A New Strategy is Needed to Prevent Pneumococcal Meningitis

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ABSTRACT

Objectives: Evaluate the ability of polysaccharide-conjugate vaccines (PCVs) to adequately protect against total pneumococcal meningitis.

Methods: References for this review were identified through searches of PubMed for articles published from January 1930 to the present by use of the terms "*Streptococcus pneumoniae*", "meningitis", "PCV", "serotype replacement", "capsule type", "capsule dependent disease", and "nasopharynx to brain transmission". Relevant articles were also identified through searches in Google and Google Scholar. Articles resulting from these searches and relevant references cited in those articles were also reviewed. Only articles written in English were included.

Results: PCVs target the pneumococcal capsular types in the US and Europe that were the most common causes of fatal pneumonia and sepsis. As these types were eliminated by the vaccines, it became apparent that in immunized populations, most invasive diseases caused by pneumococci, including bacteraemia, sepsis, and complicated pneumonia, were greatly reduced. However, the protective effects of PCVs against another invasive disease, meningitis, showed much less, or no decrease in disease incidence. Even in the presence of the PCVs, meningitis rates in children have been reported globally to be as high as 13 per 100,000 annually. The PCV type strains, which had been largely eliminated from carriage, were replaced by a broad diversity of new capsular types that generally failed to cause frequent sepsis but were able to cause meningitis at levels similar to, or in excess of, prior pneumococcal meningitis rates. We suspect that this occurred because of a direct transmission of the non-PCV strains from the nasopharynx to the brain through non-haematogenous routes.

Conclusions: Since virtually all cases of pneumococcal meningitis lead to either permanent neurological sequelae or death, it would be well worth the effort to develop a new vaccine capable of preventing pneumococcal meningitis regardless of capsular type. Such a vaccine would need to protect against colonization with most, if not all, pneumococci.

BACKGROUND

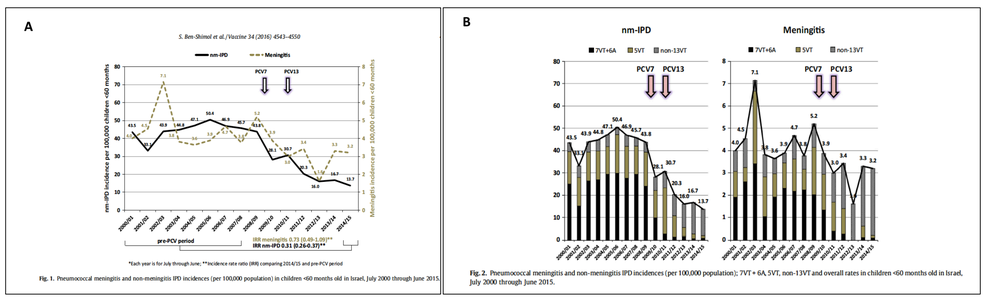

Figure 1 Graphs comparing rates of paediatric non-meningitis IPD (nm-IPD) and paediatric meningitis. (A) This figure from a study conducted in Israel by Ben Shimol et al 2016 shows that although there has been a steady decline in nm-IPD in the post-PCV period, incidence of paediatric meningitis has remained almost as high as pre-PCV levels. **(B)** The continued high level of meningitis IPD has been mainly enabled by the emergence of meningitis-causing non-vaccine type strains.

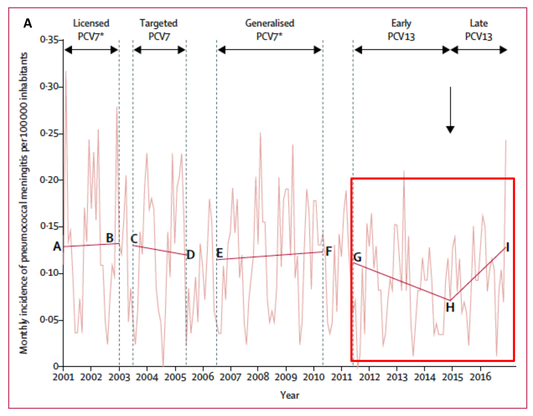

Fig 2A : fect of pneumococcal conjugate vaccines (PCVs) implementation on incidence of pneumococcal meningitis over 16 years in children

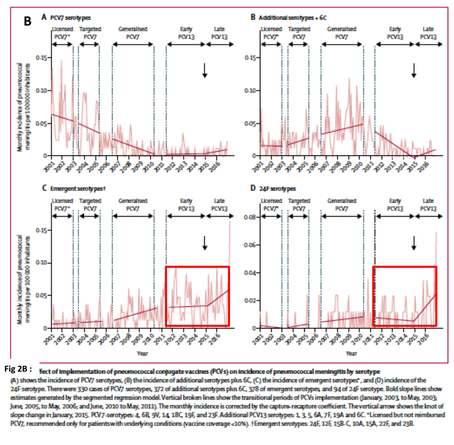

Fig 2B : fect of implementation of pneumococcal conjugate vaccines (PCVs) on incidence of pneumococcal meningitis by serotype

Figure 2 Graphs comparing rates of paediatric meningitis in the pre- and post-PCV period. (A) Figure from a study conducted in France by Ouldali et al 2018 shows that a rebound in the rates (red squares) of paediatric meningitis between the early and late PCV13 periods. **(B)** The increase in meningitis rates has been driven by non-vaccine type strains, largely by type 24F.

RESULTS

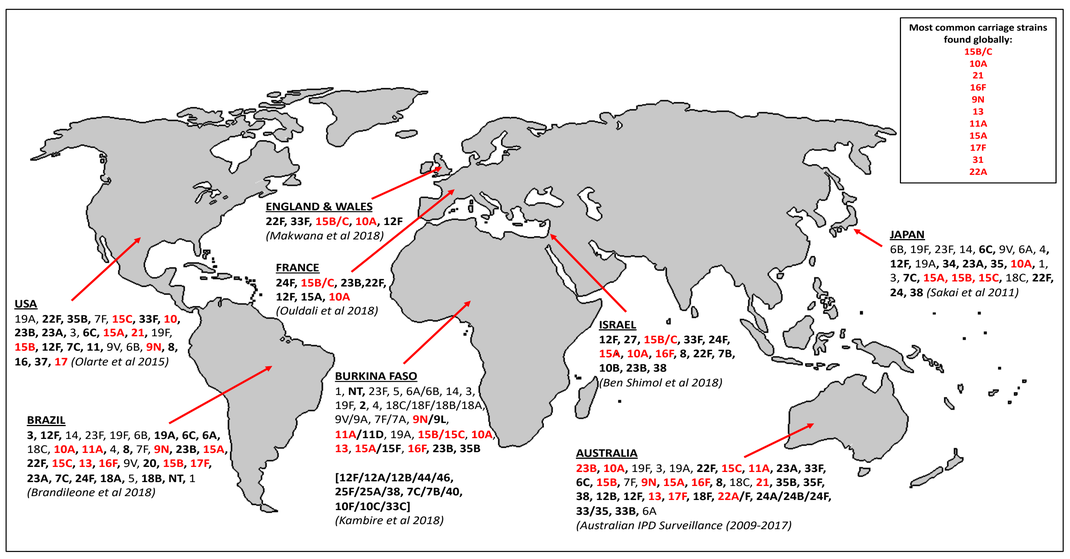

Figure 3a Worldwide distribution of paediatric meningitis strains. Each continent is represented by data from one country except the European region where data from England/Wales and France are shown . The capsular types are listed according to those causing most to least meningitis-post PCV13 introduction. Since there was no published data from Australia, data from the Australian IPD Surveillance dataset was analyzed by enumerating the number of cases of paediatric meningitis caused by each serotype for the years 2012-17 (post PCV13 period). Data from France, UK, and Israel only provides information for non-PCV type strains. North America (USA), Africa (Burkina Faso), and Australia shows both vaccine type (VT) and non-vaccine type (NVT) strains causing paediatric meningitis after the introduction of PCV13. Data from South America (Brazil) show both VT and NVT strains post PCV10 introduction. The data from Japan shows pre-PCV capsule types causing meningitis since there was no data from Japan that listed capsule types causing paediatric meningitis in the post-PCV period. Bolded strains represent NVT strains, non-bolded strains are VT strains, while capsular types colored red represent the most common carriage strains worldwide. The representative studies chosen were based on study size and recent data.

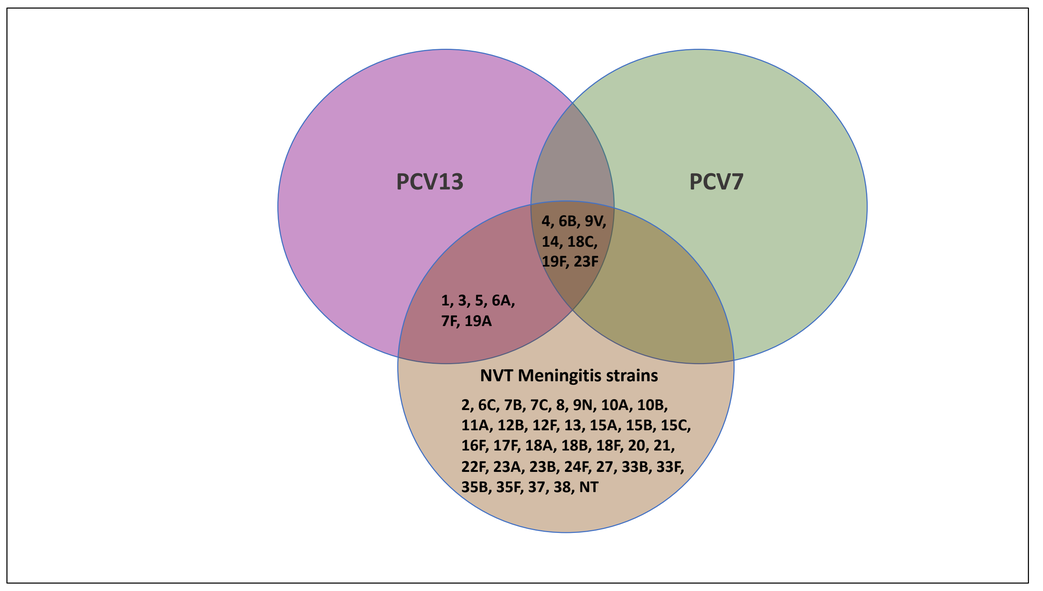

Figure 3b PCV type and non-PCV type strains that are reported to cause meningitis in the PCV era. In this figure, PCV7 and PCV13 strains are shown in green and purple circles respectively. The brown circle shows non-PCV type strains causing meningitis. The overlapping regions of the circles represent PCV type strains that have been reported to cause some meningitis post-PCV use. The serotype data shown here comes from Figure 1a except that the data from Japan was excluded as that study reported only on serotypes causing meningitis in the pre-PCV era. NT represents pneumococci of unknown capsular type.

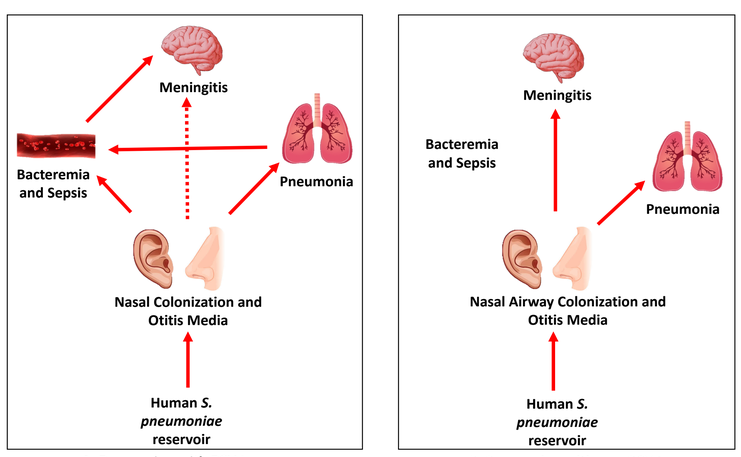

Figure 4 Model to explain our view of how pneumococcal meningitis largely escapes protection by PCV immunization. A. This figure follows PCV-capsule-type strains from acquisition to their disease manifestations. They colonize the upper airway and can spread in some cases to the middle ear where they cause otitis media. From the upper airway they can spread to the lung to cause pneumonia, which in some cases leads to detectable bacteraemia or serious sepsis. In infants they can also cause bacteraemia without a primary focus of infection. The classic view has been that meningitis is the result of pneumococci crossing the blood-brain barrier. This view is likely to be true in many/most cases of meningitis caused by PCV type strains because they are able to invade the blood. **B.** The non-PCV strains appear to be less likely to cause bacteraemia, sepsis, and complicated pneumonia than are the PCV strains. The poor virulence of the non-PCV strains in the blood is consistent with the view that their capsular structures are not compatible with survival in the blood. However, the non-PCV type strains are still able to efficiently cause pneumococcal pneumonia. The relative inability of these strains to cause bacteraemia and sepsis even though they cause most of the meningitis in PCV immune populations, strongly suggest that they reach the brain through a non-haematogenous route. If non-PCV strains can reach the brain through a non-haematogenous route, then it would seem likely that pneumococci of many of the PCV capsular types could probably also reach the brain in this manner.

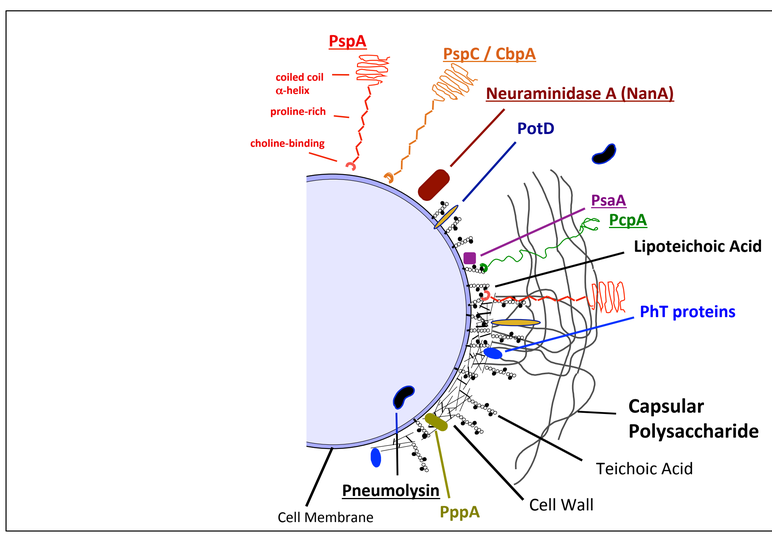

Figure 5 Model of the pneumococcal surface showing surface proteins that are being investigated as vaccine candidates. All of the molecules shown in color are proteins that have been reported to elicit protection against colonization. Pneumolysin has been reported in some cases to play a role in colonization but its ability to elicit protection against colonization in not clear. Figure modified from Briles et al 1998.

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CONCLUSIONS

1. Pneumococcal meningitis continues to cause morbidity and mortality among children and adults despite widespread use of PCVs in several countries around the globe.
2. In those countries pneumococcal meningitis is caused by non-PCV type strains that have occupied the niche created by the almost complete elimination of PCV type strains in the human nasopharynx.
3. Since the PCVs result in a major reduction in bacteraemia, sepsis, and complicated pneumonia, it is unlikely that the non-PCV type strains can generally survive well in the blood, and therefore probably enter the brain through non-haematogenous routes.
4. The high serotype diversity of these new replacement strains makes it problematic to expand the PCVs with enough capsular types to stem strain replacement and prevent the majority of pneumococcal meningitis.
5. One way to prevent pneumococcal meningitis is to completely eradicate pneumococcal colonization. This might be best done with a vaccine that targets the important pneumococcal virulence factors essential for colonization.

ACKNOWLEDGEMENTS

This research was supported by NIH grant R01AI118805

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Department of Microbiology