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Effect of the introduction of pneumococcal conjugate vaccines on serotype prevalence in Kuwait and Saudi Arabia

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ABSTRACT

Background: *Streptococcus pneumoniae* infection is a major cause of morbidity and mortality. Although pneumococcal disease burden in Kuwait and Saudi Arabia is considered high, comprehensive surveillance data on pneumococcal conjugate vaccine (PCV) effects are lacking.
Methods: Sterile isolates from patients in Kuwait (2003–2016) and Saudi Arabia (aged ≤5 years, 2000–2010; all patients, 2011–2015) were included. Serotyped isolates were classified by inclusion in the 7-valent (PCV7) or 13-valent PCV (PCV13); isolates of other serotypes were classified as "non-PCV13". Isolate frequency (number of isolates/year) and classification of isolates according to vaccine type were assessed by period (before PCV, after PCV7, and after PCV13 introduction).
Results: In Kuwait, the frequency of collected isolates was highest after PCV7 introduction. Decreased frequency of PCV7 serotypes was seen after PCV13 introduction compared with before PCV and after PCV7 introduction. Increased frequency of the 6 additional serotypes in PCV13 and non-PCV13 serotypes was observed after PCV7 introduction with a subsequent decrease in the 6 additional serotypes in PCV13 and non-PCV13 serotypes after PCV13 introduction. The percentage of isolates of vaccine serotypes in Kuwait decreased over time. In Saudi Arabia, the frequency of collected isolates was highest after PCV7 introduction. An increased frequency of PCV7 serotypes was observed after PCV7 introduction, with a further decrease after PCV13 introduction. For the 6 additional serotypes in PCV13, an increased frequency was seen after PCV7 and PCV13 introduction compared to before PCV introduction. For non-PCV13 serotypes, an increased frequency was observed after PCV13 introduction compared to after PCV7 introduction. The percentage of isolates covered by PCV13 serotypes was similar across periods, while a substantial decrease in isolates covered by PCV7 was seen after PCV13 introduction.
Conclusion: PCVs in Kuwait and Saudi Arabia resulted in decreased frequency of some vaccine serotypes and an emergence of some non-PCV13 serotypes. Further investigation is warranted.

1. Introduction

Streptococcus pneumoniae infection is a major cause of morbidity and mortality worldwide, with the greatest risk in the very young, the elderly, and those with certain medical conditions [1–4]. In developing countries, fatality rates for invasive pneumococcal disease (IPD) are estimated to be 20% (for septicemia) to 50% (for meningitis) [1].

S pneumoniae nasopharyngeal colonization is associated with transmission [1]. Subsequent infection can cause serious illnesses, such as meningitis, bacteremia, and pneumonia, and noninvasive illnesses, including sinusitis and otitis media [1]. The capacity for causing invasive versus noninvasive disease and for nasopharyngeal colonization varies by serotype [5,6]. *S pneumoniae* serotype distribution also varies by age, geography, and over time [1].

A 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been available since the 1980s but is associated with limited immunogenicity in young children and inability to provide anamnestic antibody responses on revaccination in all age-based populations [1]. PPSV23 is not recommended for routine use in the elderly or high-risk populations within resource-limited settings [1]. Owing to potential burden of disease, pneumococcal conjugate vaccines (PCVs) were first licensed globally in 2000 as a 7-valent vaccine (PCV7); from 2009, formulations protecting

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against 10 serotypes (PCV10) and 13 serotypes (PCV13) became available, offering broader protection against disease-causing serotypes [1,7]. Combined with other pneumonia control measures, the World Health Organization recommends including PCVs in pediatric vaccination programs, particularly in regions with high pneumococcal disease burden [1,7].

The Gulf region in the Middle East has a high pneumococcal disease burden, with risk factors similar to those occurring globally, as well as regional risk factors, such as those associated with the Hajj pilgrimage [2]. However, pneumococcal disease epidemiology in this region continues to be elucidated, with most data derived from individual studies rather than from large data sets [8]. In a systematic review of literature from 1990 to 2007, IPD incidence within the region was 3.4–53.5 per 100,000 children aged <5 years and 0.7–2.5 per 100,000 individuals aged <20 years; 61–100% of all bacteremia cases and 3–25% of all meningitis cases occurring in children aged <2 years were caused by *S pneumoniae* [8]. Notably, lack of uniform and compulsory surveillance and inconsistent reporting methods are thought to have resulted in underestimation of pneumococcal disease burden in the Gulf region [2,8].

Similarly, recent and comprehensive epidemiologic data regarding *S pneumoniae* burden in Kuwait before and after PCV introduction are lacking. PCV7 was introduced in Kuwait in August 2006 and PCV13 in August 2010 for children aged <2 years with scheduled doses at ages 2, 4, and 6 months, followed by a booster dose at 18 months, and with catch-up programs for those aged 2–5 years [9,10]. The Kuwait national immunization program (NIP), which is compulsory for all Kuwaiti and expatriate children, provides free vaccination and close follow-up of nonparticipants [9]. In Kuwait in 2016, PCV uptake in children was estimated to be 99% [11]. From 1981 to 1987 (ie, before PCV introduction), the bacterial meningitis rate in children aged <12 years was 13 per 100,000 individuals, with *S pneumoniae* accounting for 21% of bacterial meningitis cases [12]. Data from 2001 to 2003 suggest that *S pneumoniae* was a leading cause and the pathogen most commonly associated with sequelae in children with bacterial meningitis [13]. In Kuwait, IPD is most common at the age extremes [14].

In Saudi Arabia, comprehensive epidemiologic data on pneumococcal disease, including across age groups, are also lacking, although high prevalence and the associated effect of pneumococcal disease on health services are generally acknowledged [15,16]. PCV7 was first included in the NIP of Saudi Arabia in January 2009 [15]. PCV13 licensure in 2010 led to transition from PCV7 to PCV13 in the Saudi Arabian NIP [17]. Currently, it is recommended that all children, including those with high-risk conditions, receive PCV13 in a 4-dose series at ages 2, 4, 6, and 12 months [15,18]. In 2015, the Ministry of Health initiated a vaccination campaign of catch-up doses of PCV13 for children aged 2–5 years [19]. Following this campaign, PCV uptake in Saudi Arabia was 98.7% [20]. Before PCV introduction in Saudi Arabia, the average annual incidence of IPD was 17.4 and associated mortality was 2.1 per 100,000 children aged ≤5 years, and there was an almost 4-fold higher incidence rate (40.6 and 11.5 per 100,000; $P < 0.001$) and mortality rate (5.2 vs 1.3 per 100,000; $P = 0.043$) in the first year of life compared with the next 4 years, respectively [16]. Recent data estimate that IPD incidence in Saudi Arabia is 2.5–9.6 per 100,000 children aged <5 years, with the exception of Al-Baha City where the incidence is 21.6 per 100,000 [21].

Because pneumococcal disease epidemiology is dynamic, vaccination policies require regular reassessment [15]. Similarly, temporal variability in serotype distribution of *S pneumoniae* isolates have been observed [21]. Large-scale studies and comprehensive data from Kuwait and Saudi Arabia on true pneumococcal burden across age groups, including serotype distribution, are not available, and existing data need to be updated and expanded to better understand optimal prevention approaches to pneumococcal disease in these countries. The purpose of this study is to evaluate current evidence for the change in pneumococcal serotype prevalence in Kuwait and Saudi Arabia after PCV introduction into the respective NIPs.

2. Methods

2.1. Clinical isolates

All sterile *S pneumoniae* isolates from blood and cerebrospinal fluid (CSF) samples collected from children and adults in all general hospitals, tertiary-care hospitals, and polyclinics in Kuwait between August 2003 and December 2016 were included. One isolate per patient was used. If a patient had isolates from both blood and CSF, the CSF isolate was used.

From 2000 to 2015, *S pneumoniae* isolates from normally sterile body sites were obtained from 22 hospital clinical laboratories in Saudi Arabia representing the 3 main regions in the country. From 2000 to 2010, isolates were collected from patients aged ≤5 years; isolates from all patients were collected thereafter.

2.2. Time periods

For Kuwait, data covered the period from August 2003 to July 2006 (before PCV introduction; a period of 3 years), August 2006 to July 2010 (after PCV7 introduction; a period of 4 years), and August 2010 to December 2016 (after PCV13 introduction; a period of 6.42 years). For Saudi Arabia, data covered the period from 2000 to 2008 (before PCV introduction; a period of 9 years), 2009 to 2010 (after PCV7 introduction; a period of 2 years), and 2011 to 2015 (after PCV13 introduction; a period of 5 years).

2.3. Serotyping

Serotyping of sterile *S pneumoniae* isolates from Kuwait was performed at the Pneumococcal Reference Laboratory, Kuwait University (Jabriya, Kuwait) using the Quellung reaction with specific rabbit pneumococcal antisera in the Danish chessboard typing system (Statens Serum Institut, Copenhagen, Denmark) as described previously [22]. Serotyping of sterile isolates obtained from Saudi Arabia was performed at the King Saud University laboratory (Riyadh, Saudi Arabia) using the capsular reaction test with checkerboard titration and pneumococcal capsule specific sera (Statens Serum Institut).

For this study, serotypes were classified as PCV7, PCV13, PCV13 only, and non-PCV13. PCV13 serotypes are 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F; of these 13 serotypes, 7 are shared with PCV7 (ie, 4, 6B, 9V, 14, 18C, 19F, and 23F) and 6 are unique to PCV13 (ie, "PCV13 only" serotypes [1, 3, 5, 6A, 7F, and 19A]). Any serotypes not contained in PCV13 were grouped together as "non-PCV13"; this group included the 11 serotypes unique to PPSV23 (ie, 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F) as well as other nonvaccine serotypes.

3. Results

3.1. Kuwait

From August 2003 to December 2016, 279 invasive pneumococcal isolates were obtained in Kuwait (Table 1). The period after PCV7 introduction had the highest annual frequency (ie, number of isolates per year) collected (28.50 isolates/year) compared with the periods before PCV introduction (20.67 isolates/year) and after PCV13 introduction (16.04 isolates/year) (Table 1).

By age cohort, invasive isolates from Kuwait were most commonly obtained from patients aged 6–50 years (28%; 78/279;

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