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Meningococcal invasive disease by serogroup W and use of ACWY conjugate vaccines as control strategy in Chile

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ABSTRACT

Background: Serogroup causing invasive meningococcal disease (IMD) can change abruptly, as it occurred in Chile when serogroup predominance switched from MenB to MenW in 2012. As a response, a national vaccination strategy was implemented since 2012 using tetravalent meningococcal-conjugate vaccines (MCV–ACWY) in children 9 months through 4 years of age. The aim of this study was to describe IMD cases by MenW in Chile 2009–2016, and to analyse its trend after the introduction of MCV-ACWY.
Methods: Descriptive study of IMD cases in Chile, period 2009–2016. Cumulative incidence and mortality rate per 100,000 inhabitants, and case fatality rate (CRF) were used for descriptive analysis. Linear regression was used for post-intervention trend analysis.
Results: In 2012, MenW, mainly ST-11 cc, became predominant. MenW incidence rose from 0.01/100,000 inhabitants in 2009 to a maximum of 0.6/100,000 in 2015. Infants and adults 80 years of age and older were mostly affected, with an incidence peak of 9.7/100,000 and 1.6/100,000, respectively, in 2015. In the group of children from 1 to 4 years of age MenW incidence declined from 1.3/100,000 in 2012 to 0.1/100,000 in 2016, a 92.3% reduction after vaccination implementation. In the same period and age-cohort, CFR decreased from 23% to 0%. High mortality rates concentrated in infants and adults 80 years of age and over.
Conclusion: MenW became predominant in Chile since 2012. IMD cases increased steadily from 2009 to 2016, with higher incidence, CFR and mortality concentrating in infants and people 80 years of age and older. MCV–ACWY provided direct protection against MenW, reducing its incidence after mass meningococcal vaccine implementation. Indirect effects of vaccination are not yet observed.

1. Background

Invasive meningococcal disease (IMD) is a major public health problem, as it is one of the main causes of sepsis and meningitis worldwide. IMD is of unpredictable occurrence, abrupt clinical manifestations, and associated with high case-fatality rate (CFR) [1,2]. The majority of invasive disease reported worldwide is caused by six *Neisseria meningitidis* serogroups: A, B, C, W, X and Y. The distribution of serogroups causing disease varies with age group and geographical location [3], while serogroup predominance can change in short periods of time [4].

N. meningitidis are gram-negative bacteria that can be either encapsulated or not. Usually, *N. meningitidis* isolates associated with IMD are encapsulated. The capsule provides resistance to antibody/complement-mediated killing and inhibits phagocytosis. Also, it forms the basis for the classification of meningococci into serogroups and for licensed polysaccharide and new conjugate-polysaccharide meningococcal vaccines, with the exception of serogroup B [5].

Epidemiological surveillance is essential for infectious disease control. In Chile, IMD epidemiological surveillance began in 1976, establishing mandatory immediate notification of suspect meningococcal disease cases to the local epidemiology department [6]. Chilean surveillance data show variations in IMD through time, with incidence rates up to 4.0/100,000 inhabitants during the 1990′s due to a serogroup B outbreak and, on the other hand, a

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decline to 0.4/100,000 after the year 2000, the lowest rate observed since the beginning of surveillance [7–9]. Regarding serogroup predominance, in 2012 there was a switch from serogroup B (MenB) to serogroup W (MenW), at the same time that a two-fold IMD incidence with respect to 2011 was observed (0.8/100,000 inhabitants). In addition, CFR rose to 28% in 2012, the highest rate registered in the past 20 years. The hypervirulent genetic linage MenW: P1.5, 2:ST-11, including the allele fHbp–22, was identified as the cause for the increased number of IMD cases, whose most frequent manifestation was meningococcemia [10–13]. This clone belongs to the clonal complex 11 (cc11) reported by a number of African and European countries since the year 2000 due to MenW outbreaks within Hajj returned pilgrims. In Latin America, increase in MenW cc11 cases were reported in southern regions of Brazil and northern Argentina between 2003 and 2008 [14]. The spread of this hypervirulent clone was rapid and thus soon reached Europe, causing and increase of IMD cases between 2012 and 2016, especially in the United Kingdom [15,16].

In Chile, a mass meningococcal vaccination campaign was launched in October 2012 as part of a control strategy, followed by an administrative health alert issued by the Ministry of Health (MoH) in order to expedite the vaccination campaign. Considering that 34.5% of MenW cases occurred in children under 5 years of age and the MCV–ACWY approval available at the time, the vaccination campaign used meningococcal ACWY conjugate vaccines (MCV–ACWY) in children 9 months old through 4 years of age [17]. Children from 9 months to 23 months and 29 days of age received meningococcal vaccine conjugate to diphtheric toxoid (DT) in a two-dose schedule separated by three months. For children 2 years and older, MCV–ACWY–DT or MCV–ACWY conjugate to CRM_{197} (MCV–ACWY–CRM_{197}) were given in a one–dose schedule [17,18].

Meningococcal vaccination started in October 2012 in Santiago, the capital and largest city of Chile, for 80% of IMD cases occurred there. The intervention was expanded to the entire country three months later, lasting until December 2013. Communications strategies, including the use of social media, contributed toward achieving high vaccination uptake [17]. In January 2014, the MoH introduced routine meningococcal vaccination in the National Immunization Program (NIP) using MCV–ACWY conjugate to tetanic toxoid (TT) in a one–dose schedule at 12 month of age, replacing previous schemes [19].

The aim of this study was to describe IMD cases by *Neisseria meningitidis* serogroup W in Chile from 2009 to 2016 and to analyze its trend after the introduction of MCV–ACWY.

2. Methods

Overall study design. Descriptive analysis of IMD cases registered in Chile, regarding incidence, CFR and mortality from 2009 to 2016, and IMD trend analysis after the introduction of MCV-ACWY. Epidemiologic data was obtained from the National IMD Surveillance and Control Program of the Ministry of Health. Every suspect IMD case must immediately be notified to the regional sanitary authority (SEREMI) by phone call and electronically. SEREMI notifies the Epidemiology Department within the MoH. Meanwhile, samples from sterile sites as blood, cerebrospinal fluid, or joint fluid are taken. Positive cultures are transferred to the Public Health Institute (PHI) for confirmation, while negative cultures require the original sample be transferred to the PHI for polymerase chain reaction (PCR) testing.

IMD cases and IMD–related deaths were coded by treating physicians according to the International Classification of Diseases 10th Revision: meningitis (code A39.0), meningococcemia (A39.2), Waterhouse-Friderichsen syndrome (A39.1), other meningococcal infections (A39.8), and unspecified meningococcal infections (A39.9). Hospital discharge records and death certificates are systematically collected by the Department of Statistics and Health Information of the MoH.

Microbiologic data were obtained from the PHI. Confirmed positive cultures were serogrouped using slide agglutination with polyclonal antibodies. PCR for meningococcal *ctrA* gene identification and endpoint PCR for serogroup W and Y identification were introduced in 2009 and 2012, respectively. Sequence types (STs) and clonal complex were determined on the basis of housekeeping genes used and compared accordingly to database available at http://pubmlst.org/. Meningococcal isolates belonging to the same clinical IMD case were counted as one case.

Vaccination uptake data was obtained from the Electronic Immunization Registry of the NIP. This registry consolidates data on vaccinated children across the country, including dose number, vaccine lot, area of residence, among others. Population projections data were obtained from the National Institute of Statistics (INE).

Statistical methods. Laboratory IMD confirmed cases were described using cumulative incidence per 100,000 inhabitants, mortality rate per 100,000 inhabitants, and CFR (%). Linear regression was used to estimate post-intervention average annual change in IMD incidence, CFR and mortality. Statistical analysis was performed using STATA IC v14.0.

3. Results

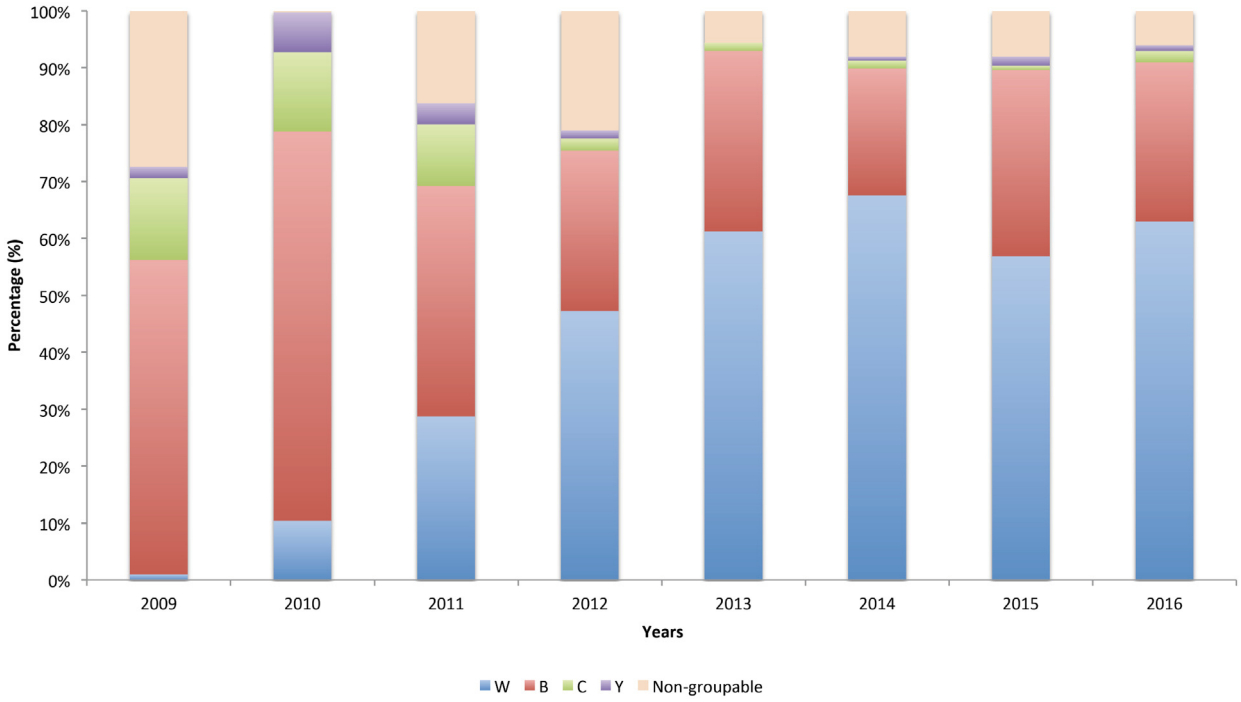
Cases description: In the 2009–2016 period, 902 IMD cases were reported to the surveillance system. Microbiologic confirmation achieved 84% (n = 759), with 13.6% (n = 103) confirmation by PCR-based techniques only.

Total MenW cases increased steadily between 2009 and 2014, from 1 to 100 cases respectively, followed by a decline in 2015 and 2016 of about 30%. By age group, 25% of MenW cases in the study period occurred in infants (n = 102), 8% (n = 32) in children 1 to 4 years of age, 8% (n = 32) in adolescents 10 to 19 years of age, and 24% (n = 98) in individuals 60 years and older.

Serogroup distribution: Of the total confirmed cases (n = 759), 54% (n = 413) were caused by MenW, followed by MenB with 38% (n = 292), and later by serogroup C (MenC) and non-groupable cases. There were no confirmed serogroup A (MenA) IMD cases. Regarding meningococcal serogroup predominance, a switch from MenB to MenW started in 2012 and persisted through 2016 (Fig. 1). According to MenW ST and cc analysis, 94% (n = 390) of MenW strains belonged to ST–11.

Meningococcal incidence: Median overall IMD incidence for the 2009–2016 period was 0.65/100,000 inhabitants (range 0.4–0.8), reaching highest values during 2012 through 2014, later decreasing to 0.6/100,000 in 2016. In the study period, median MenW incidence was 0.4/100,000 inhabitants (range: 0.01–0.6). After meningococcal vaccine implementation, median IMD MenW incidence decreased 0.4 cases/100,000 inhabitants annually between 2013 and 2016. Median IMD incidence by MenB and MenC-Y were 0.2 and 0.03/100,000 inhabitants respectively in the same period (Fig. 2).

By age, MenW incidence in infants increased in 0.9 cases of IMD/100,000 inhabitants in average annually between 2009 and 2012. The highest incidence rates concentrated in this age group each year, with a peak of 9.7/100,000 inhabitants in 2015. In children 1 through 4 years of age, MenW incidence increased 0.02 cases of IMD per 100,000 inhabitants in average annually in the period 2009–2012. After the implementation of the mass meningococcal vaccination campaign, IMD incidence declined from 1.3 to 0.1/100,000 inhabitants, equivalent to a 92.3% reduction. The second highest incidence peak of IMD was observed in adults 80 years and older in 2015, with a rate of 1.6 IMD cases/100,000 inhabitants



W: *Neisseria meningitidis* serogroup W
B: *Neisseria meningitidis* serogroup B
C: *Neisseria meningitidis* serogroups C
Y: *Neisseria meningitidis* serogroup Y
NG: *Neisseria meningitidis* non-groupable

Fig. 1. Meningococcal serogroup distribution by year, Chile 2009–2016.

(Table 1). Regarding MenB incidence, it concentrated in children younger than 5 years of age, mainly infants, during the entire study period. Cases by meningococcal serogroups C and Y were sporadic and with no concentration patterns by age group.

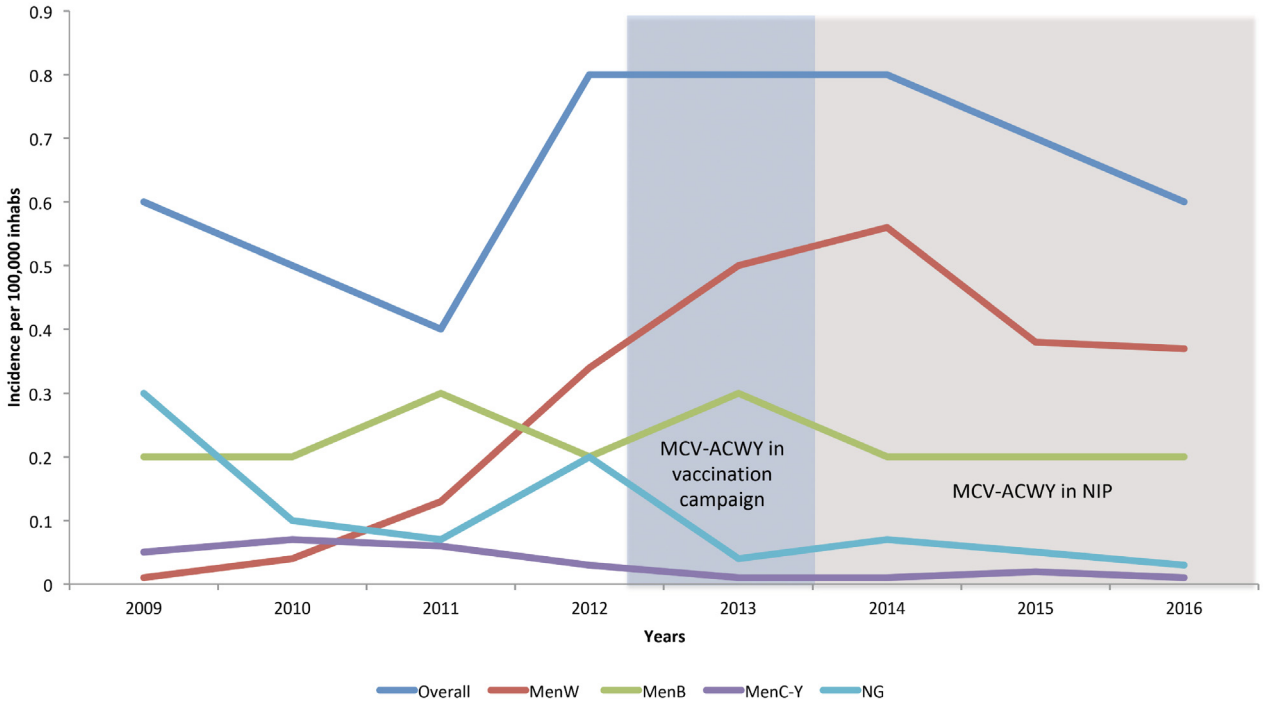
Case fatality rate: Median overall CFR was 19.7% (range: 9.1–27.9). Highest CFR (28%) was observed in 2012 and 2015. Median CFR for MenW was 18.3% (range 0–40.5), increasing from 0% in 2009 to 40.5% in 2015, followed by a decline in 2016 (29.4%) (Fig. 3). Median MenB CFR was 7% (range: 3.2–18) (Fig. 3). Non-groupable *N. meningitidis* CFR started to increase in 2009 with a peak during 2012 before the use of PCR for serogroup W identification. Since mass meningococcal vaccination implementation, MenW CFR in children 1–4 years of age declined from 23% to 0%. In adult population, particularly among subjects 60 years of age and older, CFR did not show a decline after the implementation of MCV–ACWY vaccination (Table 2).

Mortality rate: Median overall mortality annual average decline was 0.1/100,000 inhabitants. By serogroup, annual average decline after vaccine implementation was 0.1/100,000 for MenW and 0.03/100,000 for MenB. MenW mortality rate was higher in infants, with median value of 1.2/100,000 inhabitants (range: 0.4–2.8). After MCV–ACWY implementation, mortality rate in infants decreased 0.04 deaths/100,000 inhabitants in average annually. The second group most affected by IMD deaths were adults 80 years of age and older with median value of 0.3/100,000 inhabitants (range: 0–0.6), followed by children 1–through 4-years of age with median mortality of 0.25/100,000 inhabitants.

Vaccination uptake: Vaccination campaign reached an uptake of 80% in 2012 and 82% in 2013. After the introduction of MCV–ACWY–TT into the routine vaccination program, 91%, 95% and 97% uptake was observed from 2014 to 2016, consecutively.

4. Discussion

IMD is a major cause of meningitis and septicaemia worldwide. The ever changing IMD epidemiology together with sudden switches in serogroup predominance contribute to the unpredictable nature of IMD, with significant health, social and economic impact due to high CFR and long-term sequelae [1,2,20–23]. The potential epidemic nature of IMD is the main reason for primary prevention through mass vaccination strategies, as they have been implemented against serogroups A, B and C using polysaccharide, outer membrane protein-based or conjugate vaccines for disease control during outbreaks [24–28]. The change in IMD epidemiology in Chile due to the new hyper virulent invasive strain MenW: P1.5,2:ST-11 was a complex scenario that demanded a comprehensive policy design from government authorities. Known as *Action Plan W-135*, the policy health, social and communications dimensions aimed at strengthening IMD surveillance, contacts management, use of PCR for MenW serogroup determination, and mass vaccination campaign implementation in children from 9 month through 4 years of age. [10–13,17]. Previous decades of reported effectiveness of meningococcal mass vaccination had not included experience against MenW. At the time of *Action Plan W-135* implementation, evidence on MCV–ACWY vaccine safety, effectiveness, public health impact, and cost–effectiveness was scarce, and MCV–ACWY use in infants younger than 9 month of age was not yet approved [14,24,29,30]. With support from technical and scien-



MenW: *Neisseria meningitidis* serogroup W

MenB: *Neisseria meningitidis* serogroup B

Men C-Y: *Neisseria meningitidis* serogroups C and Y

NG: *Neisseria meningitidis* non-groupable

MCV–ACWY: meningococcal conjugate vaccine against serogroups A, C, W and Y

NIP: National Immunization Program

Fig. 2. Invasive meningococcal disease incidence for *Neisseria meningitidis*, overall and by serogroups, Chile 2009–2016.

tific groups, Chile's MoH decided to provide direct protection to young children, one of the most affected age groups, and thus tackled the MenW IMD outbreak vaccinating children from 9 months up to 4 years of age [17].

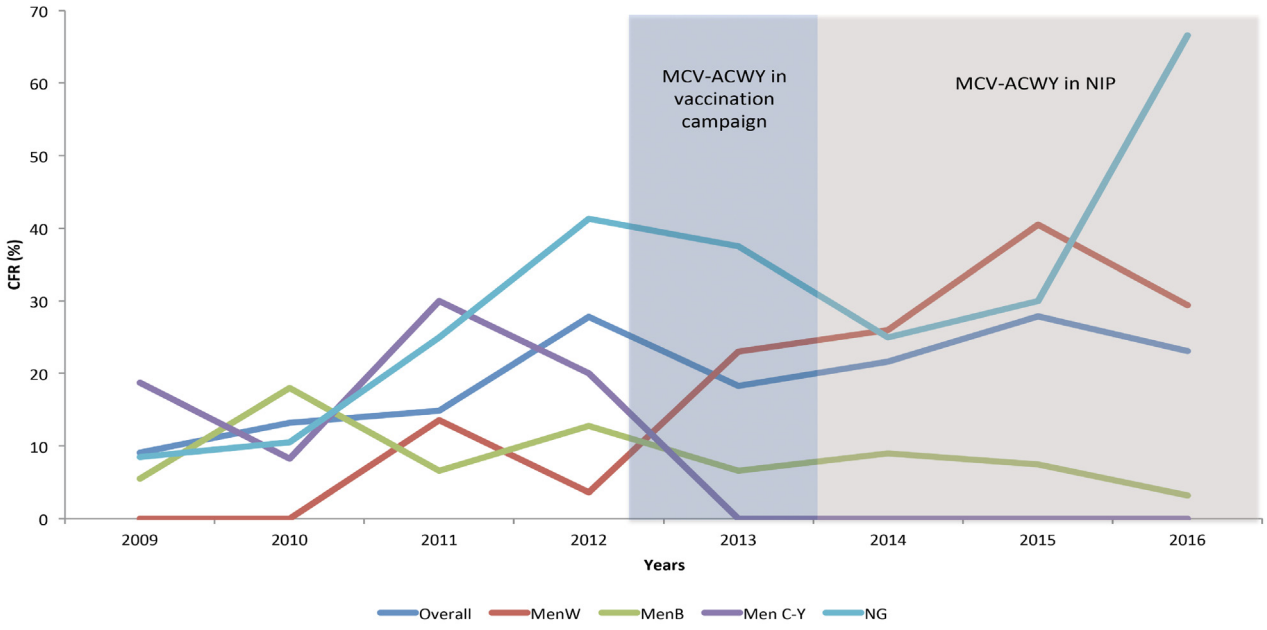
The communications strategy stemming from health authorities promoted vaccination widely, contributing toward achieving high vaccination uptake in a short period of time, ranging from 80% in 2012 during the vaccination campaign to 97% during routine immunization in 2016 [17]. Similarly to vaccination against MenC experiences reported by the UK and Brazil [27,31,32], MCV–ACWYs induced direct protection shortly after implementation, with an overall incidence decline of 92.3% between 2013 and 2016 in children from 1 through 4 years of age. After meningococcal vaccination implementation, no MenW-related deaths occurred in the target group for vaccination. Although direct protection was apparent, the vaccination strategy did not show impact on IMD burden in infants. The second highest incidence peak was observed in adults 80 years and older, suggesting that no herd effect was accomplished after the vaccination campaign. The absence of infants and adolescents as target groups for vaccination may in part explain the lack of herd effect.

According to published experience in the UK and Brazil [31–33], adolescents as an age group have been described to be meningococcal disease infection reservoir and a cornerstone for community protection by indirect mechanisms. In Chile, new insights to assess MCV–ACWY immunization strategy after 6 years of implementation are needed. Meanwhile, our results shed light on a successful experience against MenW using MCV–ACWY as a mass immunization strategy that has continued to provide protection against IMD to children after the introduction of the vaccine into the routine childhood immunization program.

Based on age group IMD incidence and results of a case–control study conducted in Chile during 2012-2013 that showed age less than one year as a main risk factor for MenW–IMD [34], the introduction of meningococcal vaccination in infants at 2 months of age and booster dose at 12 months of age seems advisable as a next step for routine immunization in this country. Additionally, separate nasopharyngeal carriage studies conducted in Chile in 2012 and 2013 showed a 7.6% overall meningococcal carriage in adolescents aged 14 to 19 years, and 4% in university students aged 18–24 years [35,36]. Inherent to this age group are frequent social contact and engagement in crowded social activities, behaviors that contribute to disease spread irrespective of carriage rates. These facts have encouraged other countries to include adolescents in their meningococcal vaccination interventions for the purpose of community protection [26,31–33,37,38]. In Chile, this approach could provide indirect protection to the most affected groups: infants and adults 80 years and older. In light of the epidemiological, immunological and environmental factors, a vaccination strategy of at least one dose of MCV–ACWY in adolescents at 13 years of age shall be considered as an extension of or in parallel with a 2 + 1 schedule of meningococcal vaccination in infants. So far, there are no robust data showing that prevention of acquisition of carriage can be obtained after use of MCV–ACWY as observed with

Table 1
Invasive meningococcal disease incidence for *Neisseria meningitidis* by serogroup W and overall, by age and year, Chile 2009–2016.

	2009		2010		2011		2012		2013		2014		2015		2016	
	MenW	Overall	MenW	Overall	MenW	Overall	MenW	Overall	MenW	Overall	MenW	Overall	MenW	Overall	MenW	Overall
<1 year	0	6.8	1.2	9.2	4.36	7.25	5.95	9.4	8.73	15.2	9.7	18.6	6	11.6	5.27	9.2
1–4 years	0	3	0	2	0.6	2.3	1.3	2.3	0	1	0.9	1.6	0.2	0.7	0.1	0.5
5–9 years	0	0.8	0	0.4	0	0.3	0.32	1.2	0.24	1.3	0.16	0.25	0	0.16	0.08	0.16
10–14 years	0	0.45	0	0.2	0	0.15	0	0.16	0.24	0.4	0.24	0.5	0.24	0.6	0.16	0.33
15–19 years	0.07	0.4	0	0.1	0	0.2	0.21	0.5	0.36	0.6	0.22	0.4	0.3	0.3	0.22	0.6
20–39 years	0	0.32	0	0.24	0	0.2	0.13	0.12	0.2	0.35	0.03	0.4	0.16	0.3	0.27	0.32
40–59 years	0	0.3	0.05	0.14	0.07	0.15	0.2	0.35	0.52	0.65	0.36	0.5	0.34	0.6	0.25	0.45
60–79 years	0	0.16	0	0.2	0.1	0.35	0.34	0.8	0.84	0.94	1	1.13	0.6	0.9	0.7	0.9
≥80 years	0	0	0.32	0.6	0	0.3	0.58	0.6	0.84	0.84	0.54	0.54	1.56	2	1	1
Total	0.01	0.63	0.04	0.5	0.13	0.4	0.34	0.8	0.5	0.8	0.56	0.8	0.38	0.7	0.37	0.6



CFR: Case fatality rate
MenW: *Neisseria meningitidis* serogroup W
MenB: *Neisseria meningitidis* serogroup B
Men C-Y: *Neisseria meningitidis* serogroups C and Y
NG: *Neisseria meningitidis* non-groupable
MCV–ACWY: meningococcal conjugate vaccine against serogroups A, C, W and Y
NIP: National Immunization Program

Fig. 3. Case fatality rate of invasive meningococcal disease for *Neisseria meningitidis*, overall and by serogroups, Chile 2009–2016.

monovalent MenC and MenA conjugate vaccines. However, a vaccination program targeting adolescents could potentially benefit the whole community if several cohorts are immunized.

Although the focus of this work was the experience using MCV–ACWY for MenW control, it is important to note that MenB IMD incidence decline was greater than that observed in MenW IMD after the introduction of the MCV–ACWY vaccine. This phenomenon possibly reflects the cyclical nature of meningococcal disease.

This ecological study has limitations. It does not establish a causal relationship between the intervention and the outcome, MCV–ACWY vaccination and MenW IMD burden of disease, respectively. However, an ecological descriptive study is most appropriate as a primary approach to the situation of MenW outbreak and use of MCV–ACWY vaccine as control strategy. Additionally, IMD surveillance in Chile is immediate and mandatory. Also, the Epidemiology Department of MoH and the National Laboratory of IPH make data check and verifications permanently. Another limitation of this study was the abbreviated post-intervention incidence measurements to assess MCV–ACWY impact. Nonetheless, our results show that use of MCV–ACWYs provided protection against MenW for MenW IMD incidence and MenW CFR were

Table 2
Case fatality rate of invasive meningococcal disease by *Neisseria meningitidis* serogroup W and overall, by age and year, Chile 2009–2016.

	2009		2010		2011		2012		2013		2014		2015		2016	
Ages	MenW	Overall	MenW	Overall	MenW	Overall	MenW	Overall	MenW	Overall	MenW	Overall	MenW	Overall	MenW	Overall
<1 year	0	6	0	17.4	9	5.5	11.7	9.3	4.7	8	12.5	15.2	13.3	13.8	7.7	8.7
1–4 years	0	3.6	0	16	0	8.7	18.7	23	0	0	0	12.5	0	14.2	0	0
5–9 years	0	0	0	20	0	0	0	21.4	0	1	0	0	0	0	0	0
10–14 years	0	16	0	0	0	0	0	0	0	0	0	0	33	14.2	50	25
15–19 years	0	0	0	0	0	0	40	43	50	37.5	33	20	20	20	0	12.5
20–39 years	0	11.7	0	7.7	0	22.2	30	33	30	26.3	27.7	22.7	89	47	20	16.6
40–59 years	0	16.6	0	0	33	28.5	36.3	50	34.7	26.6	41	30.4	62.5	43	50	36.3
60–79 years	0	66.6	0	25	33	57	40	38	22	25	41	36	28.5	25	41	36.3
>80 years	0	0	0	0	0	0	33	50	33	33	50	50	33	25	50	50
Total	0	9	0	13	15.7	14.8	25	27.8	23	18.3	26	21.6	40.5	27.8	29	23.1

reduced after mass meningococcal vaccine implementation. Still, high disease burden in infants calls for a direct protection strategy as well as the consideration of vaccination in adolescents that could contribute toward protecting older age groups from meningococcal disease.

All authors have read and approved the final draft of the manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Rodolfo Villena has received grants to support research projects from GSK and consultancy fee from Pfizer and Sanofi Pasteur. María Teresa Valenzuela does not report any conflicts of interest. Magdalena Bastías does not report any conflicts of interest. María Elena Santolaya has received grants to support research projects in Men B vaccine from GSK.

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