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REVIEW

Pneumococcal Diseases in Colombia: Epidemiological Analysis Before and During the Universal Children Immunization against *Streptococcus pneumoniae* in the Light of a Vaccine Change in 2022

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Abstract

Streptococcus pneumoniae causes meningitis, pneumonia and bacteremia, mainly in children under 5 years of age and in the elderly. Pneumococcal conjugate vaccines (PCVs) have been administered globally since the year 2000, contributing to substantially reduce the incidence of pneumococcal diseases (PDs). In 2012, Colombia implemented universal vaccination with PCV10 in children under 2 years of age, achieving a decrease and stabilization of the incidence of PDs. However, since 2014, replacement of vaccine serotypes by non-vaccine serotypes, such as 3 and 19A, predominantly, has been observed. Likewise, in 2019, there was an increase in the incidence of meningitis, coinciding with the increase of multi-resistant 19A clones. In July 2022, the vaccine formulation was changed to PCV13, which also has the potential to control serotypes 3, 6A, and 19A. This paper reviews the epidemiology of pneumococcus in Colombia, before and during the universal PCV10 vaccination.

Key words: *Streptococcus pneumoniae*, Pneumococci, Serotypes, Antibiotic Resistance, Bacterial Meningitis, Pneumonia, Epidemiology, Children, Colombia.

Enfermedades Neumocócicas en Colombia: Análisis Epidemiológico Antes y Durante la Vacunación Universal contra *Streptococcus pneumoniae*, a la Luz del Cambio Vacunal en 2022

Resumen

Streptococcus pneumoniae es la principal causa de meningitis, neumonía y bacteriemia primaria, principalmente en <5 años y en el adulto mayor. Desde el 2000 se han desarrollado vacunas conjugadas contra neumococo (VCN), que han disminuido la incidencia de la enfermedad neumocócica (EN) de manera sustancial globalmente. Desde el 2012, Colombia implementó vacunación universal con VCN10 masivamente en <2años, observándose una disminución en la incidencia de EN en los primeros años para luego estabilizarse. Sin embargo, los serotipos no vacunales 3 y 19A se han incrementado convirtiéndose en los predominantes desde 2014. El serotipo 19A se ha asociado a multiresistencia, así mismo, en 2019 se observó un aumento en la incidencia de meningitis asociada a serotipo 19A. En julio 2022 se realizó el cambio a VCN13. Este artículo ofrece una revisión de la epidemiología del neumococo en Colombia, antes y durante la vacunación universal con VCN10.

Palabras clave: *Streptococcus pneumoniae*, Neumococos, Serotipos, Resistencia a antibióticos, Meningitis bacterial, Neumonía, Epidemiologia, niños, Colombia.

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Introduction

Pneumococcal diseases (PDs) are one of the main causes of morbidity and mortality in the world. The advent of pneumococcal conjugate vaccines (PCVs) has significantly reduced the disease burden, particularly among children under 5 years of age[1]. Wahl *et al* reported a 51% reduction in deaths from PDs globally, estimating that approximately 250,000 deaths have been prevented by the application of PCVs since the year 2000[2,3]. Nevertheless, approximately 300,000 children under 5 years of age continue to die each year from PDs, of which 5,700 come from the Americas, including 900 to 1,300 from Colombia[1].

For its part, pneumonia represents more than 80% of the 318,000 annual deaths from PDs in children under 5 years of age globally, of which 4,600 occur in the Americas[2,3]. Vaccination throughout Latin America and the Caribbean has managed to reduce the incidence rate of pneumonia which ranged from 2,000-3,500 cases/100,000 children under 5 years of age in the pre-vaccination period to 358 (301-411)/100,000 children under 5 years in the post-vaccination stage (2015)[2]. Even so, almost 30% of the countries in the region maintain incidences greater than 500 cases/100,000 children under 5 years of age. Additionally, cases and deaths from acute meningitis and from non-pneumonia, non-meningitis invasive disease generate significant clinical, diagnostic, and therapeutic challenges.

Vaccines have demonstrated impact on invasive pneumococcal diseases (IPDs), pneumonia, acute otitis media (AOM), antimicrobial resistance, and herd immunity among unvaccinated populations[4,5]. Vaccine impact is influenced by several factors affecting individual and indirect or community protection[6].

The vaccination success factor is given by the balance between vaccine protection and serotype replacement[7]. Regarding protection at the community level, the vaccine to be used must include the most prevalent serotypes at the local level, those associated with greater severity and the most resistant to antimicrobials. At the individual level, protection will depend on the integrity of the patient's immune response as well as the predominance and distribution of causative serotypes[8, 9,10,11].

Serotype replacement may be induced by the type of vaccine used or by other factors (eg, pattern of antimicrobial use). The emergence of serotypes not included in the PCV7 vaccine introduced early in this century, produced a notable clinical impact and led to the advent of PCV10 formulation (which includes the serotypes 1, 5 and 7F) and PCV13 (which also included the serotypes 3, 6A and 19A). These two vaccines (PCV10, PCV13) have demonstrated adequate safety and effectiveness and have been introduced into the National Immunization Programs (NIPs) of more than 150 countries in the world[2,3]. Of particular importance was the impact of the PCV13 vaccine on PDs by serotype 19A, which had become the predominant serotype globally[12,13]. However, the phenomenon of serotype replacement continues to evolve under the pressure of conjugate vaccines and understanding the interplay between protection against vaccine serotypes and replacement by non-vaccine serotypes is essential to assess the full impact of vaccination[7,14].

According to the WHO, the regional and local prevalence of vaccine serotypes and patterns of antimicrobial resistance are key factors in guiding the choice of vaccine, making epidemiological surveillance of crucial importance[15].

In Latin America, the use of PCVs has been the primary factor to achieve the control and prevention of PDs. A multicenter, retrospective, observational study in the region showed a decrease of 82.5%-91.6% in IPDs produced by PCV10 serotypes and 58.8%-82.9% in IPDs by PCV13 serotypes in children under 5 years of age [16]. A significant increase in the reporting rate of serotype 19A was demonstrated in PCV10 countries (In Brazil, a change of +517% and in Colombia +355%)[16].

Other studies published prior to 2017 have shown the population impact of PCV13 against pneumonia and meningitis, as well as indirect protection in unvaccinated populations [17-20]. Likewise, the impact on mortality, pneumonia, and AOM with PCV10[21] has been published. No less important is the impact of serotype replacement on antimicrobial resistance. A systematic review of 129 epidemiological studies of carriage or IPDs that included 32,187 isolates from 52 countries between 2000 and 2019, showed an increase in the prevalence of resistance after the implementation of PCV7/ PCV10 in serotypes such as 6A, 6C, 15A, 15B/ C, 19A and 35B. Serotypes 19A and 19F were associated with a higher prevalence of resistance to penicillin and serotypes 14 and 6B to macrolides[2]. The aim of this study was to analyze the state of the art of pneumococcal diseases and the surveillance systems in Colombia.

Material and Methods

The most important surveillance systems for IPDs, pneumonia and bacterial meningitis were selected based on publicly accessible publications or communications. A description of the characteristics of the different surveillance systems was made.

In each publication or communication, the cases of PDs were analyzed by age (under 5 years, 5 to 14 years, 15 and 59 years and over 60 years or general population, according to the available information), clinical presentation, serotype pneumococcal strain, and antimicrobial susceptibility, by years or period.

The analysis was performed based on the isolate corresponding to the PCV10 vaccine serotype and non-PCV10 vaccine serotype for each surveillance system when appropriate.

In 2006, Colombia introduced the vaccination against pneumococcus with PCV7 for children under 2 years of age at high risk and with specific diseases. In 2008, Bogotá continued with the strategy by including children weighing 2000g or less at birth; in October of that year, the vaccine was made universal in Bogotá. Then, in 2009, coverage was extended to all children born on or after January 1, who resided in the departments with the highest proportion of deaths from acute respiratory infection. Later, in the period 2010-2011, and due to the withdrawal of the heptavalent vaccine from the industry, the PCV13 vaccine was acquired to continue with the vaccination of the target population, as well as to complete and finish schemes initiated with the heptavalent vaccine. In 2011, the PCV10 vaccine was universalized in the country and began to be administered in January 2012 to the population born on or after November 1, 2011, using a two-dose schedule and boosters at 2, 4 and 12 months of age with 89% coverage. In July 1, 2022, Colombia change to PCV13, for the cohort of children born since May 1, 2022 using a two-dose schedule and boosters at 2, 4 and 12 months of age.

For the analysis of the data, three periods were considered: pre-implementation of PCV10 in the National Immunization Program (NIP) (2006 to 2011), implementation period (2012 to 2014), and during the massive universal childhood vaccination (2015 to 2021). Data in pre-vaccination or during vaccination periods may be different for each surveillance system. In some studies, the implementation period is not presented separately from the 2015-2021 period.

Results

1. Description of the Surveillance Strategies and Information Resources on Pneumococcal Diseases in Colombia

In Colombia, different surveillance strategies have been implemented, which gathered together have made possible to get hints on the epidemiology of PDs and the impact of PCVs on them. The Tables 1 and 2 summarize the information related to the epidemiological surveillance strategies in Colombia[16,21-40].

2. Vaccine Impact on the main Invasive Pneumococcal Diseases (IPDs) in Colombia

PCV10 Effects on Acute Bacterial Meningitis (ABM)

The ABM is a notifiable event. For the year 2009, 109 cases of pneumococcal meningitis were reported in the general population, for an incidence of 0.24 x 100,000 inhabitants. However, in children under 5 years of age, an incidence of pneumococcal meningitis of 1.19 x 100,000 children under 5 years of age was reported, which decreased to 0.51 x 100,000 in 2012, explained by PCV7 implementation, remains stable between 2013 and 2018 due to the use of PCV10 but increased to 1.03 x 100,000 in children under 5 years of age in 2019. In that same year, 2019, 205 cases of pneumococcal

Table 1. Pneumococcal Diseases. Information sources by surveillance strategies, institution and actions developed in the surveillance system in Colombia. Period 2005 to 2021.

Surveillance Strategies	Responsible Institutions	Actions related to the Surveillance Strategies
Public Health Surveillance System	Instituto Nacional de Salud (INS).	Acute bacterial meningitis cases, reported on an individual bases. Acute respiratory infections cases, reported collectively[22,23].
Public Laboratory Surveillance	INS. Departmental and District Health Secretaries.	Integrated to the regional SIREVA II vaccine system in 2006. Passive and voluntary system (mandated due to meningitis). Surveillance of encapsulated bacterial strains isolated from sterile sites. In charge of the serotyping. The strains are sent from the hospitals to the departmental health secretariats, which in turn send the isolate to the INS reference laboratory in Bogotá[24].
Sentinel Surveillance of Meningitis and Pneumonia in Children Under 5 Years.	World Health Organization (WHO), Pan American Health Organization (PAHO), Ministry of Health, INS, Secretary of Health of Bogotá (BHD), HOMI Foundation.	Daily surveillance of patients under 5 years of age, admitted to the HOMI Foundation, with a diagnosis of pneumonia or bacterial meningitis is carried out. Suspected cases of pneumonia are taken a chest X-ray and if this is compatible with bacterial pneumonia (probable case) blood cultures are ordered. Patients admitted with suspicion of meningitis undergo lumbar puncture and if the cerebrospinal fluid is altered, samples are taken for cultures, molecular biology, and blood cultures. The microorganisms are sent to the BHD and the INS for identification and serotyping. The results feed the regional and global surveillance system[25,26].
Pneumo-Colombia Network	Asociación Colombiana de Infectología (ACIN) capitulo central and Sociedad Colombiana de Pediatría (SCP)	Surveillance since 2017, extended to 17 institutions (4 cities). Clinical, epidemiological and microbiological surveillance of confirmed pneumococcal disease in patients under 18 years of age. Surveillance of pneumococcal strains isolated from sterile sites[27-33].
Research Studies	Done by several Research groups.	Studies of nasopharyngeal carriage, microbiological characterization, time series, studies of acute otitis media, pneumonia, and cost-effectiveness studies of conjugate vaccines[16,22,34-40,42].

HOMI: Hospital Pediátrico la Misericordia.

Table 2. Pneumococcal Diseases (PD). Number of Cases and Contribution to the Surveillance System by Surveillance Strategy and disease in Colombia. Period 2005 to 2021.

Institution	Period or year	Population	Disease	Number of PDs, Number cases per year or rate
Public Health Surveillance System INS[22,23,31,37].	2009 to 2019	GP	ABM	1615 147 per year.
	2020	GP	ABM	67
	2021	GP	ABM	30
	2005-2019	Under 5 years of age	PARI mortality	636 per year.
	2005	Under 5 years of age	PARI mortality	25/100.000
	2019	Under 5 years of age	PARI mortality	13.37/100.000
Laboratorial Surveillance INS[24].	2016 to 2021	GP	PDs	2301 (24% < 5y, 6,7% 5 to 14 y, 35 % 14 to 59 y and 33 % over 60 y) Between 2016 to 2019 559 isolates per year In 2020 150 isolates and 2021 243 isolates.
Sentinel Surveillance[25,26].	2016 to 2021	Under 5 years of age	Pneumonia Meningitis	5.272 (46% probable case), 60 % under 2 y. 301, 70 % confirmed cases
Pneumo-Colombia Network[27-33].	2008 to 2021	Under 18 year of age	Pneumococcal Isolates from IPDs	734 (44% < 24 m, 34 % from 5 to 14 y, 35 % 24 to 59 m and 22 % from 60 to 250 m) The most frequent PDs was pneumonia 64%, bacteremia 22% and meningitis 12%

INS= Instituto Nacional de Salud, GP=general population, ABM=Acute Bacterial Meningitis, PARI= Pneumococcal Acute Respiratory infection mortality, IPD Invasive pneumococcal disease, Y= year, m= months.

meningitis were reported in the general population, with an increase in incidence of 0.41 cases per 100,000 inhabitants. Mortality in the general population increased from 13.3% to 26% between 2009-2019 and in children under 5 years of age it ranged from 44% in 2017 to 18% in 2019[22,37] (Figure 1). During the pandemic years 2020 and 2021, the incidence and lethality of pneumococcal meningitis decreased, probably secondary to the measures to control the pandemic and a decrease in epidemiological surveillance[22].

A study with data from the Pneumo-Colombia Network shows a decrease in the relative incidence of pneumococcal meningitis in children under 5 years of age from 1.2 x 100,000 inhabitants in 2008 to 0.2 x 100,000 inhabitants in 2016, with a subsequent increase of 1.5 x 100.000 inhabitants in 2019, this increase being associated with the emergence of serotypes 19A and 34 and the implementation of molecular diagnostic techniques in the last period[31]. All these data contrast with the publication by Cáceres *et al*[41] according to which the cases and incidence of disease were decreasing after the start of vaccination, in this study, the cut-off was made to 2015, so the emergence of the disease that occurred in subsequent years was not detected.

PCV10 Effects on Pneumonia

Studies have been carried out both in the pre-vaccination era and in the post-vaccination era, identifying changes in the incidence of pneumonia both in population studies and in hospitalized patients. Table 3 summarizes the published studies evaluating the positive impact of mass vaccination against pneumococcus on pneumonia.

PCV10 Effects on Primary Bacteremia

This entity is perhaps the least monitored. The report to the health system is voluntary instead of mandatory. In a recent study carried out in 17 hospitals in Colombia between 2017 and 2019, 51 cases of primary bacteremia were found out of 284 cases of IPDs, corresponding to 17.9% of all IPDs[33]. The average age was 25 months (IQR 9-49), 40 (70.8%) had some comorbidity. 47% of the patients had received at least one dose of PCV10. The average hospital stay was 10.6 days, 19 (37.2%) were admitted to the Pediatric Intensive Care Unit (PICU) and 6 (11.7%) died. The serotype was obtained in 38 (74.5%) cases. The most frequent serotypes were 19A (39.4%) and 6C (10.5%)[33].

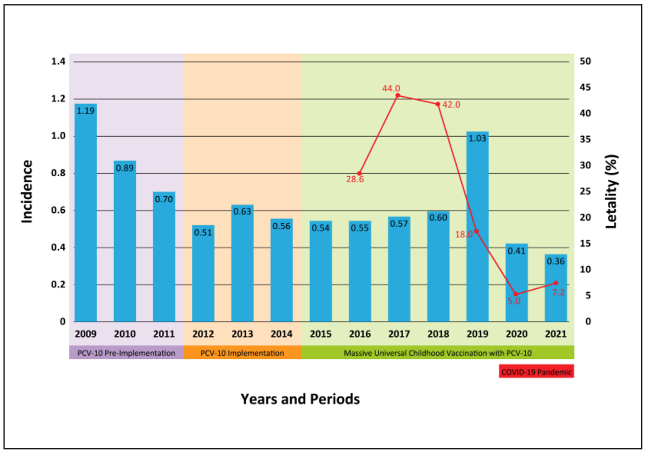

Figure 1. Bacterial Meningitis and lethality among Children under 5 Years by Annual incidence (2009 to 2021) and annual lethality (2016 to 2021) in Colombia.
Blue Bars = incidence/100.000 inhabitants, red line = lethality due to bacterial meningitis.

Table 3. Studies Related to the Vaccine Impact on Pneumonia.

Type of Study, Ages of Subjects and Study Period	Principal Outcomes	References
Retrospective ecological study in children under 2 years of age. Data from 2005 to 2016 for incidence and general mortality in Colombia, pre and post vaccination. Data from 2008 to 2016 for incidence and mortality in Bogotá, Medellín, Barranquilla, Cali and Cartagena.	Overall mean reductions in all-cause pneumonia mortality in the post-PCV period nationally of 48.8%; (95% CI: 45.5-51.8%), and in four cities, Bogotá, Medellín, Cali and Barranquilla; no substantial reduction was observed in Cartagena. Reductions in the incidence of pneumonia from any cause in Bogotá (66.0%; 65.5-66.6%), Medellín (40.6%; 39.3-41.9%) and Cartagena (15.0%; 11.2- 18.6%), while the incidence increased in Barranquilla (78.5%; 68.4-89.2%) and Cali (125.5%; 119.2-132.0%).	Carrasquilla et al [42]
Population-based prospective surveillance study, population between 28 days and 36 months of age, from 2006 to 2008, in Bogotá, Colombia.	Clinical pneumonia (CP) of 6,276 cases/100,000 patients. Image-confirmed pneumonia (ICP) in 2,120 cases/100,000 patients. Invasive pneumococcal disease (IPD) for bacteremic pneumonia (BP) of 54.2/100,000; for bacteremia of 17.2/100,000; 3.7/100,000 for meningitis and 1.2/100,000 for sepsis. Most common serotypes 14 (51.6%), 6B (9.7%) and 19F (9.7%).	Benavides et al [43].
Sentinel surveillance study of pneumonia and meningitis, under 18 years of age, 2016, HOMI Foundation, Bogotá, Colombia.	CP (suspected cases) of 15.2 cases per 100 hospitalized patients (1343 cases). Probable bacterial pneumonia of 7.3 cases per 100 hospitalized patients (654 cases). 87% (559 cases) had a complete anti-pneumococcal vaccination schedule for their age, all with PCV10. Of 41 patients with BP, *S. pneumoniae* was isolated in 17 patients; Serotype 19A in 5 patients (29.4%), serotype 3 and serotype 14 in 4 patients each (23.5%); serotype 9N in 2 more (11.7%); serotype 6A and serotype 15A in 1 patient each (5.8%). Most of the patients with serotype 19 A had a complete vaccination schedule with PCV10.	Camacho-Moreno et al [26]
Sentinel surveillance study of pneumonia and meningitis, under 18 years of age, 2016-2020, HOMI Foundation, Bogotá, Colombia.	CP (suspected cases) 5,272 cases, probable pneumonia 2,432 cases (46.1%). Blood cultures were taken from 2,223 (92%), and 127 (5.2%) were positive. *Streptococcus pneumoniae* isolated in 55 cases (43.3%); the most frequent serotypes were Serotype 19A 19 cases (40.4%), Serotype 3 12 cases (25.5%) and Serotype 14 4 cases (8.5%). Since 2017, there is no isolation of serotypes included in PCV10; by 2020, 70% of *S. pneumoniae* isolates are by serotype 19A.	Camacho-Moreno et al [25]
Network-based surveillance study (Neumo-Colombia Network), under 18 years of age, 2008-2019, 10 hospitals in Bogotá, Colombia.	The incidence of pneumonia cases after vaccination with PCV7 reached a peak in 2010, with a subsequent general decrease, which was maintained with the inclusion of PCV10 starting in 2012. In 2019, an increase in incidence occurred. There were significant differences between the pre-vaccination period (Pre-VP) (2008 to 2011) and the post- vaccination period (Post-VP) (2014-2019) for: - Pneumonia arose from 63.5% of the cases of IPD to 70% (p= 0.006). - CP increased from 70.1% to 85.4% of the Post- VP (p= 0.006). - Complicated pneumonia cases elevated from 13.4% to 31.1% (p < 0.001). - Decrease in PCV10 serotypes from 42.5% to 13.5% (p < 0.001). - Non-PCV10 serotypes included in PCV13 went from 3.7% to 50.5% (p < 0.001). - Non-PCV10 and non-PCV13 serotypes increased from 6% to 19.8%. - The number of days of hospitalization increased from 8 (5.5-15) to 12 (7-22) days (p< 0.001). - The frequency of admission to the PICU increased from 32.8% (44) to 51.6 % (99) (p=0.001). - PCV10 PICU admissions cases fell from 31.8% to 4.6% and in contrast PCV 13 PICU admissions cases rose from 4.6% to 59.6% (p < 0.0001).	Gutierrez-Tobar IF et al [28].

3. Vaccine Impact on the main Non-Invasive Pneumococcal Diseases (IPDs) in Colombia

PCV10 Effects on Acute Otitis Media

The impact of the PCV10 vaccine on AOM was evaluated in a cohort of 876 patients followed from birth to 15 months of age. The effectiveness of the PCV10 was evaluated in a case-control study nested in a cohort. The OR (Odd Ratio) of having acute otitis media was 0.66 (95%CI 0.27-1.61) and the vaccine effectiveness was 33.3% (95%CI 61-73). PCV10 was not effective in preventing AOM [34]. Another study found that the incidence of AOM decreased in Medellín (42.1%) and Bogotá (51.1%), but increased in Barranquilla (95.8%)[42].

4. Vaccine Impact on the *Streptococcus pneumoniae* Serotype Distribution in Colombia

PCV10 Effects on the Serotypes Included in its Formulation

There has been a significant impact of the PCV10 vaccine in the 2+1 scheme on the vaccine serotypes. According to data from the National Institute of Health (INS from its initial in Colombia), the frequency of PCV10 serotypes has decreased by 84%, from 73.8% in the pre-PCV10 period (2006-2010) to 8.8% in the post-PCV10 period (2015-2018), in bacterial isolates from children under 5 years of age with PDs (Figure 2, Figure 3). In 2019, the few cases of PDs due to PCV10 seroty-

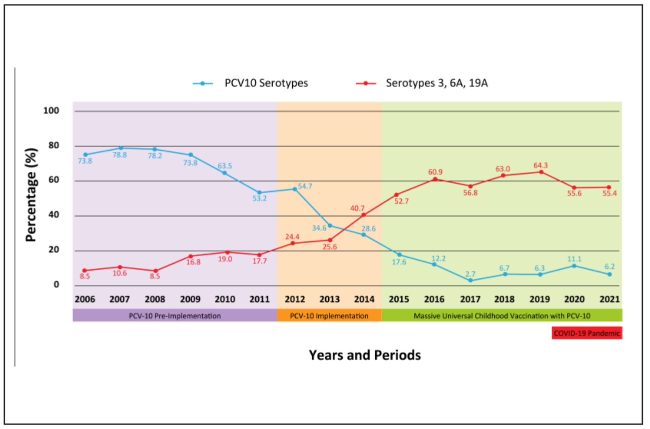

Figure 2. Annual Distribution of Pneumococcal Isolations from PDs Cases in Children under 5 years of Age in Colombia. The data were retrieved from SIREVA between 2006 and 2021.
Blue line and dots= percentage of pneumococcal isolates, grouped as the serotypes included in the PCV10 formulation. Red line and dots = percentage of pneumococcal isolates grouped as the serotypes 3, 6A and 19A, which are part of the PCV13.

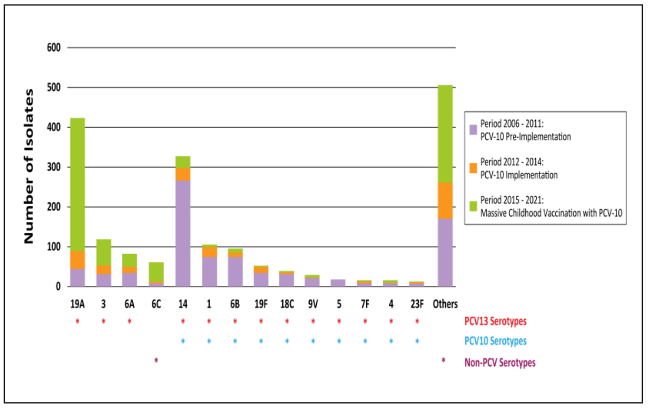

Figure 3. Distribution of Serotypes in IPD Cases in Children under 5 years of age. In sentinel surveillance, no isolates of serotypes of PCV10 have been observed since 2016 [25,26]. In the data from the Pneumo-Colombia Network, a decrease in Serotype 14 was observed from 35.3% in the 2008-2011 period to 9.5% in the 2015-2019 period and in Serotype 1 from 18.2% in the 2008-2011 period to 1.4% in the period 2015-2019[30].

pes were mainly due to serotype 14[24,44]. Another study using data retrieved from the System of Surveillance Networks of the Agents Responsible for Bacterial Pneumonia and Meningitis (SIREVA) showed a decrease in the serotypes included in PCV10 from 84.7% (63.1% in the period 2009-2011 to 9.7% in the period 2015-2017)[16].

In children between 5-14 years of age, a decrease in PDs due to PCV10 serotypes was observed from 60% in 2012 to 8% in 2018[45]. In contrast, in children over 14 years of age and adults, no significant decrease in PCV10 serotypes has been demonstrated[35,45,46] (Figure 4).

PCV10 Effects on the Emergence of Serotypes 3, 6A, 19A

A constant increase in the three PCV13 serotypes (those not included in PCV10) has been evidenced in all age groups. In children under 5 years of age, the proportion of these serotypes increased from 12.4% in the pre-PCV stage (2006-2010) to 58.7% in the 2015-2018 period. In 2021 this proportion was 65%[24,44] (Figure 2, Figure 3). Moreover, this trend has been consistent in children over 5 years of age and adults: in 2018, in the population between 5-14 years of age and in those over 14 years of age, the serotypes 3, 6A and 19A were 31% and 28% of all the isolates, respectively (Figure 4). In 2021 the serotypes 3, 6A and 19A were 40% in adults over 60 years of age. A study in adults showed that the predominant serotypes were 19A and 3[24,44,46]. A study carried out in Bogotá, with the aim of determining which pneumococcal serotypes isolated in IPDs were associated with major cardiovascular events (MACE) in the adult population, found that serotype 19A was the most frequent (13%) and that 21% of patients with this serotype developed MACE. It was also found that serotype 3 (OR 1.48 (1.21-2.27) and serotype 9N (OR 1.29 (1.08-2.24)) were independently associated with the presence of MACE during the course of IPDs[47].

The 19A serotype presents a trend of significant and very worrying increase in the post-PCV10 era. Figure 3 and Figure 4 show how, according to the INS laboratory report, in the post-vaccination period (2015-2018), serotype-19A has been the main cause of PDs in all age groups[24,44,48]. In the period 2019-2021, serotype 19A represented 51% of all isolates analyzed at the INS in children under 5 years of age that arrived at the INS[24]. In the Agudelo study, an increase was observed from 8.7% in the 2009-2011 period to 39.8% in the 2015-2017 period, representing a percentage change of +354.9%, with an rise in the reported annual rate of 0.27 x 100,000 children under 5 years of age to 1.26 x 100,000 children under 5 years of age[16].

This trend has also been seen in children with PDs included in the Pneumo-Colombia Network. A multicenter study carried out in 10 hospitals in Bogotá found that serotype 19A was the most frequent, with an increase in its prevalence in children under 5 years of age going from 4.7% in the period 2008-2011 to 36.8% in the period 2014-2017[27]. Another study that includes 17 hospitals in Colombia showed that the 19A serotype increased from 4.3% (5/116) in 2008-2011 to 10.7% (10/93) in the period 2012-2014 and 56% (112/ 202) in the period 2015-2019[30]. In a study conducted with data from the Bogotá District Health Secretariat, an increment in prevalence was observed from 3.2% in the 2007-2011 period to 18.2% in the 2012-2017 period[35]. In the cases of ABM, serotype 19A is the most frequent serotype since 2016[22,31,37]. In the data of the Pneumo-Colombia Network between 2008 and 2019, 81 cases of pneumococcal meningitis were documented; serotype 19A rose from 0% in the pre-vaccination stage to 31.2% in the post-vaccination stage[31]. In a study that analyzes the behavior of pneumococcal pneumonia in Bogotá between 2008 and 2019, an increase in the prevalence of this serotype was observed from 3% in the period 2008-2011 to 30.2% in the period 2014 to 2019[28].

Serotype 3 frequency augmented from 3.4% (4/116) in 2008-

2011 to 13.8% (28/202) in the period 2015-2019[24,30]. This increase was also observed in the INS data, from 5.7% in the 2009-2011 period to 11.1% in the 2015-2017 period [24,44]. In pneumonia, there was observed a rise from 0.7% in the period 2008-2011 to 16.7% in the period 2014-2019[28].

Isolates of serotype 6A went from 1.7% (2/116) between 2008-2011 to 6.4% (6/93) in the transition period 2012-2015 and to 4.4%, in the period 2016-2019[49].

PCV10 Effects on the Emergence of Non-PCV13 Serotypes
Agudelo *et al*. found that serotypes not included in PCV10/13 increased between 2006 and 2017[16]. Regarding non-vaccine serotypes in Colombia during the period before the introduction of PCV10 (2009-2011), they had been reported in 18.9% (69/366), with an increase to 33.2% (117/352) in the period 2015-2017, after the introduction of PCV10, with a percentage change of +76.3%. The most frequent non PCV10 non PCV13 serotypes were 6C (5.4%), 23A (4%), 24/24F (2.8%) and 15A and 23B (2.3% each)[16]. The non-vaccine serotypes also increased in children under 5 years of age in 2019, representing 30% of all isolates, with a similar behavior in the other age groups [24,30] (Figure 4). The 6C serotype has positioned itself as the most frequent nonPCV10 nonPCV13 serotypes. Figure 3 and Figure 4. For the period 2008-2011, no isolates were registered in the Pneumo-Colombia Network, while for the period 2016-2019, 10 of the total 12 cases were detected[49].

5. Considerations on the Evolution of the Antimicrobial Susceptibility/Resistance during the Periods Pre- and Post-PCV10

The resistance of *S. pneumoniae* to antimicrobials has experienced a notable increase in recent years. This phenomenon has occurred more markedly since 2015. According to the latest surveillance report by the *S. pneumoniae* laboratory in Colombia from 2016 to 2021 from the INS, in children under 5 years of age, resistance to penicillin fluctuated between 33% and 70.6% in meningeal isolates and between 30% and 48% in non-meningeal isolates. By the year 2021, resistance to penicillin was 50% and 44% in meningeal and non-meningeal isolates, respectively[24]. Similarly, resistance to ceftriaxone has shown a significant increase, reaching percentages of 35% in 2017 and 2018 for meningeal isolates and 42% for non-meningeal isolates. Additionally, a rise in isolates with intermediate sensitivity has been found, reaching 38% of non-meningeal isolates and 10% of meningeal isolates in 2018[24]. By 2020, it is worth noting the marked decrease in isolates sent to the system, which meant that resistance to this agent was only detected in 33% of non-meningeal cases. Other agents under surveillance have high rates of resistance in this same age group. Thus, resistance to erythromycin stood at 60% by 2021 and 57% for trimethoprim-sulfamethoxazole[24]. Data from the Pneumo-Colombia Network show that an increase in resistance to penicillin was observed in meningeal isolates from 4.5% in 2008-2011 to 40% in 2015-2021; resistance to

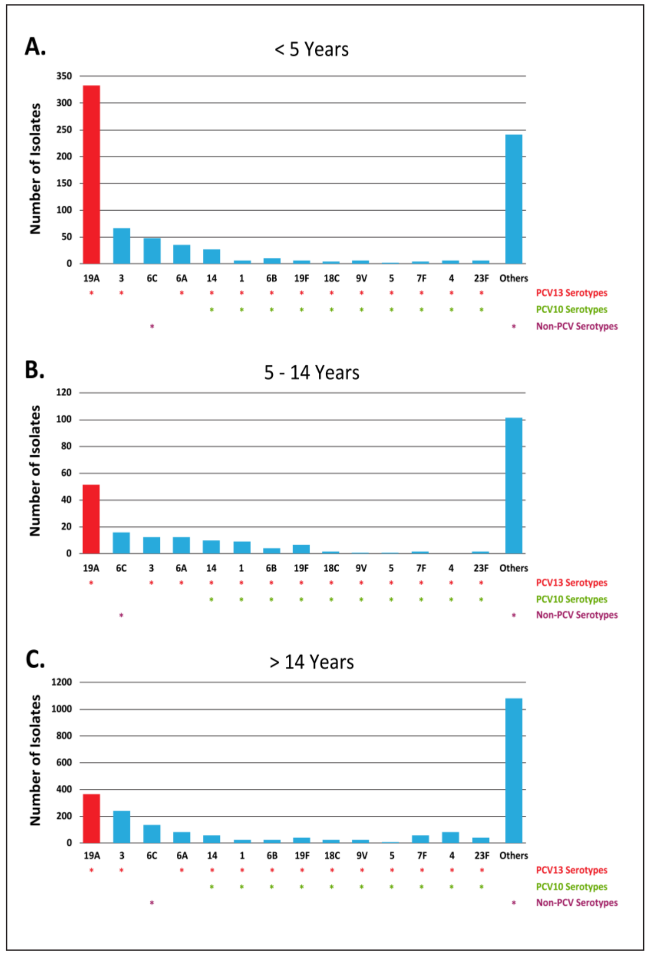

Figure 4. Distribution of Serotypes Isolated from IPD Cases during massive childhood vaccination with PCV10 (period 2015-2021) in Colombia. Isolates are shown by group of age: <5 years (A), between 5 and 14 years (B) and >14 years (C). The red bar highlights the emergence of the serotype 19A in the three group of ages.

ceftriaxone increased from 4.5% to 14% for the same periods respectively. In the case of non-meningeal isolates, resistance to penicillin incremented from 9.4% in 2008-2011 to 22% in 2015-2021 and to ceftriaxone of 1.4%; up to 9% for the same periods respectively[32] (Figure 5).

A study by the Pneumo-Colombia Network on the characterization of pneumococcal pneumonia in Bogotá from 2018 to 2019, reported an increase in the percentages of resistance in the period after the implementation of PCV10 compared to the period before its introduction. Resistance to penicillin increased from 9% to 21%, to erythromycin from 4% to 34%, and to clindamycin from 3% to 28%[28]. Additionally, a 2019 study to determine the rate of nasopharyngeal carriage in children under 5 years of age, conducted in Cali, reported high rates of resistance. Decreased sensitivity to penicillin (57%), ceftriaxone (21%), erythromycin (40%), trimethoprim-sulfamethoxazole (36%), and clindamycin (24%) was detected, evidencing the importance of colonization as a reservoir of multi-resistant isolates with an impact on transmission and subsequent IPDs in this population[50]. Finally, data from the

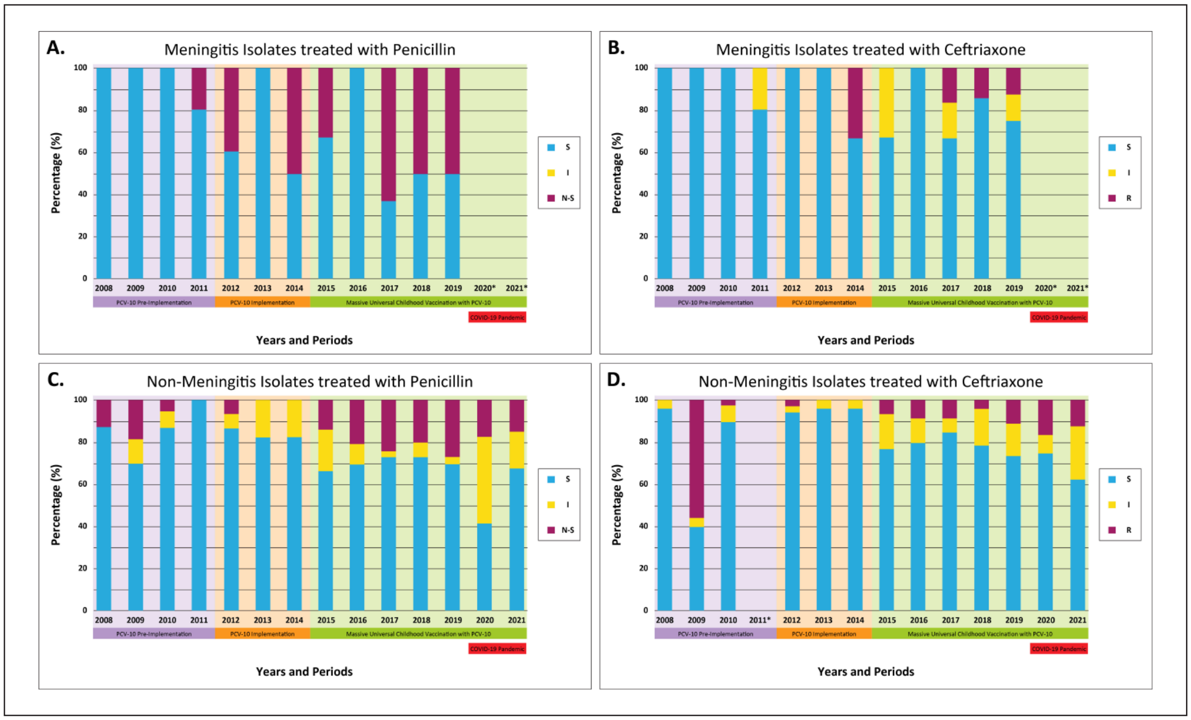

Figure 5. Susceptibility/Resistance of *S. pneumoniae* in Colombia. The susceptibility/resistance to Penicillin (A and C) and Ceftriaxone (B and D) of Meningeal (A and B) and Non-Meningeal (C and D) pneumococcal isolates are shown, according to the data collected by the Pneumo-Colombia Network between 2008 and 2021. *Data not available.

Pneumo-Colombia Network have shown that serotypes 19A, 6A, 14, 23F and 6C are the ones that exhibit a higher resistance pattern. In the case of 19A, data from the network reported a 20% increase in isolates not susceptible to penicillin for the period 2008-2011 and 43% for the period 2014-2017, with an increase, in addition, in resistance to ceftriaxone and erythromycin. 37% of the isolates were sensitive to all antibiotics, 14% were resistant to one family of antibiotics, 25% to 2 families, 7% to 3 families, 12% to 4 families, and 4% to 5 families of antibiotics (Figure 4). 48% of the serotype 19A isolates were multi-resistant[27,32].

6. Phenotypic and Molecular Considerations on the *Streptococcus pneumoniae* Serotype 19A Emergence in Colombia

The significant increase of *Streptococcus pneumoniae* serotype 19A in the post-PCV10 era in Colombia could be associated with the expansion of clones genetically related to Sequence Types ST320, ST276, and ST1118, characterized by MLST (Multi-Locus Sequence Typing)[51]. According to the INS report, in the post-vaccination period (2015-2021), serotype 19A has been the main cause of PDs in all age groups. Associated with this emerging serotype, the phenotypic characteristic of multi-resistance (MDR) to several families of antimicrobials has been demonstrated[24,48]. Worldwide, this close relationship between emerging serotype 19A and multi-resistance has been demonstrated, reporting strain clusters and clinical isolates, where clone ST320 stands out above the rest[27,52]. At the molecular level, the international clone ST320, in addition to having the complete arsenal of virulence factors with which the pneumococcus is capable of causing disease in children under 5 years of age and adults over 50, also has the two types of Pilus (Pilus-1 and Pilus-2), widely recognized as adhesion and virulence factors in the pathogenic processes of these microorganisms[53]. On the other hand, the hope of cross-protection against serotype 19A, based on the slight structural difference (but not conformational) existing between the polysaccharide capsules of serotypes 19F and 19A[54], seems to fade over time and the growing evidence and findings related to the emergence of this serotype 19A, especially that related to the international clone ST320, MDR and Double-Positive for Pili that are emerging in Colombia, as a result of the lack of vaccine selection pressure to which has not been subjected[51].

7. Considerations on the Cost-Effectiveness Studies: PCV10 vs PCV13

Three recently published studies on the cost-effectiveness in Colombia of the change from PCV10 to PCV13 conclude that, in the current epidemiological scenario, PCV13 could show better health outcomes, which is why it is considered more cost-effective. PCV10 would have lower immunization costs, being a cost-effective alternative when compared to not vaccinating. From a cost-effectiveness point of view, with the results of the study, switching to PCV13 would be the preferred policy in the competitive analysis[38-40]. PCV13 is a cost-saving strategy compared to PCV10, as part of a universal coverage vaccination program for colombian children under one year of age. PCV13 is expected to lead to a greater decline in infant mortality from PDs and greater cost savings by preventing more PDs compared to PCV10 in a 5-year projection[40].

Discussion

The correct choice of the most appropriate pneumococcal conjugate vaccine to be implemented in a given geographic region or country will depend on the level of a detailed knowledge of the local epidemiological scenario and the evolution of the serotype distribution involved in the burden of pneumococcal diseases. Likewise, once a selected vaccine has been implemented, its impact will be influenced by several factors, such as the coverage of serotypes included in its formulation, the efficacy/effectiveness of the vaccine against the pneumococcal diseases (direct protection) and against nasopharyngeal carriage (indirect protection), the selection of *S. pneumoniae* clones due to the use of antimicrobials, and the characteristics of the vaccination program (coverage, schedule, post-introduction time, etc)[4-6].

In its most recent recommendation, the WHO is emphatic in highlighting the additional benefits of vaccinating with PCV13 in an epidemiological scenario where serotypes 19A and 6C are responsible for a significant pneumococcal disease burden, serotype 6C has a seasonal behavior, a lower incidence has been observed in countries that administer PCV13 compared to those that administer PCV10[15]. In Colombia, a significant increase in PD cases produced by serotype 19A and 6C has been observed in the country at all ages. This significant rise is associated with an increase in resistance and, therefore, with a poorer clinical prognosis, as has been described and published by the Pneumo-Colombia Network[27,28]. Additionally, there has been evidence of an increase in mortality from acute respiratory infection (ARI) during the last 3 years, which has not allowed us to continue maintaining the downward trend that had been achieved in the previous decade[23].

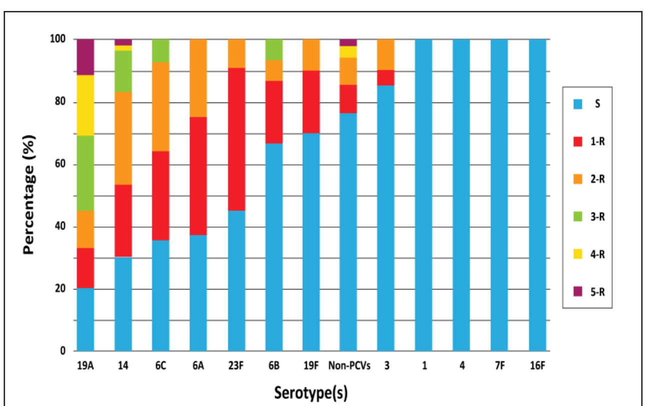

Figure 6. Susceptibility/Resistance of *S. pneumoniae* in Colombia by Serotypes and number the antimicrobials. The antimicrobial resistance of the pneumococcal serotypes is shown, according to the data collected by the Pneumo-Colombia Network between 2008 and 2021. In red, resistance to one antimicrobial agent (1-R); in orange, resistance to two antimicrobials (2-R); in green, resistance to three (3-R); in yellow, resistance to four (4-R); and in purple, resistance to five (5-R).

This phenomenon is not particular to Colombia and is becoming evident in other countries, including some with very robust surveillance systems such as Finland, Chile, and Brazil[55-60]. The probable cross-protection of serotype 19F (present in PCV10) to serotype 19A[61] seems to be of short duration, demonstrating an increase in serotype 19A in recent studies published both in Brazil[58,60] and in Finland[56]. The direct immune response measured in IgG levels to serotype 19A is 6-15 times higher with PCV13 than with PCV10[55]. In the particular case of Chile, the decision to change the vaccine from PCV10 to PCV13 was made based on an increase in serotype 19A less remarkable than the one we appreciate in Colombia[59]. Belgium presents a quasi-experimental public health scenario: the country had made the decision to go from PCV13 (applied since 2011) to PCV10 in 2015, prioritizing the issue of costs with an epidemiology that supported the change. However, in June 2018, its authorities reversed the strategy, restarting PCV13 in the face of a notable and significant increase in cases due to serotype 19A[62].

In Colombia, the epidemiological data described in the literature support the change to PCV13, which was announced by the Ministry of Health in April 2022 and implemented as of July 1, 2022, for the cohort of children born since May 1, 2022[63]. Based on the experiences published in Italy and Taiwan, we believe that the administration of a catch-up dose of PCV13 to children under 5 years of age can reduce the incidence of IPDs, especially that produced by serotype 19A[63-65].

As conclusion, in Colombia, a decrease in the serotypes included in PCV10 has been observed after its massive administration since 2012, which has led to less than 10% of the currently circulating serotypes being included in this vaccine. Concomitantly, after the introduction of PCV10, there has been an increase in the number of cases, in the incidence and in deaths where serotypes 19A, 3 and 6A have been responsible, both from a global analysis perspective of pneumococcal diseases, as one discriminated by its main invasive manifestations (ABM, pneumonia and primary bacteremia). This increase occurs due to the phenomenon of serotype replacement, it is not seasonal and is clearly more accentuated than the emergence of other non-vaccine serotypes. Particularly, serotype 19A is associated with an increase in bacterial resistance. There are cost-effectiveness studies in Colombia that conclude that the inclusion of PCV13 in the NIP is cost-effective. The two vaccines are useful to prevent IPDs due to the serotypes included in the vaccine. Currently, Colombia presents the epidemiological scenario (including an increase in serotype 6C) in which the WHO considers that PCV13 will have an additional benefit, we strongly agree with this change towards an expanded-valence vaccines according to the epidemiological scenario which should be complemented with a catch-up dose for children under 5 years of age.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this review work.

Right to privacy and informed consent. The authors declare that no data that enables identification of the patients appears in this paper.

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Conflict of interest. CTM has received fees for lectures and has been a consultant for MSD, Pfizer, Sanofi, Takeda, Annar, Tecnofarma/Moderna, Farma. He has received grants for academic meetings from Pfizer, Sanofi, MSD, Takeda and done Academic activities with Medscape with unrestricted grants from Sanofi and Takeda. GCM has received fees for lectures and other events from Pfizer, MSD, and Sanofi. He has received support for participation in congresses from Pfizer, MSD, Tecnopharma/Moderna. He is part of the Pneumo-Colombia Network that is supported by the "Asociación Colombiana de Infectología" (ACIN) central chapter, through an independent grant from Pfizer. JPN has received fees as a speaker for Pfizer, has served on the advisory board for Pfizer; has received support for participation in congresses from Pfizer; He has conducted research for new antimicrobial drugs in pediatrics with MSD; He participates in the research grant of the Pneumo-Colombia Network, which is supported by the ACIN central chapter, through an independent research grant from Pfizer. WC has received fees as a speaker from Pfizer, GSK, Astrazeneca, Tecnofarma/Moderna, Sanofi. Received grant for research by Sanofi. He has received fees for participating in the advisory boards of Pfizer, Sanofi and GSK. He is part of the Pneumo-Colombia Network. ALL has received speaking fees from Pfizer, Becton Dickinson, and Biomerieux. Pfizer Research Grants. She has received support for participation in Pfizer congresses. She has served on the Advisory Board for MSD. She is part of the Pneumo-Colombia Network that is supported by the ACIN central chapter through an independent grant from Pfizer. GG has no conflict of interest.

Author contributions statement. Conceptualization: CTM, GCM, JPN, WC, ALL and GG; Methodology and Investigation: CTM, GCM, JPN, WC, ALL and GG; Formal Analyses: CTM, GCM, JPN, WC, ALL; Data Curation: CTM, GCM, and ALL; Writing Original Manuscript: CTM, GCM, JPN, WC, ALL and GG; Figures and Tables: CTM, GCM, JPN, ALL, GG; Writing Review and Editing: GCM and GG; All authors have read and agreed to the published version of the manuscript.

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