



## Perspective

# From individual to herd protection with pneumococcal vaccines: the contribution of the Cuban pneumococcal conjugate vaccine implementation strategy



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## SUMMARY

A new pneumococcal conjugate vaccine is currently undergoing advanced clinical evaluation prior to its planned introduction in Cuba. The implementation of the pneumococcal vaccination strategy has been designed with consideration of the need to maximize both its direct and indirect effects. A novel approach is suggested, which addresses preschool children as the first-line target group to generate herd immunity in infants and to have an impact on transmission at the community level. The clinical evaluation pipeline is described herein, including evaluations of effectiveness, cost-effectiveness, and impact. The scientific contribution of the Cuban strategy could support a paradigm shift from individual protection to a population effect based on a rigorous body of scientific evidence.

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## Introduction

Pneumococcal infection is the leading cause of death at the extreme ages of life (Poland et al., 2003). The severe forms of pneumococcal disease remain a leading cause of vaccine-preventable disease in young children less than 5 years of age (Harboe et al., 2010). The asymptomatic nasopharyngeal carriage of pneumococci is highly prevalent among young children and is often the first in a sequence of events that leads to disease (Austrian, 1986; Gray et al., 1980).

Pneumococcal conjugate vaccines (PCVs) are available in many parts of the world and are highly effective in preventing invasive disease in infants and young children, with favorable safety and immunogenicity profiles. Much of the evidence regarding the impact of PCVs has focused on infants as the target population. It implies the early introduction of pneumococcal vaccination (in the first 6 months of life) to prevent nasopharyngeal colonization and

invasive pneumococcal disease (IPD) (Pavia et al., 2009; Pilishvili et al., 2010).

The feasibility of introducing PCVs into childhood immunization programs has grown, and there is expert consensus about the need to better understand the number and timing of doses to maximize both the direct and indirect effects (Vujicic et al., 2016; Hombach et al., 2005).

The cost-effectiveness of pneumococcal vaccines has been evaluated globally, mostly in regard to the strategy centered on targeting children less than 1 year of age. Evaluations performed in low- and middle-income countries have generally supported the efficiency of the 10- and 13-valent vaccines versus the 7-valent vaccine or non-immunization (Urueña et al., 2011; Giachetto Larraz et al., 2010; Nakamura et al., 2011; Muciño-Ortega et al., 2011; Bolaños Díaz et al., 2011; Kulpeng et al., 2013; Ngabo et al., 2015; Ordóñez and Orozco, 2015; Peña Kieninger et al., 2015; Mezones-Holguin et al., 2015; Saokaew et al., 2016). However, cost-effectiveness studies in regard to children living in lower income countries are limited (Saokaew et al., 2016). One possible factor that could explain this apparent discrepancy is the high price of vaccines and the consequent out-of-pocket expenses or effects on public budgets. From the early 2000s to the present, it has been

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found that the price of the vaccine is one of the determinants of the feasibility of vaccination programs in infants (Constenla, 2008; Atienza Merino, 2010; Beutels et al., 2011; Mo et al., 2016).

Given this reality, some countries, such as those in Eastern Europe (Castiglia, 2014), have chosen to adopt a vaccination strategy that focuses on programs outside of routine childhood immunization, mainly aimed at particular risk groups. Others have opted for innovative approaches to financing, such as advanced market commitment (AMC) projects in which the companies that benefit are obliged to provide the vaccine for an extended period at a reduced price (Vujicic et al., 2016; Braine, 2008).

Hence, economic aspects continue to form the basis of health policies regarding the introduction of pneumococcal vaccination. However, it remains necessary to investigate novel approaches to immunization strategies that go beyond the cost-effectiveness analyses and that integrate vaccination effectiveness, efficiency, and economic sustainability at the population level.

If a vaccination strategy could be developed based on lower prices, fewer doses, and at least the same effectiveness, this would represent a sustainable proposal particularly for low-income countries and families. This should not be impossible to achieve, and this issue could perhaps be resolved addressing other target population as part of the vaccination strategy. There are still unanswered questions that could help with this. For instance, could the vaccination of toddlers stop transmission of vaccine serotypes at the community level, providing a herd effect in infants, even if they are not vaccinated? What coverage will be necessary to achieve herd protection in infants? Is the available scientific evidence sufficient to support this hypothesis? (Urueña et al., 2011; O'Brien et al., 2007a; Isaacman et al., 2010)

Previously published studies (Pilishvili et al., 2010; Loo et al., 2014a; Bonner et al., 2015) have explored the impact of infant PCVs immunization on unvaccinated older children and adults, because the primary target has always been infants. Many of these studies took place over relatively short periods of time and comprised small and/or sub-studies of clinical trials. The primary immunization of children before infant immunization has been limited.

Reducing the nasopharyngeal colonization burden among young children less than 5 years old could have an important impact on disease transmission and the reduction in carriage of vaccine serotype strains (O'Brien and Dagan, 2003; Constenla, 2008; Atienza Merino, 2010; Beutels et al., 2011; Mo et al., 2016), as they probably play the most important role in sustaining the transmission of pneumococcal infections within the community (Bogaert et al., 2004; Simell et al., 2012). The presence of children in the household has a marked effect on the pneumococcal carriage rate in adults (18–29% nasopharyngeal carriage in households with children less than 6 years of age vs. 6% in households without children) (Levine and Cutts, 2007). In addition, daycare attendance is considered a significant risk factor for IPD (Johnson et al., 2010; Takala et al., 1995). Also, living with a sibling younger than 5 years of age (odds ratio 2.51, 95% confidence interval 1.82–3.48) and daycare attendance (odds ratio 2.36, 95% confidence interval 1.26–4.33) have been found to be determinants of nasopharyngeal carriage in Cuba (Toledo et al., 2017a).

Published data suggest that vaccine coverage of around two-thirds of children younger than 5 years is sufficient to induce herd protection at the population level (Adams et al., 1993; Miller et al., 2011; Maiden et al., 2008; Trotter and Ramsay, 2007; O'Brien et al., 2007b).

Pneumococcal vaccination has not yet been introduced in Cuba. The major epidemiological burden of IPD concerns children less than 5 years old (Toraño et al., 2014; Dickinson Meneses Felix and Toraño Peraza Gild, 2015), and the prevalence rate of nasopharyngeal colonization is more than 20% in infants  $\geq 2$  months of age (Toledo et al., 2017a).

A new Cuban heptavalent vaccine candidate (PCV7-T) is currently undergoing clinical evaluation (Dotres et al., 2014; González et al., 2015; Linares-Pérez et al., 2017). This vaccine contains seven highly prevalent serotypes worldwide, accounting for around 50–70% of isolate serotypes (Johnson et al., 2010; Toraño-Peraza et al., 2017). The composition of the vaccine candidate includes 2.2  $\mu\text{g}$  of capsular polysaccharide from serotypes 1, 5, 14, 18C, 19F, and 23F, as well as 4.4  $\mu\text{g}$  from serotype 6B, all conjugated to tetanus toxoid as the carrier protein and adsorbed on aluminum phosphate as adjuvant (Linares-Pérez et al., 2017). The quality specifications of the vaccine are in accordance with World Health Organization (WHO) requirements (WHO, 2012). The candidate vaccine has 24 months of demonstrated stability for the final product. The manufacturing process has been subject to several successful regulatory inspections by the national regulatory agency of Cuba. The preclinical research stages for this vaccine demonstrated immunogenicity and safety in animal models. Currently the technology has been scaled up and several batches have been produced for clinical trials.

The safety and immunogenicity of the new vaccine candidate have been demonstrated in clinical trials conducted in adults, young children, and infants (Dotres et al., 2014; González et al., 2015). Preliminary results from a non-inferiority study on the protective efficacy of PCV7-T that included 1135 preschool children showed the following proportions of vaccinated children with a geometric mean titer (GMT)  $\geq 0.35$  (serotype-specific): 89% serotype 1, 77% serotype 5, 96% serotype 6B, 99% serotype 14, 96% serotype 18C, 99% serotype 19F, 96% serotype 23F. The prevalence of nasopharyngeal colonization was reduced from 32.2% (pre vaccination) to 6.5% (1 year post vaccination) (unpublished data).

This article focuses on the potential contribution of the Cuban pneumococcal vaccination implementation strategy in the national and international context, shifting the paradigm from individual protection to the population effect of pneumococcal vaccination supported by a rigorous body of scientific evidence.

### The Cuban PCV implementation strategy

The Cuban vaccine development and registration program for each population group represents a situation completely different to previous PCVs introduction experience around the world. The vaccine will be administered to children aged 1–5 years before being introduced for infant use.

It is expected that the mass immunization of preschool children with high coverage will have a significant impact on nasopharyngeal carriage in those directly vaccinated and also on bacterial circulation at the population level. To estimate the impact on bacterial circulation, a prevalence in the vaccinated population at baseline of approximately 22–31.1% was assumed on the basis of nasopharyngeal colonization studies conducted in Cuba (Toledo et al., 2017a; Toledo et al., 2017b). A prevalence reduction range of between 25% and 60% (lower and upper reduction limits) has been reported in a systematic review and observational studies (Loo et al., 2014b; Fleming-Dutra et al., 2014). The number of doses necessary to reduce one carrier is an average 9 for the population aged 3–5 years and 26 for the population aged 1–2 years. Generally, the vaccination of children will require 17 doses to reduce one carrier, which compares very favorably with 39 doses in infants to attend a similar effect on bacterial circulation at the population level.

The initial Cuban PCV introduction strategy and associated studies will address numerous questions and expectations: (1) the importance of toddlers as a reservoir of pneumococci, (2) the direct and indirect effects of addressing toddler vaccination, (3) the herd immunity generated in infants, (4) the effects on nasopharyngeal

colonization, and (5) the duration of this effect in the vaccinated and unvaccinated populations.

From the standpoint of an international contribution to scientific knowledge, the Cuban pneumococcal vaccination implementation strategy was designed to obtain new knowledge that could shift the actual individual protection paradigm to a potentially more efficient population protection with PCV.

There are several advantages to targeting young children for vaccination. Firstly, the vaccination of this age group through a vaccination campaign held over a short period of time and with high coverage will confer direct protection against the disease and target transmission within the community as a whole (Schranz, 2009). Another at least empirical advantage of this proposed phased approach is related to the 'reemergence phenomenon', which is also considered an indirect effect of vaccination and is defined as an increase in the proportion of individuals in a population who harbor non-vaccine types in their nasopharynx after vaccine introduction (Urueña et al., 2011; Regev-Yochay et al., 2010; Pichon et al., 2013). Key scientific questions on this topic are whether it could be possible to reduce the effect of serotype replacement in pneumococcal disease by reducing asymptomatic carriers and the vicious circle of antibiotic use and resistant strains in preschool children, and whether a new generation of pneumococcal vaccines targeting vaccine replacement serotypes could address this target population to reduce the global burden of disease at the population level.

The follow-up of young vaccinated children and infants cohabiting with them will allow the direct and indirect effects to be explored using disease syndromes (meningitis, pneumonia, acute otitis media, and IPD) as the endpoint through a sentinel surveillance system. A panel survey will be held in vaccinated children and infants to identify changes in colonization associated with the vaccination and serotype replacement.

Testing the hypothesis of whether it is possible to generate herd immunity in infants by addressing preschool children could on the one hand facilitate the design of new vaccines containing emerging serotypes (to administer to preschool children) and on the other hand be used to reduce the schedule in infants.

The Cuban PCV implementation strategy provides the unique opportunity to include an effectiveness evaluation (direct and indirect effects) of a large population cohort in a stepped-wedge cluster trial. Selected children aged 1–5 years will be vaccinated and followed up alongside infants living at the study sites to explore changes in nasopharyngeal colonization. The short- and mid-term protection will be explored at 6 months, 1, 3, and 5 years after vaccination.

In a second step, the vaccine will be licensed for use in infants. They will also be included as a target group as part of the Cuban expanded program on immunization. The safety, immunogenicity, non-interference with other vaccines, and booster effect will be explored in infants using a reduced dose schedule (3 + 0 and 2 + 1). The phase 1–2 clinical trial will involve 880 infants. Head-to-head comparisons will be done to demonstrate the non-inferiority of the new heptavalent Cuban vaccine against the licensed vaccine Prevnar 13, with respect to the seven common serotypes. This will be done taking into account WHO parameters for the registration and licensing of new pneumococcal vaccines (WHO, 2012). Changes in nasopharyngeal colonization post primo vaccination and post booster dose will be explored.

To demonstrate the clinical efficacy on pneumococcal disease and pneumonia, meningitis syndromes, and acute otitis media, complementary epidemiological studies will be performed to include case–control (using the indirect cohort method) and case series studies based on the sentinel surveillance system implemented in six pediatric hospitals. The National Reference

Laboratory will document changes in distribution of the circulating serotypes.

Finally, and importantly, a cost-effectiveness evaluation will be included in the Cuban PCV implementation strategy. Cost-effectiveness studies will be implemented from the social perspective using the TRIVAC methodology (Pichon et al., 2013; Clark et al., 2013; Jauregui et al., 2015). International experts from the Pan-American Health Organization will monitor the quality of the primary information and results.

## Final comments

There is no doubt that there are challenges for the new PCV7-T vaccine in the PCV13 era. However, the scientific contribution made by the Cuban implementation strategy could improve the body of evidence on pneumococcal vaccination. Taking into account that there is no agreement on the minimum schedule required for direct and indirect protection and that this could vary widely depending on the epidemiology of transmission, population structure, and mixing patterns, the results of clinical trials conducted in Cuba could provide new evidence on this topic. In the Cuban context, preschool children have a high burden of pneumococcal disease and nasopharyngeal colonization, influenced by an institutionalization regime, hence targeting them for vaccination could be efficient. The herd effect generated in infants by addressing preschool children will also provide new information.

## Declaration of interests

The main authors of this paper – Nivaldo Linares-Pérez, PhD, Dagmar García-Rivera, PhD, Darielys Santana-Mederos, BSc, Yury Valdés Balbín, BSc, and Vicente Verez-Bencomo, PhD – work at the center manufacturing the vaccine, the Finlay Vaccine Institute. María E. Toledo-Román, PhD and Anaí García-Fariñas, PhD work in the National Health System and do not have any contract or receive financing from the manufacturing center.

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## References

- Adams WG, Deaver KA, Cochi SL, Plikaytis BD, Zell ER, Broome CV, et al. Decline of childhood *Haemophilus influenzae* type b (Hib) disease in the Hib vaccine era. *Jama* 1993;269(2):221–6.
- Atienza Merino G. Evaluación económica de un programa de vacunación frente al neumococo en población pediátrica. Santiago de Compostela: Consellería de

- Sanidade, Axencia de Avaliación de Tecnoloxías Sanitarias de Galicia, avalia-t. Serie Avaliación de tecnoloxías. Consultas Técnicas; 2010 CT2010/03.
- Austrian R. Some aspects of the pneumococcal carrier state. The Journal of antimicrobial chemotherapy 1986;18:35.
- Beutels P, Blommaert A, Hanquet G, Bilcke J, Thiry N, Sabbe M, et al. Cost-effectiveness of 10- and 13-valent pneumococcal conjugate vaccines in childhood. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2011 Report 155C. D/2011/10.273/21.
- Bogaert D, de Groot R, Hermans P. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. The Lancet infectious diseases 2004;4(3):144–54.
- Bolaños Díaz R, Mezones-Holguín E, Fiestas Solórzano V, Suárez Moreno V, Sanabria C. Evaluación económica de las vacunas hepta-, deca- y trece-valente para la prevención de neumonía asociada al Streptococcus pneumoniae en niños menores de 5 años en el Perú. Lima: INS-NAGESP; 2011 (INS, Serie de Notas Técnicas; 2011-6).
- Bonner K, Welch E, Elder K, Cohn J. Impact of Pneumococcal Conjugate Vaccine Administration in Pediatric Older Age Groups in Low and Middle Income Countries: A Systematic Review. PLoS one 2015;10(8):e0135270.
- Braine T. Controversial funding mechanism to fight pneumonia New financing methods show promise in fight against pneumonia, the biggest killer of children. Bulletin of the World Health Organization 2008;86(5):321–416.
- Castiglia P. Recommendations for Pneumococcal Immunization Outside Routine Childhood Immunization Programs in Western Europe. Adv Ther 2014;31(10):1011–44.
- Clark A, Jauregui B, Griffiths U, Janusz CB, Bolanos-Sierra B, Hajjeh R, et al. TRIVAC decision-support model for evaluating the cost-effectiveness of Haemophilus influenzae type b, pneumococcal and rotavirus vaccination. Vaccine 2013;31: C19–29.
- Constenla DO. Economic impact of pneumococcal conjugate vaccination in Brazil, Chile, and Uruguay. Rev Panam Salud Publica 2008;24(2):101–12.
- Dickinson Meneses Felix ROM, Toraño Peraza Gilda. Pneumococcal meningitis in Cuban children and adolescents: A fifteen years follow up. Pediatrics Research International Journal 2015;2015; doi: <http://dx.doi.org/10.5171/2015.596251>.
- Dotres CP, Puga R, Ricardo Y, Brono CR, Paredes B, Echemendía V, et al. Safety and preliminary immunogenicity of Cuban pneumococcal conjugate vaccine candidate in healthy children: A randomized phase I clinical trial. Vaccine 2014;32(41):5266–70.
- Fleming-Dutra KE, Conklin L, Loo JD, Knoll MD, Park DE, Kirk J, et al. Systematic review of the effect of pneumococcal conjugate vaccine dosing schedules on vaccine-type nasopharyngeal carriage. The Pediatric infectious disease journal 2014;33(Suppl 2):S152–60.
- Giachetto Larraz G, Telechea Ortiz H, Speranza Mourine N, Giglio N, Cané A, Pérez García MC, et al. Costo-efectividad de la vacunación universal antineumocócica en Uruguay. Rev Panam Salud Publica 2010;28(2):92–9.
- González N, Paredes B, Pérez S, Mirabal M, Rivero I, González C, et al. Safety and immunogenicity of Cuban antipneumococcal conjugate vaccine PCV7-TT in healthy adults. MEDICC Review 2015;17(4):32–7.
- Gray BM, Converse GM, Dillon HC. Epidemiologic studies of Streptococcus pneumoniae in infants: acquisition, carriage, and infection during the first 24 months of life. Journal of Infectious Diseases 1980;142(6):923–33.
- Harboe ZB, Valentiner-Branth P, Benfield TL, Christensen JJ, Andersen PH, Howitz M, et al. Early effectiveness of heptavalent conjugate pneumococcal vaccination on invasive pneumococcal disease after the introduction in the Danish Childhood Immunization Programme. Vaccine 2010;28(14):2642–7.
- Hombach J, Solomon T, Kurane I, Jacobson J, Wood D. Report on a WHO consultation on immunological endpoints for evaluation of new Japanese encephalitis vaccines. WHO, Geneva, 2–3 September, 2004. Vaccine 2005;23(45):5205–11.
- Isaacman DJ, McIntosh ED, Reinert RR. Burden of invasive pneumococcal disease and serotype distribution among Streptococcus pneumoniae isolates in young children in Europe: impact of the 7-valent pneumococcal conjugate vaccine and considerations for future conjugate vaccines. International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases 2010;14(3):e197–209.
- Jauregui B, Janusz CB, Clark AD, Sinha A, Garcia AGF, Resch S, et al. ProVac Global Initiative: a vision shaped by ten years of supporting evidence-based policy decisions. Vaccine 2015;33:A21–7.
- Johnson HL, Deloria-Knoll M, Levine OS, Stoszek SK, Hance LF, Reithinger R, et al. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. PLoS medicine 2010;7(10):e100034.
- Kulpeng W, Leelahavarong P, Rattanavipapong W, Sornsrivichai V, Baggett HC, Meeyai A, et al. Cost-utility analysis of 10- and 13-valent pneumococcal conjugate vaccines: Protection at what price in the Thai context?. Vaccine 2013;31(13):2839–47.
- Levine OS, Cutts FT. Pneumococcal vaccination and public health. Lancet 2007;369(9568):1144–5.
- Linares-Pérez N, Toledo-Romaní ME, Casanova MF, Paredes B, Váldes-Balbín Y, Santana-Mederos D, et al. La nueva vacuna cubana antineumocócica, de las evidencias científicas disponibles, a la estrategia de evaluación clínica y de impacto. Rev Cub Ped 2017;89(sup):71–86.
- Loo JD, Conklin L, Fleming-Dutra KE, Knoll MD, Park DE, Kirk J, et al. Systematic review of the indirect effect of pneumococcal conjugate vaccine dosing schedules on pneumococcal disease and colonization. The Pediatric infectious disease journal 2014a;33:S161–71.
- Loo JD, Conklin L, Fleming-Dutra KE, Deloria Knoll M, Park DE, Kirk J, et al. Systematic review of the effect of pneumococcal conjugate vaccine dosing schedules on prevention of pneumonia. The Pediatric infectious disease journal 2014b;33(Suppl 2):S140–51.
- Maiden MC, Ibarz-Pavón AB, Urwin R, Gray SJ, Andrews NJ, Clarke SC, et al. Impact of meningococcal serogroup C conjugate vaccines on carriage and herd immunity. Journal of Infectious Diseases 2008;197(5):737–43.
- Mezones-Holguín E, Canelo-Aybar C, Clark AD, Bess Janusz C, Jauregui B, Escobedo-Palza S, et al. Cost-effectiveness analysis of 10- and 13-valent pneumococcal conjugate vaccines in Peru. Vaccine 2015;33S:A154–66.
- Miller E, Andrews NJ, Waight PA, Slack MP, George RC. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study. The Lancet Infectious diseases 2011;11(10):760–8.
- Mo X, Gai Tobe R, Liu X, Mori R. Cost-effectiveness and Health Benefits of Pediatric 23-valent Pneumococcal Polysaccharide Vaccine, 7-valent Pneumococcal Conjugate Vaccine and Forecasting 13-valent Pneumococcal Conjugate Vaccine in China. Pediatr Infect Dis J 2016;35:e353–61.
- Mucio-Ortega E, Mould-Quevedo JF, Farkouh R, Strutton D. Evaluación Económica de un Programa de Inmunización Infantil en México Basado en la Vacuna Neumocócica Conjugada 13-Valente. Value in Health 2011;14:S65–70.
- Nakamura MM, Tasslimi A, Lieu TA, Levine O, Knoll MD, Russell LB, et al. Cost effectiveness of child pneumococcal conjugate vaccination in middle-income countries. Int Health 2011;3(4):270–81.
- Ngabo F, Levin A, Wang SA, Gatera M, Rugambwa C, Kayunga C, et al. A cost comparison of introducing and delivering pneumococcal, rotavirus and human papillomavirus vaccines in Rwanda. Vaccine 2015;33(51):7357–63.
- O'Brien KL, Dagan R. The potential indirect effect of conjugate pneumococcal vaccines. Vaccine 2003;21(17):1815–25.
- O'Brien KL, Millar EV, Zell ER, Bronsdon M, Weatherholtz R, Reid R, et al. Effect of pneumococcal conjugate vaccine on nasopharyngeal colonization among immunized and unimmunized children in a community-randomized trial. Journal of Infectious Diseases 2007a;196(8):1211–20.
- O'Brien KL, Millar EV, Zell ER, Bronsdon M, Weatherholtz R, Reid R, et al. Effect of pneumococcal conjugate vaccine on nasopharyngeal colonization among immunized and unimmunized children in a community-randomized trial. The Journal of infectious diseases 2007b;196(8):1211–20.
- Ordóñez JE, Orozco JJ. Cost-effectiveness analysis of the available pneumococcal conjugated vaccines for children under five years in Colombia. Cost Effectiveness and Resource Allocation 2015;13(1):6.
- Pavia M, Bianco A, Nobile CG, Marinelli P, Angelillo IF. Efficacy of pneumococcal vaccination in children younger than 24 months: a meta-analysis. Pediatrics 2009;123(6):e1103–10.
- Peña Kieninger M, Giménez Caballero E, Arbo Sosa A, Torres Amarilla C, Jáuregui B, Bess Janusz C, et al. Cost-effectiveness analysis of pneumococcal conjugate vaccine introduction in Paraguay. Vaccine 2015;33S:A143–53.
- Pichon B, Ladhani SN, Slack MP, Segonds-Pichon A, Andrews NJ, Waight PA, et al. Changes in molecular epidemiology of Streptococcus pneumoniae causing meningitis following introduction of pneumococcal conjugate vaccination in England and Wales. Journal of clinical microbiology 2013;51(3):820–7.
- Pilishvili T, Lexau C, Farley MM, Hadler J, Harrison LH, Bennett NM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. The Journal of infectious diseases 2010;201(1):32–41.
- Poland GA, Shefer AM, McCauley M, Webster PS, Whitley-Williams PN, Peter G, et al. Standards for adult immunization practices. American journal of preventive medicine 2003;25(2):144–50.
- Regev-Yochay G, Hanage WP, Trzcinski K, Rifas-Shiman SL, Lee G, Bessolo A, et al. Re-emergence of the type 1 pilus among Streptococcus pneumoniae isolates in Massachusetts, USA. Vaccine 2010;28(30):4842–6.
- Saokaew S, Rayanakorn A, Bin-Chia Wu D, Chaiyakunapruk N. Cost Effectiveness of Pneumococcal Vaccination in Children in Low- and Middle-Income Countries: A Systematic Review. Pharmacoeconomics 2016;34(12):1211–25.
- Schranz J. Pneumococcal conjugate vaccines: what do we know and what do we need?. Procedia in Vaccinology 2009;1(1):189–205.
- Simell B, Auranen K, Kayhty H, Goldblatt D, Dagan R, O'Brien KL, et al. The fundamental link between pneumococcal carriage and disease. Expert review of vaccines 2012;11(7):841–55.
- Takala AK, Jero J, Kela E, Rönneberg P-R, Koskeniemi E, Eskola J. Risk factors for primary invasive pneumococcal disease among children in Finland. Jama 1995;273(11):859–64.
- Toledo ME, Casanova MF, Linares-Pérez N, García-Rivera D, Toraño Peraza G, Barcos Pina I, et al. Prevalence of Pneumococcal Nasopharyngeal Carriage Among Children 2–18 Months of Age: Baseline Study Pre Introduction of Pneumococcal Vaccination in Cuba. Pediatr Infect Dis J 2017a;36(January (1)):e22–8.
- Toledo ME, Chávez D, Casanova MF, Toraño G, Linares N. Colonización nasofaríngea por neumococos en la población infantil cubana, evidencias basadas en estudios de prevalencia. Rev Cub Ped 2017b;89(sup):51–64.
- Toraño G, Pías L, Capote M, Rodríguez M, Dickinson F, Varcárcel M. Serotipos y resistencia antimicrobiana de aislamientos meníngeos de Streptococcus pneumoniae. Cuba, 2007–2012. VacuMonitor 2014;23(3):117–23.

- Toraño-Peraza G, Suárez D, Abreu M, Barreto B, Toledo-Romaní ME, y Linares-Pérez N. Serotipos de *Streptococcus pneumoniae* responsables de enfermedad invasiva en niños cubanos. *Rev Cub Ped* 2017;89(sup):31–6.
- Trotter CL, Ramsay ME. Vaccination against meningococcal disease in Europe: review and recommendations for the use of conjugate vaccines. *FEMS microbiology reviews* 2007;31(1):101–7.
- Urueña A, Pippo T, Betelu MS, Virgilio F, Giglio N, Gentile A, et al. Cost-effectiveness analysis of the 10- and 13-valent pneumococcal conjugate vaccines in Argentina. *Vaccine* 2011;29:4963–72.
- Vujicic M, Weber SE, Nikolic IA, Atun R, Kumar R. An analysis of GAVI, the Global Fund and World Bank support for human resources for health in developing countries. *Health policy and planning* 2016;2012:czs012.
- WHO. Pneumococcal vaccines WHO position paper –2012–recommendations. *Vaccine* 2012;30(32):4717–8.