Serotype prevalence of Streptococcus pneumoniae in Malaysia – the need for carriage studies

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SUMMARY

Pneumococcal disease, caused by the bacterium *Streptococcus pneumoniae*, is a major burden to global health. Although the World Health Organisation (WHO) strongly recommends the inclusion of pneumococcal conjugate vaccines in national immunisation programmes (NIP's) worldwide, this has not occurred in many countries in the WHO South East Asia and Western Pacific regions – particularly longstanding middle-income countries. It is widely accepted that carriage of *S. pneumoniae* is a precursor to developing any pneumococcal disease. The reduction in pneumococcal disease from vaccine serotypes (VT) following widespread implementation of the pneumococcal conjugate vaccine (PCV) is believed to be through the direct immunogenic protective effect of immunised individuals as well as indirectly through herd immunity diminishing the incidence of disease in non-immunised individuals. In Malaysia, pneumococcal disease is not included in national surveillance programmes and although PCVs have been licensed, they have not been included in the NIP. Hence, the vaccine is only available privately and the majority of the population is not able to afford it. There is an urgent need to develop surveillance programmes in Malaysia to include pneumococcal serotype data from carriage and invasive disease so that it may help guide national vaccine policy prior to a decision being taken on the inclusion of PCVs in the NIP.

KEY WORDS:
Streptococcus pneumoniae, serotype, pneumococcal conjugate vaccine, surveillance

INTRODUCTION

Streptococcus pneumoniae (the pneumococcus) is an important cause of pneumonia, meningitis and bacteraemia worldwide, particularly among the very young. According to the World Health Organisation (WHO) between 3.4 – 6.8% of the estimated 8.8 million global deaths of children <5 years of age in 2008 were attributable to pneumococcal infection.[1] Prevention of the mortality and morbidity associated with pneumococcal disease by immunisation is therefore an attractive proposition. The first pneumococcal conjugate vaccine (PCV), the 7-valent Prevenar™ (Wyeth/Pfizer), was licensed in the USA and Europe in 2000. It has since been superseded by a 10 valent pneumococcal non-typeable *Haemophilus influenzae* protein D vaccine (PHiD-CV; Synflorix™, GSK) and a 13 valent PCV (Prevenar 13™, Pfizer). Only routine immunisation with PCVs has shown sufficient evidence of benefit to be recommended for use by the WHO for pneumococcal immunisation in resource-limited settings.[1] The 23-valent polysaccharide vaccine is therefore discounted from this review.

Pneumococcal Conjugate Vaccine

The efficacy of PCV7 has been demonstrated in several countries where numerous studies have shown a correlation between a reduction in VT serotypes implicated in invasive pneumococcal disease (IPD) and PCV uptake.[2-5] Infants and children under 5 years of age, the demographic target for PCVs, are believed to be the main reservoir for pneumococci, with nasopharyngeal (NP) carriage rates ranging from 27% to 85% in developed and developing countries respectively.[1] Colonisation is a prerequisite to pneumococcal disease and widespread use of PCV7 has resulted not only in a dramatic reduction in IPD and other pneumococcal infections among the immunised target age group, but also among older, unimmunised age groups through herd immunity. This indirect effect of immunisation also benefits infants too young to receive or complete the course of PCV vaccination, as well as older children, the immunocompromised and other high-risk groups. In consequence, the WHO considers that the PCV should be prioritised for inclusion in national immunisation programmes (NIP's). PCV's have since been added to the childhood immunisation schedules in numerous countries.[6]

In South East Asia, however, there has been a notable delay in the adoption of PCV's. Four South East Asian nations are currently eligible for full support to introduce PCV's via the Global Alliance on Vaccination and Immunisation (GAVI) funding programme. Only two of them have implemented widespread and free childhood PCV13 immunisation however, Laos in 2013 and Cambodia from January 2015. Myanmar is scheduled to introduce PCV10 in quarter one of 2016.[7] Other countries with developing economies in South East Asia have licensed the use of PCVs, some even including them in their NIPs, but they are not freely available, such as the Philippines, which constrains vaccine use and coverage. These countries are ineligible for GAVI assistance in implementing free universal childhood PCV immunisation as they are not among the world's very poorest nations. PCV7 which was licensed for use in Malaysia since 2005, has been superseded by PCV13, but pneumococcal immunisation has

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yet to be included in the country's NIP. National coverage is unknown but presumed to be very low, as PCVs have only ever been available privately in Malaysia. Although the indirect effects of immunisation are often greater than the direct effects, particularly in developing countries, it is unlikely that there is yet any PCV generated herd immunity in Malaysia.

Serotype Carriage

A decline in colonisation by VT serotypes and associated reduction in disease burden resulting from immunisation programmes leaves the NP microbiome open to colonisation by other non-vaccine serotypes (NVT) of pneumococci. Post-PCV implementation disease surveillance and carriage programmes, primarily in industrialised, Western settings, have reported increased prevalence of NVT of pneumococci concomitant with a decline in VTs. [5, 8-10] Although this serotype replacement induced by the selective pressure of immunisation has been shown to increase the proportion of IPD caused by NVT, the increase is generally more than offset by the overall decline in disease caused by *S. pneumoniae*. [2] Research in regions of widespread PCV7 rollout, predominantly in Europe and the USA, suggests that many of the replacement NVT serotypes are less invasive to children than the PCV7 serotypes.[11] Much implementation of the higher valency PCV10 and PCV13, is yet to occur in lower income countries. It is strongly anticipated that the higher valency PCVs will greatly offset the burden of IPD and other pneumococcal disease that resulted from the expansion in NVT serotypes following PCV7 introduction. It should be noted that the WHO's stance on serotype replacement is that it should not impede the introduction of PCVs. Additionally, non-vaccine factors, such as secular trends in serotype prevalence, masking and variation in serotype invasiveness may have confounded interpretation of the link between an increase in NVT and introduction of PCV7. [12, 13]

Pneumococcal Surveillance

Surveillance programmes of serotypes causing IPD, such as the Center for Disease Control's Active Bacterial Core Surveillance in the USA and Public Health England's Enhanced Surveillance of IPD, are exemplars for assessing the burden of IPD and success of immunisation programmes.[14] Such programmes have drawbacks however, especially applicable to developing countries; namely the necessity for microbiology and diagnostic resource and infrastructure. They require the medical and laboratory capacity to ensure large numbers of clinical samples are taken, as well as sufficient clinical samples cultured, to detect any effect of immunisation on prevalence of pneumococcal serotypes. As a result, clinical serotyping data from the developing countries of Africa, Asia and Latin America is generally scarcer than from industrialised countries. NP serotype carriage is therefore receiving attention as a means to predict and infer the effect of immunisation on pneumococcal disease as pneumococcal colonisation is an accepted prerequisite to IPD and other forms of pneumococcal disease. [15-17] Although such studies do not provide a direct measure of any reduction in pneumococcal disease, decreases in VTs detected via surveillance of carriage can be used to infer indirect benefits of PCV rollout in the population as a whole, including the unvaccinated majority. Surveillance of pneumococcal carriage serotypes is not only capable of alerting the scientific community to likely changes in prevailing serotypes, but compared with disease surveillance, requires smaller cohorts as the incidence of colonisation is far more common than invasive disease. The smaller scale of sampling required for carriage studies makes them faster and cheaper than disease surveillance studies to run, and consequently more likely to continue longer, which compounds the value of the data collected.

Pneumococcal Epidemiology in Malaysia

Considering the complexities in the dynamics that determine pneumococcal serotype prevalence, there is an urgent need to increase the data available for pneumococcal carriage and disease in Malaysia. At present there are limited data in Malaysia on the incidence of pneumococcal disease although there are an estimated 2,809 cases of pneumococcal meningitis each year[18]. Although more pneumococcal serotyping data is available for Malaysia than for several other countries in South East Asia, for an upper-middle income country, data on the prevalence of circulating pneumococcal serotypes in carriage or disease are scarce. Several epidemiological studies have described pneumococcal serotype prevalence in Malaysia or South East Asia but they focus on a single centre with a relatively small number of isolates, [19-22] focus on a limited timescale, [23, 24] are dated, [21, 24-26] or provide little or no serotyping data.[21, 25, 26] They are summarised in Table I. It is therefore difficult to fully assess the serotypes likely to be carried or causing disease in the wider community; and the benefits of pneumococcal immunisation in Malaysia is therefore poorly understood.

The most recent comprehensive analysis of the distribution of pneumococcal disease serotypes across South East Asia showed that amongst a total of 484 invasive isolates, the most common VTs in Malaysia were 19F, 14, 6B, 1 and 19A.[27] Serotypes 6A and 6B were more common in children under the age of five years, while 19F, 1 and 6B were more common in patients over the age of five years old. Unfortunately, in the case of the majority of disease strains isolated, the patient age was not co-reported, so any association between disease serotype and age could not be examined. Based on the findings of this study the potential coverage of serotypes by PCV7, PCV10 and PCV13 was 47%, 59% and 75% respectively. However, given that the pneumococcal serotype epidemiology is continually in flux due to natural fluctuations and uptake in PCV immunisation around the world, the actual serotype coverage of contemporary vaccines is difficult to determine. Moreover, the two currently available PCV's, PCV10 and PCV13, may affect carriage differently, due to their distinct protein and polysaccharide constituents, which could affect species composition and prevalence of respiratory microbiota differently.

Despite the paucity of prior data on the prevailing serotypes, with the assistance of the GAVI Alliance, PCV immunisation is becoming increasingly common in the poorest countries. However, as data on serotype prevalency prior to widespread PCV rollout with GAVI assistance is limited, the scope for monitoring the epidemiological effects of vaccination in these countries, including in South East Asia is constrained. The likely negligible PCV herd immunity in Malaysia

Table I: Summary of pneumococcal surveillance studies in Malaysia in reverse chronological order of study period

Study	Setting/design	Years	Age group	No. of isolates	Serotypes (top 5)	Limitations
Yatim *et al.* 2013 [22]	Carriage study in day care centres.	2010	Aged 5 years or under	69	6A, 23F, 19A, 6B, 19F	• Single geographical area. • Small number of participants.
Yasin *et al.* 2011 [23]	Laboratory based surveillance, 15 state hospitals	2008-2009	All ages	433	19F, 6B, 19A, 14, 1, 6A (last two equal 5th)	• 50% were non-invasive isolates.
Foh *et al.* 2011 [19]	Laboratory based surveillance	1999-2007	All ages	151	19F, 23F, 1, 6A/6B	• Single centre study. • Limited number of isolates over 8 year period. • Invasive and non-invasive isolates included.
Lim *et al.* 2007 [20]	Laboratory/clinical based surveillance	1999-2004	<14 years	50	Not reported	• Single centre study. • Small number of isolates. • No serotyping.
Rohani *et al.* 1999 [24]	Laboratory based surveillance	1995-1996	All ages	201	1, 6B, 19B, 19F, 23F	• One year study. • Only six hospitals included.
Cheong *et al.* 1988 [26]	National hospital-based acute respiratory infections study.	1984-1985	1 month to 5 years	250	Not representative	• Only 92 of 250 isolates serotyped. • Invasiveness of serotypes unknown
Malik *et al.* 1998 [25]	Carriage study in kindergarten students, in-patients and pediatric clinics.	Not known	1 month to 6 years	355	Not reported	• Single centre. • No serotyping.
Jamal *et al.* 1987 [21]	Laboratory based surveillance	Not known	All ages	57	6A, 14, 19A, 6B, 1	• Limited number of isolates over 4 year period. • Study included both invasive and carried isolates.

Adapted from Jauneikaite *et al.*[27]

presents an opportunity to investigate pneumococcal serotype dynamics before, and potentially post, widespread PCV immunisation, which would be rare for Asia and many other non-industrialised countries. Awareness of pneumococcal disease has increased in recent years, yet there remains a need for improved data to inform guidance on vaccine policy. Without such data, it will not be possible to understand the true burden of pneumococcal disease, the most appropriate PCV to introduce and the extent of the benefit of adding PCV to the country's NIP, should it occur.

Prospects for Pneumococcal Research and Immunisation Policy in Malaysia

The Malaysian Ministry of Health continues to review the potential benefit of a PCV programme in Malaysia. It is therefore essential to understand the carriage of pneumococci and circulating serotypes before any introduction of PCV to help direct national vaccine policy. The WHO advocates that disease surveillance should begin at least 2 years prior to the introduction of a PCV programme but also states that a lack of population-based surveillance should not be an impediment to PCV introduction.[1] However, there is still time for those in public health, primary care, infectious disease and microbiology to undertake carriage studies in order to guide national policy decisions. Carriage studies should continue in one of two scenarios. Firstly, if any decision for PCV implementation is delayed it facilitates the gathering of a more comprehensive epidemiological dataset to better inform any later policy decision on pneumococcal immunisation in Malaysia. Secondly, if PCV implementation occurs soon, then the direct and indirect effects should be monitored. Enhanced surveillance of pneumococcal disease should also be undertaken so that its true burden can be understood in Malaysia, with surveillance of disease incidence ideally continuing for at least five years post introduction according to the WHO.[1]

CONCLUSION

Conducting well-designed carriage studies and pneumococcal disease surveillance of prevalent serotypes, prior to adding PCV to a NIP presents an opportunity to assess the direct and indirect benefits of widespread immunisation, and any effect it may have on serotype replacement in Malaysia. It is also an opportunity to evaluate the consequences of introducing a higher valency PCV in a population where the pre-existing herd effect from PCV7 is likely to be negligible, in contrast to the epidemiological setting in the majority of Western countries where most post-PCV10 and -PCV13 introduction surveillance, has occurred. Gathering much needed information of this nature from a region in the globe where pneumococcal epidemiology is poorly characterised can help inform decisions towards selecting the most appropriate PCV to implement in a NIP, as well as improve understanding of the impact of PCV upon addition to any NIP. This has the potential to assist further development of pneumococcal vaccines in not only Malaysia, but also South East Asia more broadly.

Conflict of interest statement

SCC receives unrestricted research funding from Pfizer Vaccines (previously Wyeth Vaccines) and has participated in advisory boards and expert panels for GSK, Pfizer and Novartis. SCC is an investigator on studies conducted on behalf of University Hospital Southampton NHS Foundation Trust/University of Southampton/Public Health England that are sponsored by vaccine manufacturers but receives no personal payments from them. SCC has received financial assistance from vaccine manufacturers to attend conferences. All grants and honoraria are paid into accounts within the respective NHS Trusts or Universities, or to independent charities.

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