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ORIGINAL ARTICLE

Analysing the effect of the introduction of the PCV10 into the National Immunisation Schedule on the number of Pneumococcal infections

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Background

Vaccinating children with the 10- valent pneumococcal vaccine (PCV10) was introduced to the Maltese National Immunisation Schedule (NIS) in 2020. The aim of this study was to analyse the effect of the introduction of the PCV10 on the number of paediatric pneumococcal infections that needed hospitalisation.

Method

A retrospective analysis of the cases of Streptococcus pneumoniae in paediatric patients admitted to Mater Dei Hospital (MDH) during the winter months of January to March during the years 2017, 2018 (prior to introduction of the PCV10 vaccination) and 2022, 2023 (following the introduction of the PCV10 vaccination) was performed. Both respiratory screens and invasive samples (e.g., CSF, blood) which tested positive for *S. pneumoniae* were included in this study.

Results

The mean percentage of cases of *S. pneumoniae* detected from the total number of admissions to MDH prior to the introduction of the PCV10 into the NIS was 64.8% (n=6, SD=27.0) as compared to 56.8% (n=6, SD=33.5) following the introduction of the PCV10 into the NIS.

Conclusion

This audit has demonstrated that a statistically significant reduction has been achieved in the percentage of pneumococcal admissions among the paediatric population following the introduction of PCV10 into the Maltese NIS.

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Streptococcus pneumoniae is a gram-positive coccus and a common cause of bacterial infections including pneumonia, meningitis and pleural effusions in both children and adults.[1] Whilst *S. pneumoniae* is often found as a commensal residing in the microbiome of the upper respiratory tract, it can also be responsible for causing life-threatening invasive pneumococcal disease (IPD). IPD is defined as isolation of *S. pneumoniae* from a normally sterile site, such as blood, cerebrospinal fluid, pleural, peritoneal or joint fluid.[2]

The aim of this study was to analyse the effect of the introduction of the PCV10 on the number of paediatric pneumococcal infections that needed hospitalisation. Infections caused by *S. pneumoniae* peak during the winter months and early spring.[3] This is the reason why this study took into consideration the number of pneumococcal infections that occurred during the months of January to March. *S. pneumoniae* is widespread mainly due to its ability to colonize the nasopharynx. About 40%-50% healthy children and 20%-30% of healthy adults are carriers of *S. pneumoniae*. Carriage of *S. pneumoniae* involves a symbiotic relationship between the host and the bacterium.[4] Moreover, establishment of invasive pneumococcal disease mostly depends on a complex interplay between the host's innate immunity and the pathogen's virulence.[6] Local spread, aspiration of the pneumococcal organism and spread to the bloodstream can give rise to invasive inflammatory diseases such as otitis media (especially in children), community-acquired pneumonia, meningitis, and sepsis.[5]

MATERIALS AND METHODS

Access to all specimens collected from the paediatric population (i.e., children aged less than 16 years old) which tested positive for *S. pneumoniae* between January to March of 2017, 2018, 2022 and 2023 including respiratory screens, blood cultures, cultures of sterile sites such as cerebrospinal fluid cultures, PCR on EDTA blood and CSF was eventually granted. Access to the total number of paediatric admissions to MDH during the timeframes indicated was also requested and granted. The access to the total number of paediatric admissions excluded admissions to Paediatric Surgery and Nursery. Excel Office 16 was used to collect the data and create charts to display the information in the form of bar charts. SPSS was then used to perform statistical tests on the data collected. The paired T-test was used to analyse the data provided and determine if significant statistical differences existed between the pre-vaccination group and the post-vaccination group.

RESULTS

An overall decrease in the number of cases of *S. pneumoniae* was noted in the post-vaccination years as compared to the pre-vaccination years. Two years prior the introduction of the PCV10 vaccine, a total number of 389 paediatric admissions tested positive for *S. pneumoniae* in the winter and early spring months of 2017 and 2018. Two years after the introduction of the PCV10 vaccine into the Maltese NIS, a total number of 314 paediatric patients tested positive for *S. pneumoniae* from January till March of 2022 and 2023. The detection of *S. pneumoniae* among paediatric patients has therefore reduced by 75 cases (i.e., by 19.3%) two-years post-introduction of the PCV10 vaccine from January till March (Figure 1).

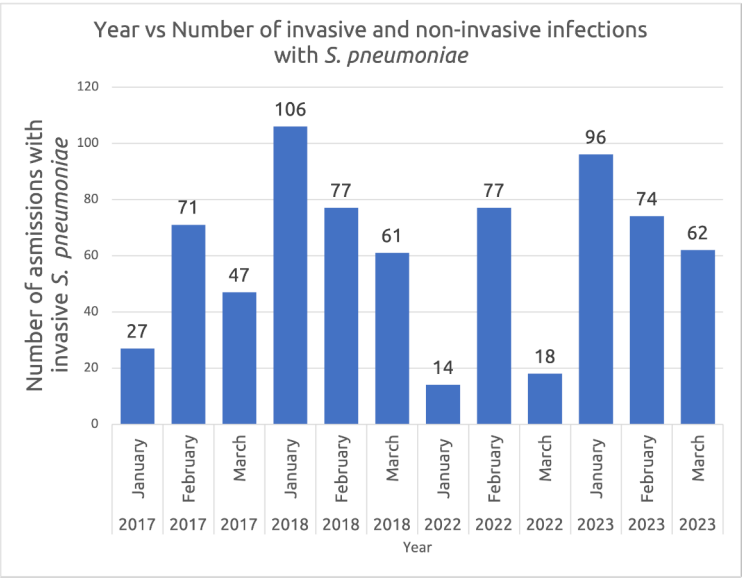

Figure 1 *Bar chart showing the year and month vs the number of cases of invasive and non-invasive S. pneumoniae. The orange dotted line demarcates the introduction of the PCV10 vaccine as part of the NIS and thus highlights the effect of the PCV10 vaccine on the number of admissions of S. pneumoniae.*

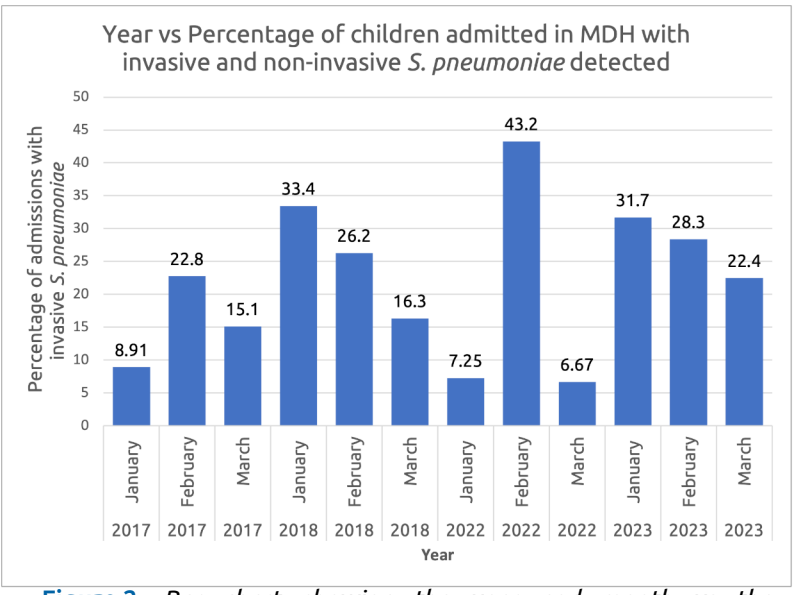

Figure 2 *Bar chart showing the year and month vs the percentage of children admitted to MDH with invasive and non-invasive S. pneumoniae detected. The orange dotted line demarcates the introduction of the PCV10 vaccine as part of the NIS and thus highlights the effect of the PCV10 vaccine on the number of cases of S. pneumoniae.*

This study also looked at the effect of the PCV10 vaccine on the percentage of paediatric patients who were admitted to Mater Dei Hospital (MDH) and tested positive for *S. pneumoniae* (Figure 2).

Overall, a marginal decrease was noted in the percentage of paediatric patients admitted to MDH who tested positive for S. pneumoniae. However, February of 2022 (2 years post-introduction of PCV10 vaccine) was the month which saw the greatest percentage of paediatric patients who were admitted to MDH and tested positive for S. pneumoniae (Table 1). A limitation of this study was unavailability of the physical files and therefore inability to determine whether these children had symptomatic infection or were simple carriers for *S. pneumoniae*.

Statistical Package for the Social Sciences (SPSS) was used as a statistical software to analyse the data collected. A paired t-test is used to study if there is a significant difference between two variables for the same subject. In the study, the paired T-test was used to determine if a significant statistical difference exists in the number of of *S. pneumoniae* admissions between January and March in 2017 and 2018 (the years prior to the introduction of the PCV10 vaccine) and between January and March in 2022 and 2023 – that is, the years following the introduction of the PCV10 vaccine into the NIS).

The paired T-test was used to compare the mean number of admitted cases of *S. pneumoniae* prior to and after the introduction of the PCV10. The number of cases of *S. pneumoniae* detected in the months (January till March of 2017 and 2018) of pre-vaccination group varied from 27 to 106. The number of cases of *S. pneumoniae* detected in the months (January till March of 2022 and 2023) of the post-vaccination group varied between 14 and 96. Similarly, the paired T-test was also used to compare the mean percentage of cases of *S. pneumoniae* detected from the total number of paediatric admissions to MDH prior to the introduction of the PCV10 and following the introduction of the PCV10.

The null hypothesis specifies that the number of cases of *S. pneumoniae* detected vary marginally between the pre- and post-PVC10 eras and is accepted if the p-value exceeds the 0.05 level of

Table 1 *Table showing the p value for the number of cases of S. pneumoniae pre-introduction of the PCV10 vaccine and post-introduction of the PCV10 vaccine into the NIS*

	Mean	N	Standard deviation	p-value
Total cases of S. pneumoniae detected prior to the introduction of the PCV10 into the NIS	20.5	6	8.80	*0.049*
Total cases of S. pneumoniae detected following the introduction of the PCV10 into the NIS	23.3	6	14.3	
Percentage of cases of S. pneumoniae detected from the total number of admissions to MDH prior to the introduction of the PCV10 into the NIS	64.8	6	27.0	*0.03*
Percentage of cases of S. pneumoniae detected from the total number of admissions to MDH following the introduction of the PCV10 into the NIS	56.8	6	33.5	

significance. The alternative hypothesis specifies that the number of cases of *S. pneumoniae* vary significantly between the two phases and is accepted if the p-value is smaller than 0.05. The P value for the total number of cases of *S. pneumoniae* detected prior to the introduction of the PCV10 into the NIS as compared to the total number of cases of Strep. pneumoniae post-introduction of the PCV10 vaccine into the NIS was 0.049. The P value is less than the 0.05 level of significance and thus, the null hypothesis was rejected, and the alternative hypothesis could be accepted (**Table 1, Figure 3**).

Furthermore, the P value for the percentage of cases of *S. pneumoniae* detected from the total number of admissions to MDH prior to the introduction of the PCV10 as compared to post-PCV10 introduction was 0.03 (**Table 1**, **Figure 4**). The P value was once again less than 0.05 and the alternative hypothesis could be accepted. Thus, it can be concluded that the PCV10 had a significant effect on the number of hospital admissions secondary to *S. pneumoniae*.

The mean number of cases of *S. pneumoniae* is represented by the cross within the box. The median

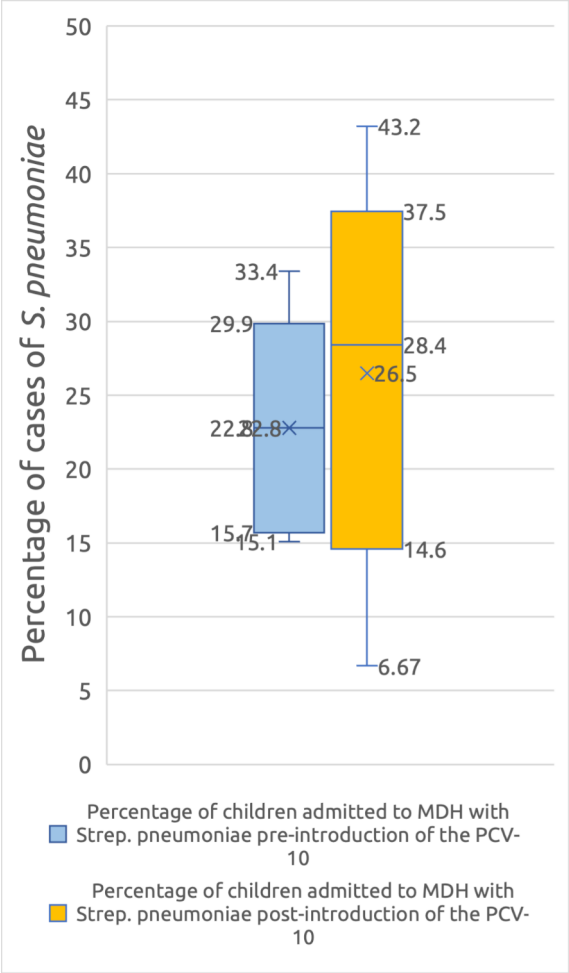

Figure 3 *Box and whisker plots for comparing the percentage of cases of S. pneumoniae detected in children admitted to MDH prior to the introduction of the PCV10 into the NIS to the percentage of cases of S. pneumoniae detected in children admitted to MDH following the introduction of the PCV10 into the NIS. The mean percentage of cases of S. pneumoniae is represented by the cross within the box. The median percentage of cases of S. pneumoniae is represented by the line within the box. The interquartile range is represented by the bottom and top edge of the box. The minimum and maximum percentage of cases of S. pneumoniae are represented by the bottom and top 'whisker', respectively.*

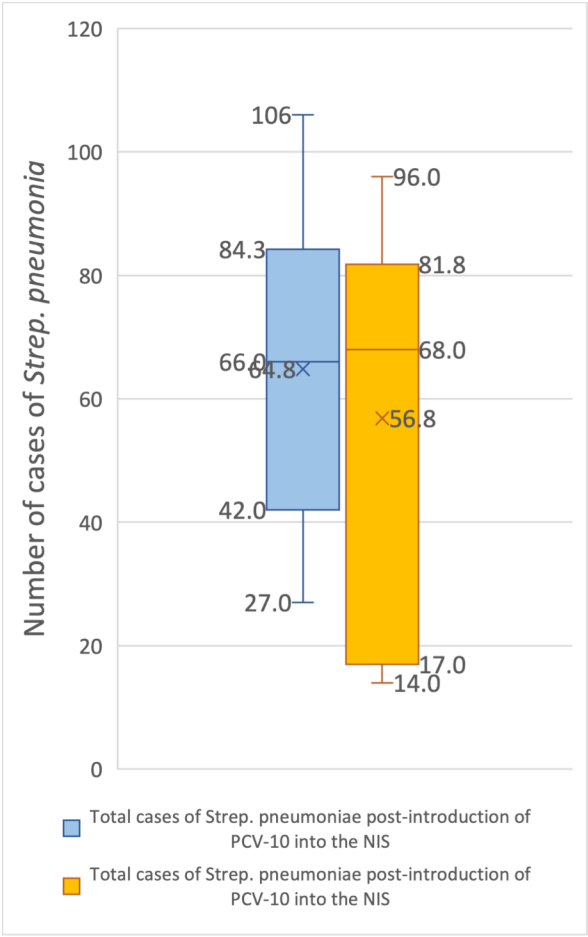

Figure 4 *Box and whisker plots for comparing the total number of cases of S. pneumoniae detected in children admitted to MDH prior to the introduction of the PCV10 into the NIS to the total number of cases of Strep. pneumoniae detected in children admitted to MDH following the introduction of the PCV10 into the NIS. The mean number of cases of S. pneumoniae is represented by the cross within the box. The median number of cases of S. pneumoniae is represented by the line within the box. The interquartile range is represented by the bottom and top edge of the box. The minimum and maximum number of cases of S. pneumoniae are represented by the bottom and top 'whisker', respectively.*

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DISCUSSION

Pneumococcal infections confer a burden on the healthcare system not only in view of morbidity and mortality, but also in terms of cost-effectiveness. The introduction of the PCV10 vaccine into the Maltese NIS aimed to reduce the incidence of potentially life-threatening pneumococcal disease among the paediatric population. This study therefore aimed at assessing the effectiveness of the PCV10 vaccine at reducing the number of hospitalisations with *S. pneumoniae*.

Results interpretation and analyzing the impact of Pneumococcal nasal carriage on infection rates

The impact of PCV-13 on the nasopharyngeal carriage and invasive pneumococcal disease was studied in Atlanta, Georgia, United States of America (USA). Similarl to our study, following the introduction of routine infant immunisation in March 2010, a significant decrease was found in the nasopharyngeal carriage of PVC serotypes and resistant strains of *S. pneumoniae*.[25] The difference from our study was that our study considered all investigations (including invasive specimens) rather than exclusively analysing results of nasopharyngeal aspirates. An observational cohort study performed by Shrestha et. al studying the effect in PCV-10 in Nepal four years following its introduction in 2015 also showed a decline in carriage of vaccine serotypes. This applied to both children with no co-morbidities living in urban and rural communities and in children admitted with pneumonia younger than two years. In children younger than two years who experienced clinical pneumonia, vaccine serotype carriage decreased by 82% by 2019.[28] However, this study also showed that carriage of serotypes 19A and 3 in healthy children increased by 2.2 times by 2019. A future recommendation from our study would be to analyse the serotypes which were detected and check if these serotypes are covered by the vaccines offered in the NIS. This would would be crucial for surveillance and to guide optimal vaccine policy and choice of product.

A prospective study performed by Martinez-Osorio et alin patients with invasive pneumococcal disease admitted to two tertiary care hospitals in Spain aged less than 60 months, showed that following the introduction of the PCV13 instead of the PCV7, there was a significant reduction of cases of invasive pneumococcal disease. The incidence of invasive pneumococcal disease declined from 89.7% in the pre-PCV13 era to 34.4% of cases per 100,000 participants in the post-PCV13 era (-62%; $P < 0.001$).[29] This study defined cases of IPD as the detection of *S. pneumoniae* in any normally sterile body fluid in association with clinical manifestations of the infection. Very few cases of IPD were detected in our study population for any statistical testing to be conducted. The study performed by Martinez-Osorio et al further emphasizes the importance of taking into consideration the serotypes of *S. pneumoniae* when analysing the effectiveness of vaccines.

Another factor that increases the risk of invasive pneumococcal disease are antibiotic resistant strains of *S. pneumoniae*. The carriage of *S. pneumoniae* is widely prevalent among the paediatric population. This has been linked to spread of the pathogen and subsequent development of disease.[24] A steady rise in the colonisation of the nasopharynx with antibiotic resistant strains of *S. pneumoniae* has also been found over the years, particularly among infants and young children. Colonisation with antibiotic resistant serotypes is recognised as one of the common causes for invasive disease among the paediatric population.[26] Analysing the effect of antibiotic resistant strains on the development of invasive pneumococcal disease could be another aspect to explore in future studies.

Reasons why the chosen years were specifically selected for the study

The COVID-19 pandemic and precautions taken on a national level in order to curb its spread, could have contributed to a decrease in the number of cases of *S. pneumoniae* being detected post-introduction of the PCV10 into the Maltese NIS due to parental reluctance to resort to secondary care during the

pandemic. In order to mitigate the effect of the COVID-19 pandemic on the number of cases of *S. pneumoniae* detected, data about cases of *S. pneumoniae* detected during 2020 and 2021 was excluded. During the span of these two years, the influence of COVID-19 would have compromised the validity of our data, as the pandemic led to several mandatory restrictive measures aimed at preventing further spread of COVID-19. These measures would in turn also have also been effective at reducing the spread of *S. pneumoniae*. The pandemic led to the obligatory use of medical masks (such as surgical masks or more advanced masks ex. N-95 masks) or visors in the community which would have influenced the number of cases of *S. pneumoniae* infections, as similarly to COVID-19, its mode of transmission is via respiratory droplets. Increased awareness with regards to hand hygiene and use of hand sanitisers would also have influenced the number of positive cases of *S. pneumoniae*. Furthermore, repeated lockdowns, isolation measures and shutting down of schools and childcare centres would also have contributed to decreased spread of *S. pneumoniae* as close contact between children from different households would have been restricted. Thus, the efficacy of the PCV10 could not be reliably tested during the peak of the COVID-19 pandemic, during 2020 and 2021.

Limitations of the study

A limitation in this study is that especially in 2022, a contributing factor to the decreased number of cases of *S. pneumoniae* could have been a set of COVID restrictions that remained mandatory. The restrictive measure of obligatory use of masks in schools was only lifted in April 2022 and thus prior to this period, reduced transmission and a decline in the detection rate of *S. pneumoniae* were to be expected. Furthermore, increased awareness with regards to contact precautions in the post-COVID era is a recognised confounding factor with regards to spread of *S. pneumoniae* in the community. Moreover, a larger number of respiratory screens were taken in 2022 era which has led to a greater detection rate of *S. pneumoniae*.

Invasive disease is defined as detection of *S. pneumoniae* within a sterile body fluid such as blood and CSF. Only 9 children were diagnosed with invasive *S. pneumoniae* and therefore no statistical significance could be yielded from such a small sample size. Ideally, more years would have been taken into consideration in order to increase the sample size. However, at the time of writing of this

SUMMARY BOX

What is already known about the subject?

- Infection with Streptococcus pneumoniae is an important cause of morbidity and mortality across the globe.
- Since pneumococcal disease and COVID-19 share the same route of transmission (i.e., respiratory droplets), public health measures aimed at controlling the COVID-19 pandemic are expected to also impact on the spread of pneumococcal disease. Therefore, the PCV10 vaccine is not the only factor responsible for the reduction in the number of S. pneumoniae cases.
- Studies conducted abroad showed pneumococcal vaccines to be effective at reducing the risk of invasive pneumococcal disease.
- Whilst the Maltese National Immunisation Schedule has been offering the PCV10 vaccine for free to the paediatric population since 2020, literature shows that the PCV13 offers the most extensive coverage against different serotypes of S. pneumococcus

What are the new findings?

- The PCV10 vaccine was effective at decreasing the number of S. pneumoniae cases compared to the pre-vaccination years.
- A marginal decrease was noted in the percentage of paediatric patients admitted to MDH who tested positive for S. pneumoniae following introduction of the PVC-10 vaccine into the NIS.
- Invasive pneumococcal disease is such a rare occurrence in Malta that no statistical analysis was possible to study the effect of the PVC-10 vaccine on IPD

audit, the sample size was limited by the fact that only 3 years had passed since the introduction of vaccination against *S. pneumoniae*.

Although the aim of this audit was to analyse the effectiveness of the PCV10 vaccine on the severity of *S. pneumoniae* infections, it would be interesting for future audits to take into consideration the symptomatology of patients who test positive for *S. pneumoniae*. Documentation of the presence of symptoms would analyse the effect of the PCV10 vaccine on the carrier status for *S. pneumoniae*, on number of cases of invasive disease and non-invasive disease. In our audit, this was not possible to explore as we lacked access to the physical files and no documentation is available on hospital online platforms.

Furthermore, this study did not consider the number of individuals who were vaccinated with PCV10. Prior to 2020, the PCV10 and the PCV13 vaccines were only available in the private sector while after 2020, it became available as part of the Maltese National Immunisation Schedule. This study assumed that no individuals were vaccinated with the PCV10 / 13 prior to 2020, whereas actually, there are children that had been vaccinated with PCV10 or PCV13 in the private sector. Unfortunately we did not have access to this data. Taking the vaccination status of diagnosed cases into consideration would allow us to determine with a greater accuracy the impact of the PCV10 on the number of children infected with *S. pneumoniae*. In such an audit, all admissions with respiratory symptoms between January and March during 2022 and 2023 would be considered, (ex: wheezing, shortness of breath, pneumonia) and the PCV10 or 13 vaccination status of these participants would then be cross-checked against the National Immunisation services database. Past records of respiratory tract admissions between January and March 2017 and 2018 would also be checked and their PCV vaccination status noted. For such an audit, access to the Paediatric Casualty admission lists to identify the children admitted with respiratory symptoms (MaterDei) and access to Immunization databases in the community would be needed. This is a suggestion for future audits.

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ABBREVIATIONS

COVID-19	Coronavirus disease 19
IPD	Invasive pneumococcal disease
NIS	National Immunisation Schedule
PCV7	Pnemococcal conjugate vaccine 7
PCV10	Pnemococcal conjugate vaccine 10
PCV13	Pneumococcal conjugate vaccine 13

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