Cocontribution of Rotavirus and Pneumococcal Conjugate Vaccines to the Reduction of Pediatric Hospital Visits in Young Children

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Objective To assess rotavirus vaccine and pneumococcal conjugate vaccines (PCVs) cumulative impact on the pediatric emergency department visits and hospitalization rates in children <2 years of age in southern Israel between April 2006 and March 2014.

Study design This prospective, population-based observational study calculated the rates of rotavirus gastroenteritis (RVGE), non-RVGE, community-acquired alveolar pneumonia (CAAP), nonalveolar lower respiratory tract infection, and all-cause hospital visits. PCV7, PCV13, and rotavirus vaccination programs were implemented in Israel in July 2009, November 2010, and January 2011, respectively.

Results From 2006-2009 to 2013-2014, the rates of hospitilizations for RVGE, non-RVGE, CAAP, and nonalveolar lower respiratory tract infection decreased by 78%, 21%, 46%, and 7%, respectively. In outpatients, the respective decreases were 80%, 16%, 67%, and 14%. All-cause outpatient pediatric emergency department visits and hospitalization rates were reduced by 12% and 11%, respectively. During the peak season (October through March), RVGE, non-RVGE, CAAP, and nonalveolar lower respiratory tract infection hospitalization rates decreased significantly by 86%, 44.6%, 23.3%, and 10.5%, respectively. In outpatients, the respective decreases were 81.7%, 73.5%, 13.8%, and 10.7%. The proportion of RVGE and CAAP (grouped) of all-cause hospitalizations and outpatient pediatric ED visits decreased from 19.9% to 12.3% and from 6.9% to 1.8%, respectively.

Conclusions Rotavirus vaccine and PCV introduction cocontributed to a rapid, considerable reduction in hospital burden in children <2 years of age. Because seasonalities of both diseases overlap, this reduction is particularly helpful in relieving burdens of disease and care during the most cumbersome morbidity season. *(J Pediatr 2017;182:253-9).*

Pneumonia and diarrhea are leading causes of morbidity and mortality among children worldwide.[1] These infectious diseases result in numerous hospitalizations, outpatient visits, and antibiotic prescriptions and lead to productivity loss for parents and caregivers.[2-4] In developed countries, the burden on medical health services resulting from both pneumonia and diarrhea in young children peaks in late fall and winter months.[5-7] Both pneumonia and diarrhea can be caused by multiple pathogens, but *Streptococcus pneumoniae* and rotavirus, respectively, are the leading pathogens,[1,4,6,8] and are, in large part, vaccine preventable. Indeed, the widespread introduction of rotavirus vaccines (RVVs) and pneumococcal conjugate vaccines (PCVs) resulted in substantial reductions of diarrhea and respiratory diseases burden.[5,6,8,9]

The impact of RVVs and PCVs may not be limited to rotavirus gastroenteritis (RVGE) and the "classical" syndromes usually reported as pneumonia. In the case of diarrhea, RVVs also may influence the rate of what is perceived as non-RVGE, because RVVs typically prevent the most severe disease, and thus also may prevent further diarrheal episodes that occur as sequelae of RVGE.[5,10,11] Similarly, radiologically proven pneumonia episodes are shown to be caused frequently by pneumococci.[12] However, PCVs can prevent other lower respiratory tract infections (LRIs), because pneumococci also play a role in these infections.[13] Moreover, 1 study suggested that diarrhea may increase the risk of subsequent pneumonia in young children,[14] pointing to potential synergistic benefits of RVVs and PCVs.

In Israel, PCVs and RVVs were introduced to the National Immunization Plan (NIP) within a 1.5-year interval, enabling observation of their cocontribution to reduction in burden of diseases. Indeed, a substantial reduction of both RVGE and alveolar pneumonia was observed in young children in southern Israel after rapid uptake of PCV and RVV.[5,6]

Our current aim was to assess cocontribution introduction of RVV and PCV on reduction of hospital burden caused by diarrhea and LRI in children <2 years of age in southern Israel. Specifically, we examined the following

LRI	Lower respiratory tract infection	PCV13	13-valent pneumococcal conjugate vaccine
NIP	National Immunization Plan		
PCV	Pneumococcal conjugate vaccine	RVGE	Rotavirus gastroenteritis
PCV7	7-valent pneumococcal conjugate vaccine	RVV	Rotavirus vaccine
		SUMC	Soroka University Medical Center

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community-acquired entities: RVGE, gastroenteritis not caused by rotavirus (non-RVGE), alveolar pneumonia, and nonalveolar LRI. We studied the associated reduction in burden on rates of both outpatient pediatric emergency department visits and hospitalizations.

Methods

This prospective, population-based observational study was conducted over an 8-year period (April 2006 to March 2014). The study was approved by the Institutional Ethics Committees of the Soroka University Medical Center (SUMC). The SUMC is the only hospital in the Negev district of southern Israel, providing primary and referral health services to the entire population of the region (>640 000 inhabitants and approximately 30 000 children under 2 years of age in 2012).[5,6,15] More than 95% of the children living in the region are served by the SUMC, enabling incidence rate calculations. Similarly, even though patients from other regions are treated in our hospital, this is the case in <5% of all pediatric ED and hospitalization cases.

Two distinct ethnic populations reside side by side in southern Israel: The Bedouin Muslim population, similar to a developing population, and the Jewish population, whose lifestyle is similar to that of a developed population.[5,6] The socioeconomic conditions and lifestyles of the 2 populations differ and social contacts between them, especially between children, are uncommon. However, both have access to the same medical services (both clinic and hospitalization services). The proportion of children of each ethnic group born at the SUMC during the study period was similar; approximately 7500 Jewish children and approximately 7200 Bedouin children.[6,15] Hospitalization rates for respiratory infections and gastroenteritis were reported previously to be higher among the Bedouin population.[5,6]

PCV and RVV Introduction to the Israeli NIP and Uptake

The 7- and 13-valent PCVs (PCV7 and PCV13) and RVV were introduced into the Israeli NIP in July 2009, November 2010, and January 2011, respectively.

The PCV7 was licensed in Israel in mid 2007, and was used sporadically until 2009. In July 2009, the PCV7 was introduced to the NIP (administered at 2, 4, and 12 months of age) with a catch-up campaign in children <2 years of age. In November 2010, PCV13 gradually replaced PCV7, without a further catch-up program.[16] It was estimated that in 2007-2008, the proportion of 12- to 23-month-old Jewish and Bedouin children with ≥2 PCV doses was approximately 25% and <5%, respectively.[16]

In June 2010, 2011, 2012, and 2013, the proportion of 7- to 11-month-old children who had received ≥2 doses of any PCV was 81%, 90%, 89%, and 89%, respectively. The respective figures for PCV13 were 3%, 30%, 86%, and 89%.[6] These rates were similar in the Jewish and Bedouin populations.

Two RVVs (a monovalent vaccine, Rotarix, and a pentavalent vaccine, Rotateq) were licensed in Israel in 2007 but initially were used scarcely. From mid-2008 to December 2010, they were distributed at reduced costs by the health maintenance organizations, covering approximately 25% of the Jewish children with ≥1 doses. In contrast, the Bedouin population did not use any RVV during that period.[5] In January 2011, the pentavalent RVV was introduced into the Israeli NIP, and offered free of charge to all infants born after September 1, 2010; it was administered at 2, 4, and 6 months of age.[5]

RVV uptake was rapid and by the end of 2012, approximately 95% and approximately 85% of the Jewish children 7-11 months of age received ≥2 and full 3 doses, respectively. The respective rates among Bedouin infants were approximately 90% and approximately 65%.[5]

Alveolar Pneumonia. A child was diagnosed radiologically as having alveolar pneumonia according to the World Health Organization's "Standardization of Interpretation of Chest Radiographs" working group, as described previously.[6] Briefly, alveolar pneumonia was defined as a dense opacity that may be a fluffy consolidation of a portion, whole of a lobe, or the entire lung, often containing air bronchogram(s) and sometimes associated with pleural effusion. All chest radiographs were collected daily and were evaluated separately by 2 pediatric infectious disease specialists who read all the chest radiographs independently. Further analysis was performed by an independent pediatric radiologist who was unaware of the clinical data and the pediatricians' analysis. The presence of radiologically diagnosed alveolar pneumonia was confirmed by agreement between ≥1 of the study pediatric infectious disease specialists and the study pediatric radiologist.

LRI (Other Than Alveolar Pneumonia). LRI was diagnosed clinically by the treating physician. Diagnoses compatible with LRI (eg, bronchiolitis, respiratory distress, hypoxemia, pneumonia) were made by *International Classification of Diseases, 9th edition* codes, and radiologically confirmed alveolar pneumonia was excluded from these cases. For pediatric ED visits and hospitalized cases, a study member went over all medical charts and determined (coded) the diagnosis. If the coding for the pediatric ED patient did not include LRI, but the study coordinator coded it as LRI, it was counted as LRI. For double coding (both ER and hospitalized patient), cases were only counted once, as hospitalized LRI.

RVGE. Episodes were defined as acute diarrhea lasting <7 days before enrollment, with a positive stool enzyme immunoassay for rotavirus antigen, as previously described.[5] Briefly, study staff located at the pediatric ED identified all eligible children daily, year round. All children <5 years with a history of diarrhea/vomiting (≥3 watery or looser-than-normal stool within a 24-hour period and/or forceful vomiting) were offered participation in the study upon presentation to the pediatric ED. A stool sample was collected from the diaper or directly from the child within 48 hours of admission. All samples were tested by enzyme immunoassay for rotavirus.[5]

Non-RVGE. Episode was defined as a diarrheal disease lasting from <7 days before enrollment with a negative stool enzyme