and sepsis [2]. In high-income countries, vaccination with pneumococcal conjugate vaccines (PCVs) have been shown to reduce vaccine-type carriage through direct (individual) and indirect (population) effects, although serotype replacement with non-vaccine serotypes does occur. However, in low- and middle-income countries (LMICs) where most of the pneumococcal disease burden is, carriage effects by PCVs are more variable due to differences in pneumococcal exposure and transmission [3]. This poses additional challenges in the control of pneumococcal disease in these settings.

Human challenge models have significant advantages over other conventional animal disease models (e.g. mouse) and have been used for several infectious pathogens, including typhoid, dengue, *Streptococcus pyogenes*, RSV, malaria and many others [4]. Use of such models offers important insights into host-pathogen interactions, immune response profiling and can be extended to the evaluation of novel vaccines. A key advantage of establishing a pneumococcal challenge model in a LMIC setting such as Malawi offers both researchers and clinicians the possibility of addressing biologically relevant questions in the field. Firstly, understanding the immune correlates of protection against pneumococcal carriage in humans is a major knowledge gap. It is believed that much higher antibody levels are needed to protect against mucosal disease and carriage than what is required to protect against invasive pneumococcal disease [5]. Several other immunological markers have been proposed to protect against human carriage acquisition, most notably Th17 cells and memory B cells. While Th17 cells can prevent carriage and disease in mice, a similar effect in humans has been more difficult to determine. Memory B cells have perhaps shown the greatest promise as a marker of carriage protection, as shown previously in challenge studies by the authors [6], while pneumococcal protein-specific antibody responses were associated with carriage protection in an earlier pneumococcal challenge study [7]. A randomised controlled trial of alternative PCV dosing schedules in Vietnam is also undertaking analyses of memory B cells and carriage, with results anticipated in the near future [8]. Human challenge models are therefore uniquely placed to answer these questions.

One of the important applications of developing a pneumococcal human challenge model is to evaluate novel pneumococcal vaccines. This relies on a robust protocol that can be replicated in terms of clinical, microbiological and immunological features. The collection of serial mucosal and blood samples before, during and after inoculation enables a deeper appreciation of the complex cellular and molecular factors involved in protection against pneumococcal carriage and disease. The novel mucosal sampling techniques used by the authors provides a simpler and less-invasive approach to directly study the immune response in the respiratory tract. Such information is needed to better understand mucosal immunity to the pneumococcus and will advance the development of novel pneumococcal vaccines targeting these responses. A number of next generation pneumococcal vaccines are in development, including new conjugate vaccines as well as serotype-independent vaccines [9]. The evaluation of vaccines using human challenge studies is also useful to inform improved strategies to protect populations at high-risk of disease (e.g. malnutrition, HIV-infection) as well as investigating alternative dosing

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schedules, effects on other serotypes of interest (e.g. serotype 3) or to examine bacterial-viral interactions such as influenza or RSV.

While this study offers great promise, an important aspect that needs to be considered is how translatable such human challenge studies that are conducted in adults are in relation to infants and children who are most susceptible to pneumococcal disease. Given that the respiratory microbiome changes with age [10] as does the immune system, these may result in differential biological impacts on the response to the challenge itself and potentially vaccine efficacy. Nevertheless, the findings presented in this feasibility study are an important first step in unravelling some of the key knowledge gaps related to host protection against pneumococcal carriage and disease. Such innovations are needed in order to improve health outcomes in children and adults living in high pneumococcal disease burden settings.

## Contributors

This commentary was solely written by PVL.

## Declaration of Competing Interest

None.

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