Enfermedad meningocócica: la complejidad de la protección

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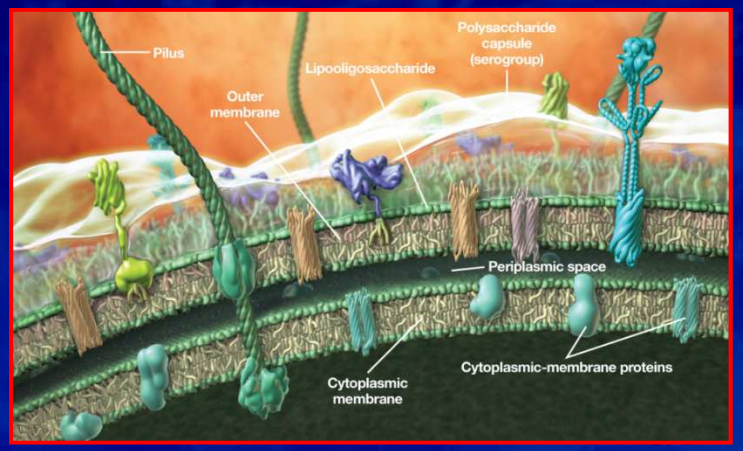
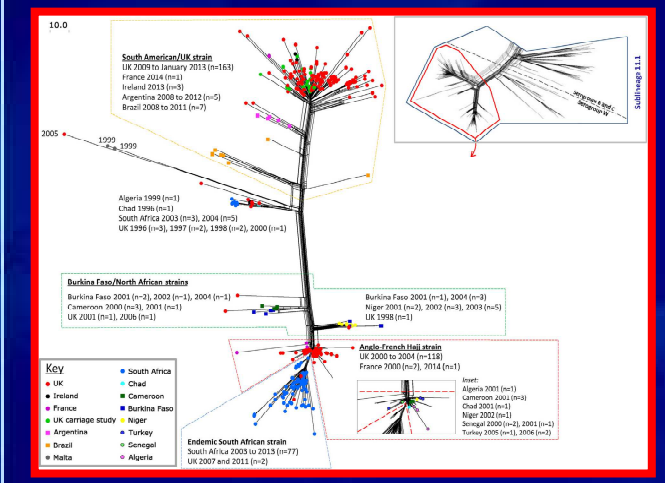
Neisseria meningitidis

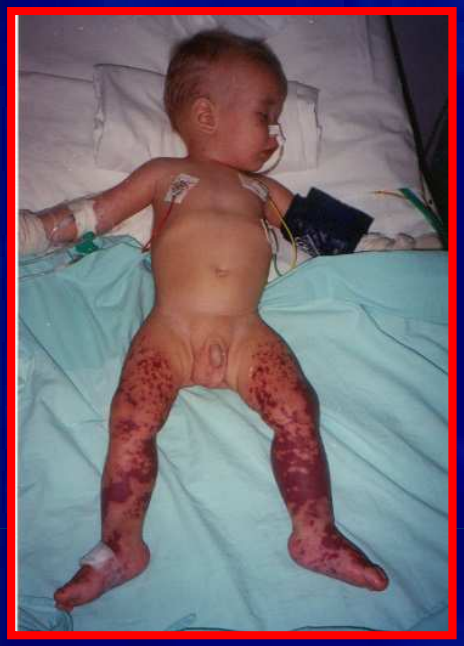


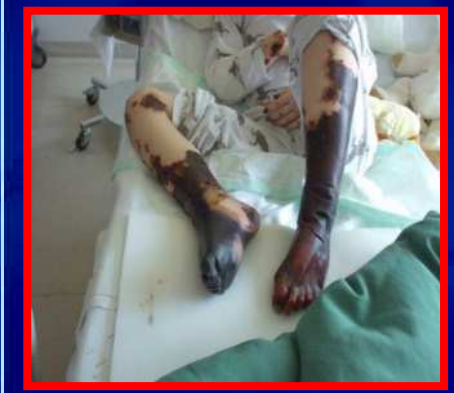


- Polysaccharide capsule (12 serogroups) A, B, C, Y, X and W....
- Genetic characterization (DNA sequencing of 7 housekeeping genes - MLST)
- Whole genome phylogenetic analyses

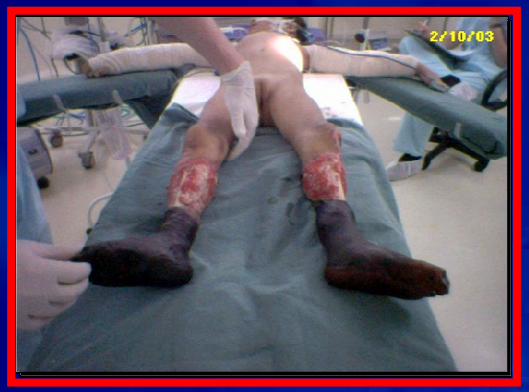
Lucidarme J et al. J Infect, 2015

Neisseria meningitidis





Safadi M



Clinical syndromes

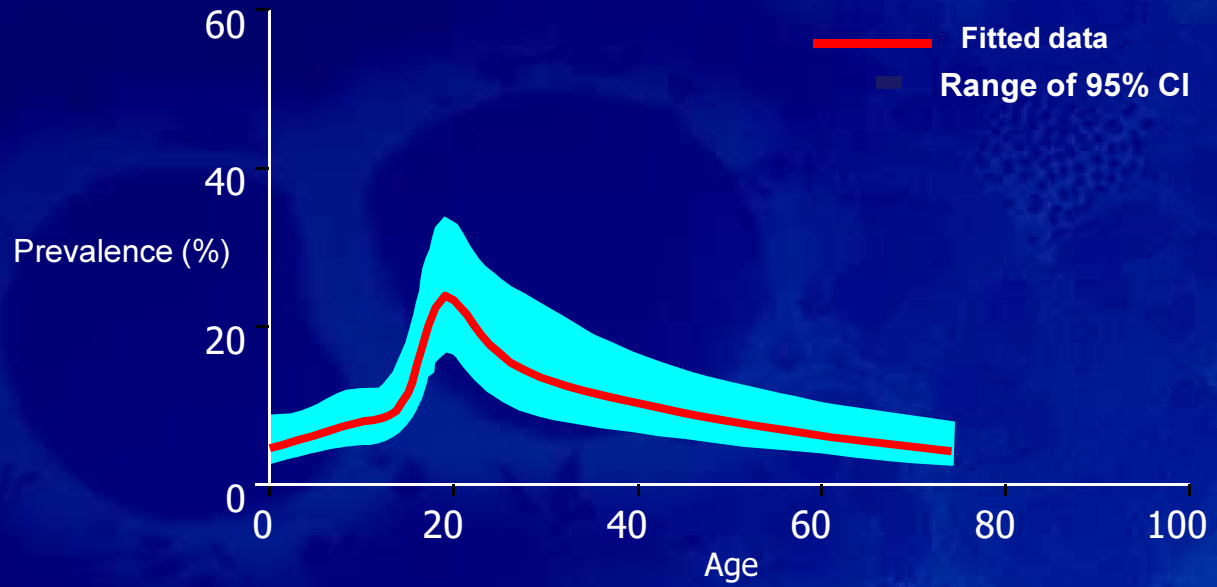
- Bacteriemia (37.5%) - Meningococcemia
- Meningitis (50%)
- Pneumonia (9%)
- Conjunctivitis arthritis, pericarditis, urethritis

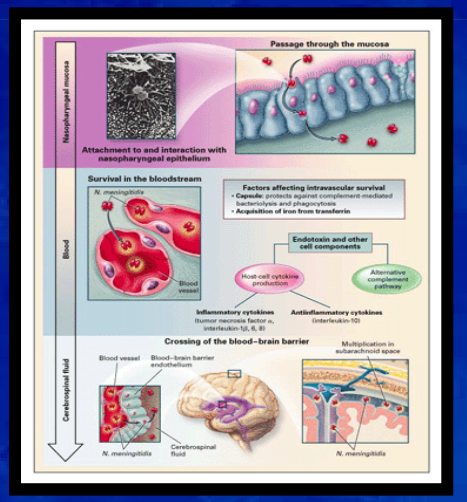
Complications	Frequency (%)
Overall	
Neurological impairment	7
Hearing impairment	4
Meningitis	
Hearing loss	2.6
Profound hearing loss	2.1
Seizures	0.5
Visual impairment	1.6
Motor deficits	0.6
Behavioural difficulties	0.6
Septicaemia	
Chronic pain	21
Skin scarring	13
Amputations	3

D. Pace, A.J. Pollard / Vaccine *30S (2012) B3–9*

Carriage and transmission

- **Pharyngeal carriage is a prerequisite for invasive meningococcal disease.**
- **Asymptomatic carriage (may last a long time) -nasopharynx (< 1% - 30%)**
- ***N. meningitidis* is predominately carried by teenagers/young adults.**





Christensen H et al. Lancet Infect Dis. 2010;10:853.

Cual entre las siguientes opciones mejor describe las características de la epidemiología actual de la enfermedad meningocóccica en Argentina ?

1- predominio del serogrupo W, incidencias más altas en adolescentes.
2- predominio del serogrupo W, incidencias más altas en niños pequeños.
3- predominio de serogrupo B, incidencias más altas en niños pequeños.
4- predominio del serogrupo W, incidencias más altas en adultos.
5- predominio del serogrupo B, incidencias más altas en adolescentes.

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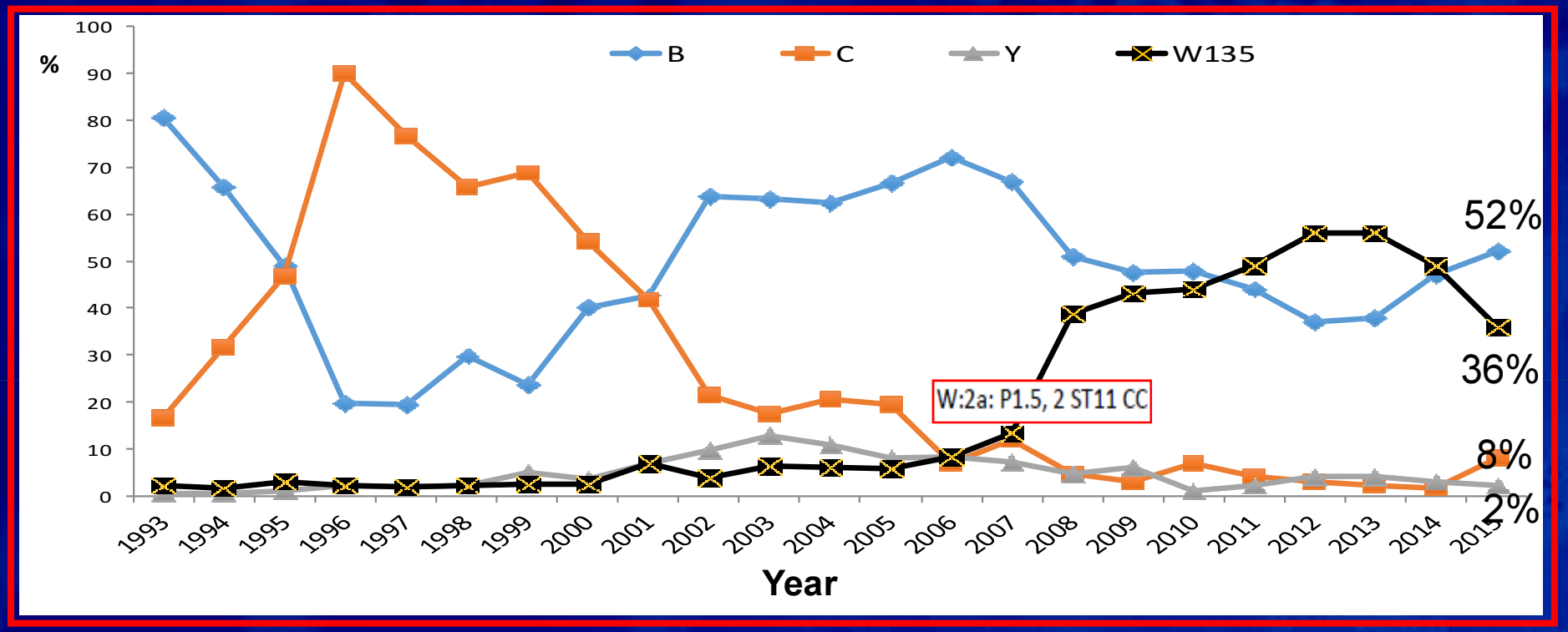
Epidemiology of Meningococcal Disease in Argentina 1993-2015.



- Incidence rate of 0.7 /100,000 hab. 43.3% (368) < 2 years, 78.8% < 1 year.
- I.R. in infants: 14.7/100.000; 57% of the cases in < 5 years of age.
- Argentina decided to implement ACWY-CRM vaccine in infants (3, 5 and 15 m). Adolescents with 11 years will receive one dose

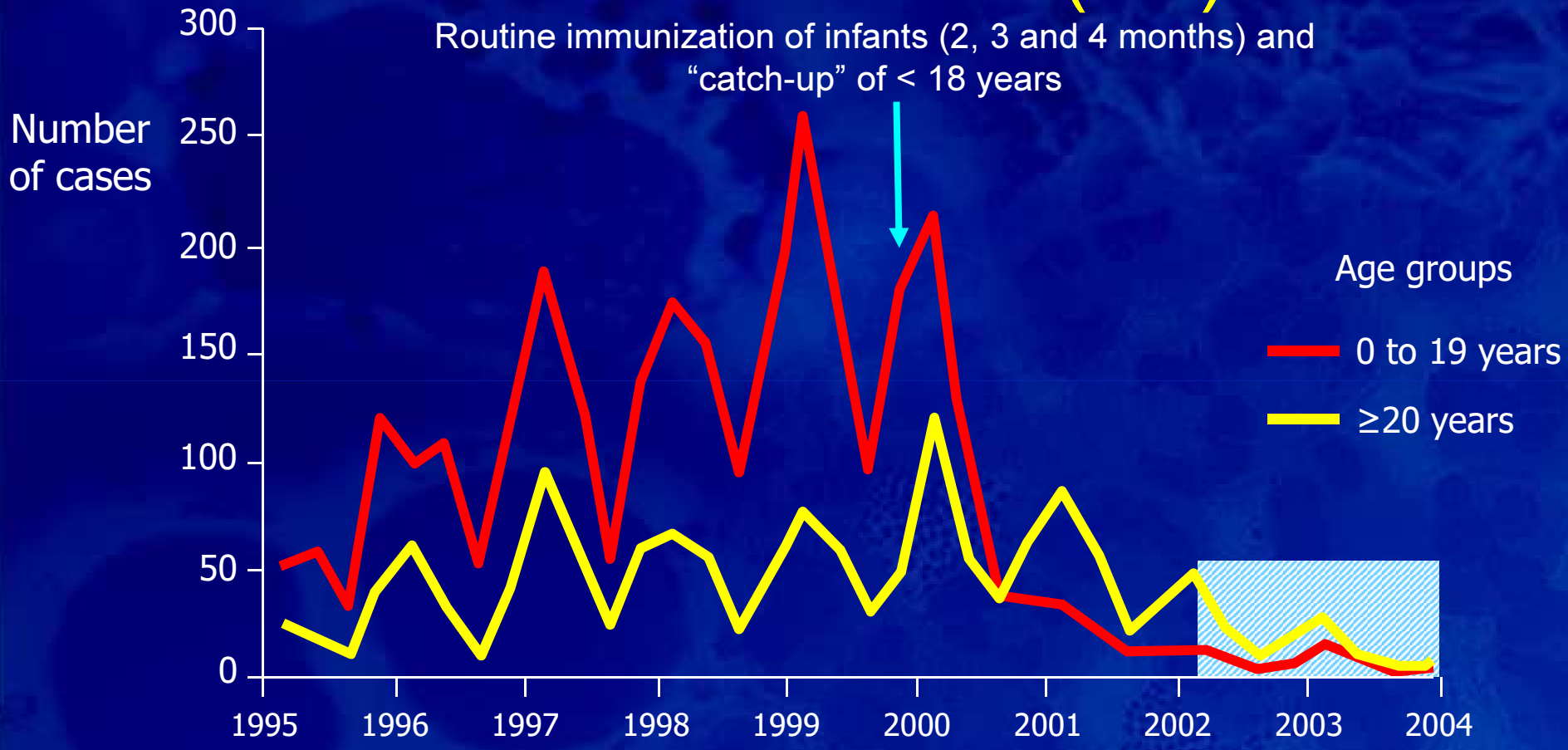
Servicio Bacteriología Clínica. INEI-ANLIS C.G. Malbrán /SIREVA 2016

Rancano C et al. SADI, 2015

What have we learned with Meningococcal Vaccines Programs?

Meningococcal conjugate vaccination programs with catch-up campaigns.....

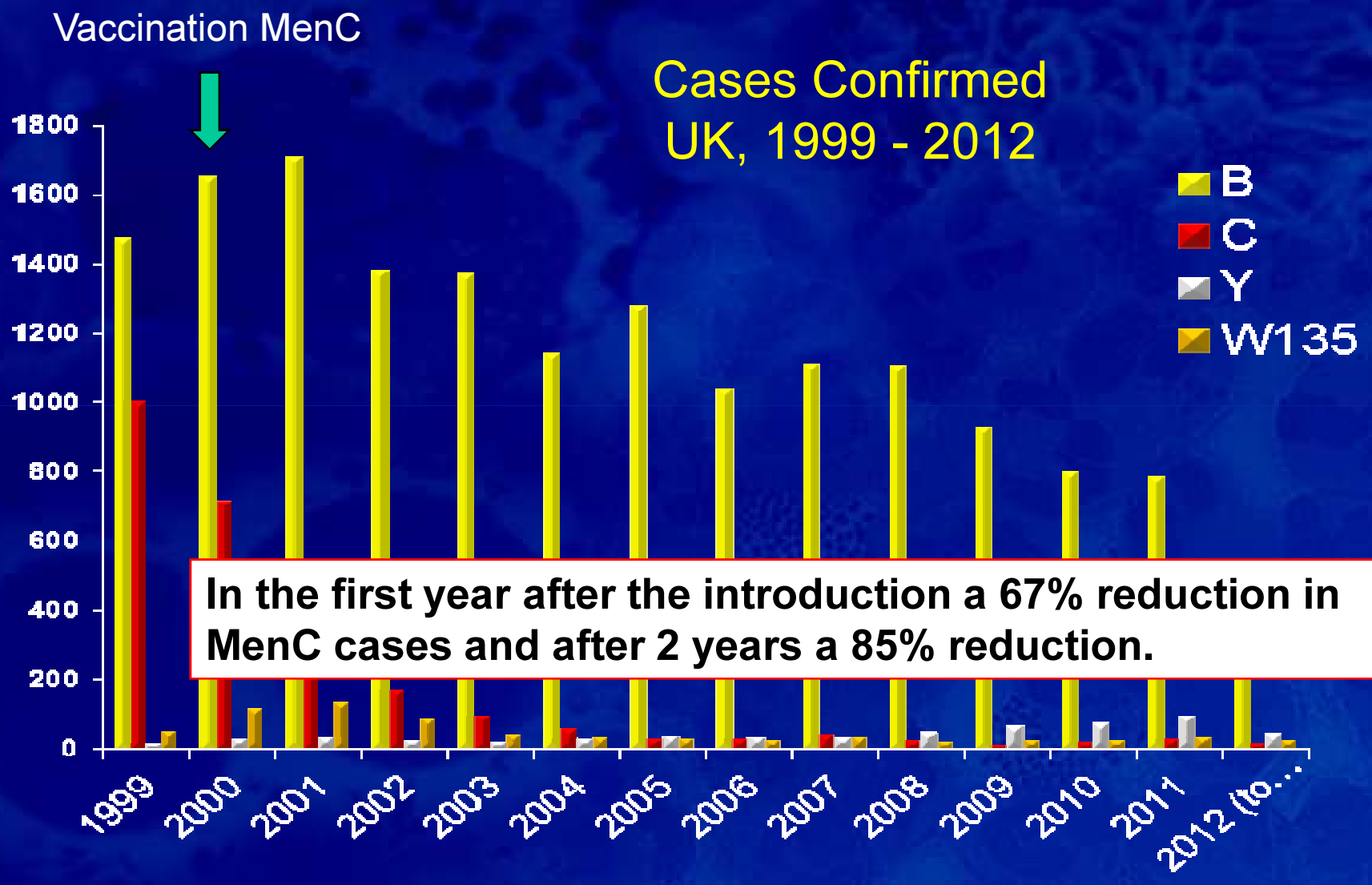
Impact of MenC Conjugate Vaccine on Disease Rates (UK)



Rapid, sustained and marked decline in the number of MenC cases, with evidence of herd immunity

Trotter C. et al. Lancet, 2004

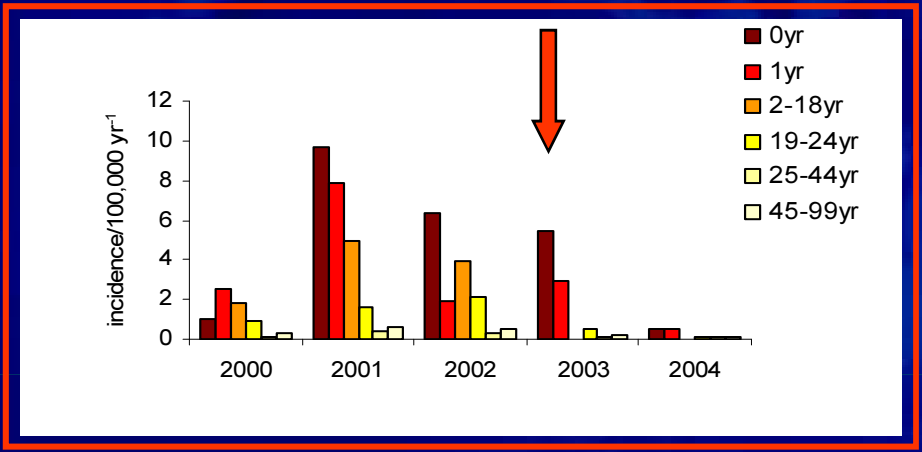
Impact of MenC vaccination – UK

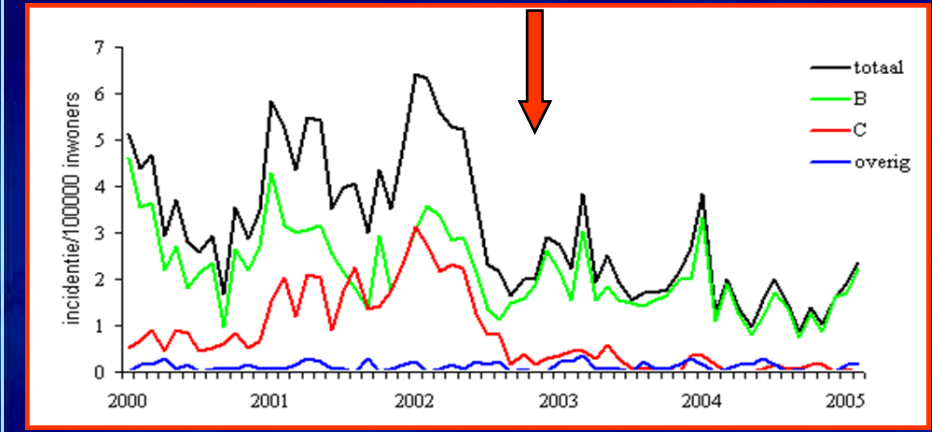


In the first year after the introduction a 67% reduction in MenC cases and after 2 years a 85% reduction.

http://www.immunisation.nhs.uk/publications/CMO120706.pdf

Impact: incidence of MenC disease by age group after the vaccination - Holland



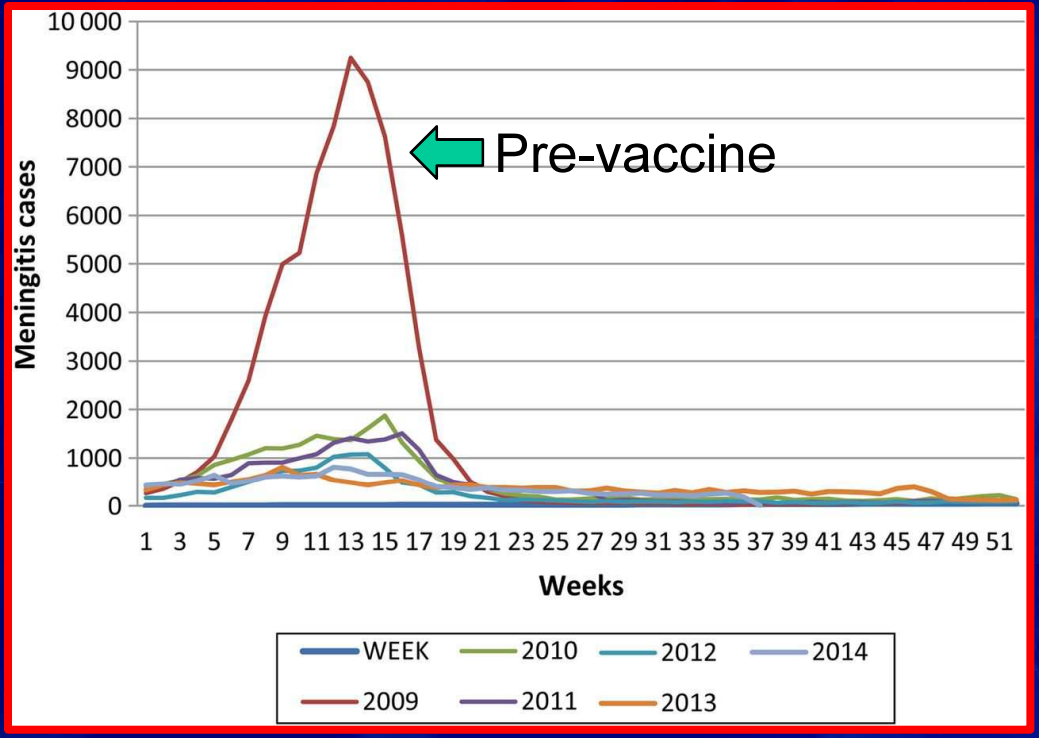


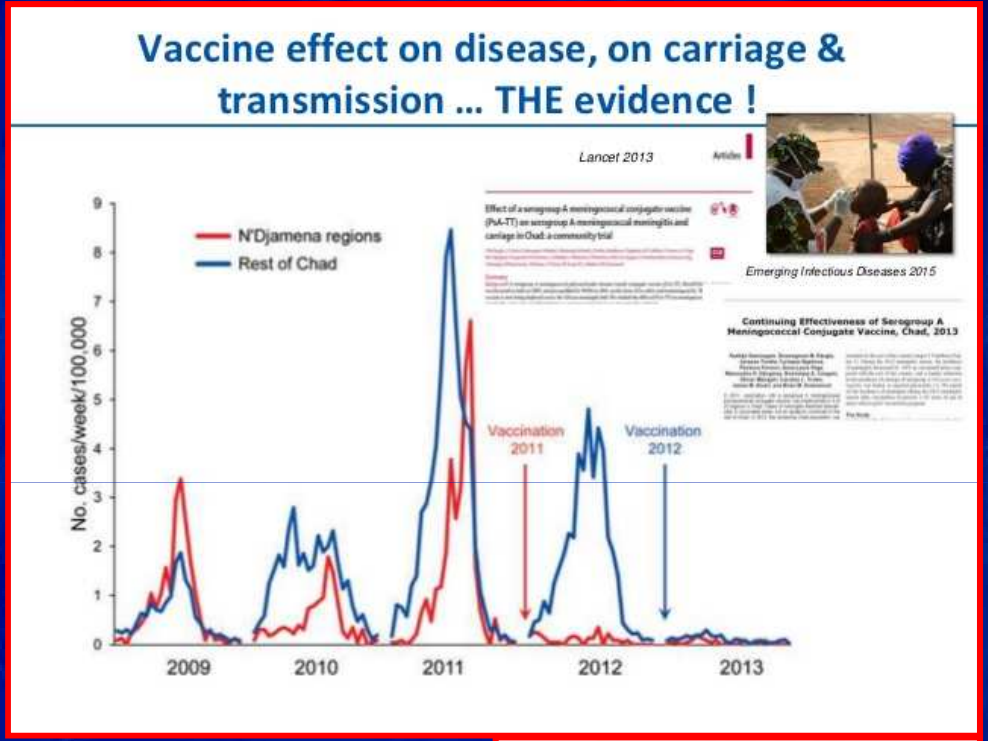
Single dose of MenC-TT vaccine at 14 months + catch-up from 1 to 18 years in 2002

Percentage reduction 2004 / 2001:	
0yr	95%
1yr	94%
2-18yr	99%
19-24yr	95%
25-44yr	66%
45-99yr	83%
overall reduction:	94%

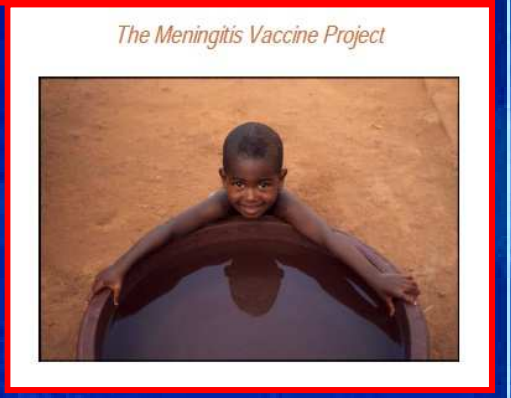
http://www.rivm.nl/isis/rbm/meningokok_RBM.html

Impact of MenA-TT vaccination in the “African belt”, 2009–2014.





- Between 2011- 2015 > 217 million (1 – 23 y) vaccinated in 15 countries from the “meningitis belt” with MenA-TT
- Immediate decrease of cases among vaccinates and unvaccinated groups, (herd protection)



Fabien V. K. Diomandé et al. Clin Infect Dis. 2015;61:S467-S472

Al revés de los países europeos, Brasil y Chile decidieron introducir vacunas conjugadas meningocóccicas sin campañas de captación o *catch up*, vacunando solamente al grupo de edad con las tasas de incidencia más elevadas.

Que se espera en tales situaciones?

1-Rápida disminución de las tasas de incidencia en ambos grupos, vacunados y no vacunados.

2- No se observa impacto.

3- Reemplazo de serogrupos

4- Impacto en grupos de edad vacunados y carencia de impacto temprano en grupos no vacunados.

5- Impacto solamente en grupos de edad no vacunados.

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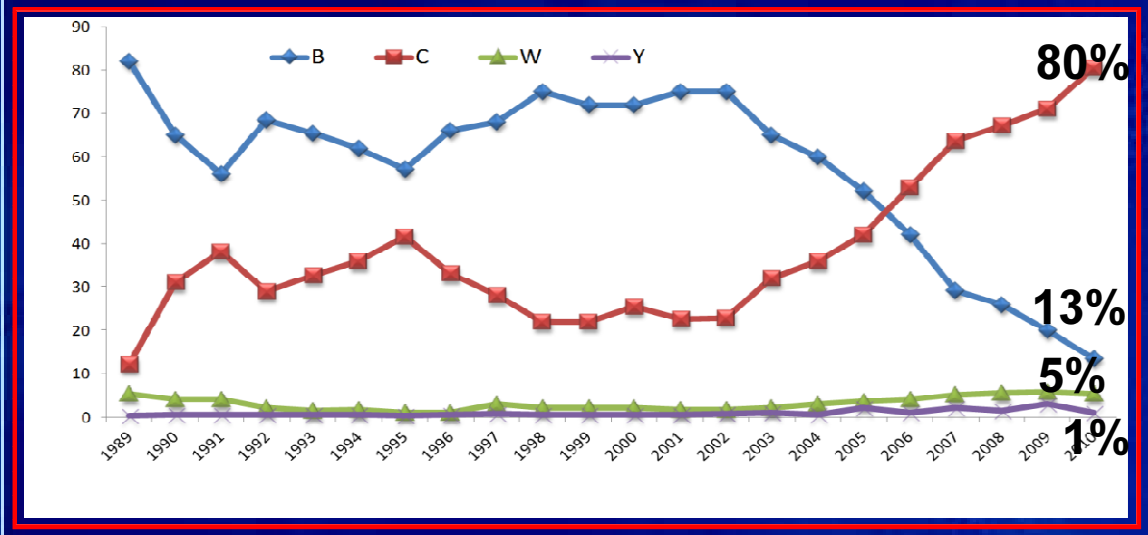
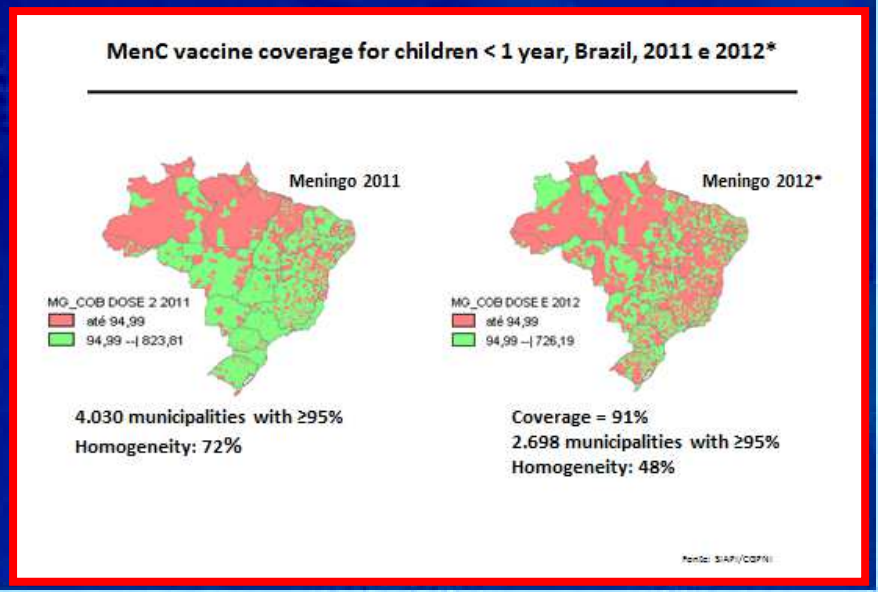
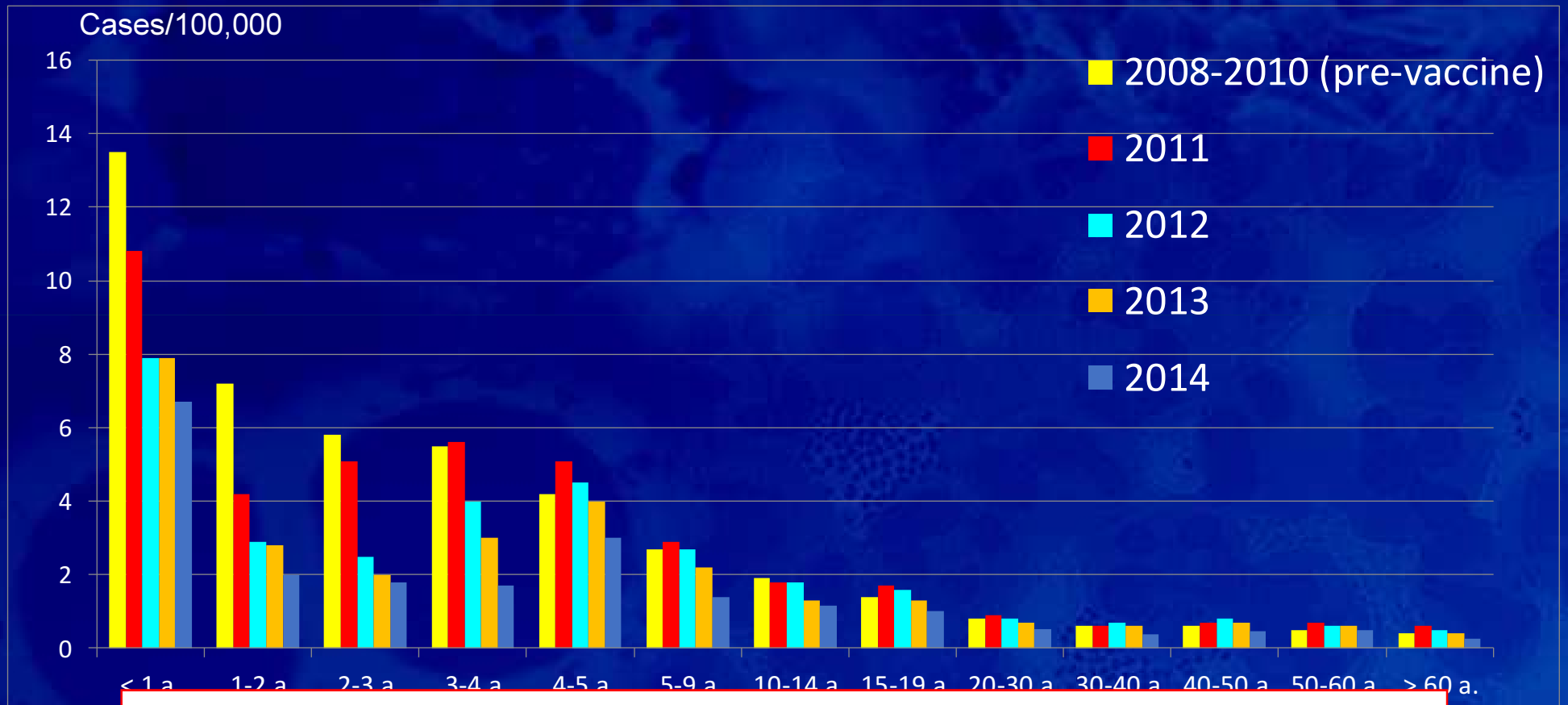
Brazil started vaccination with MenC Vaccine for all children < 2 years of age on late 2010.

- Infant immunization (3 and 5 months) with booster dose at 12 months.
- Children between 12 and 23 months: 1 dose
- No catch up campaign in older age groups





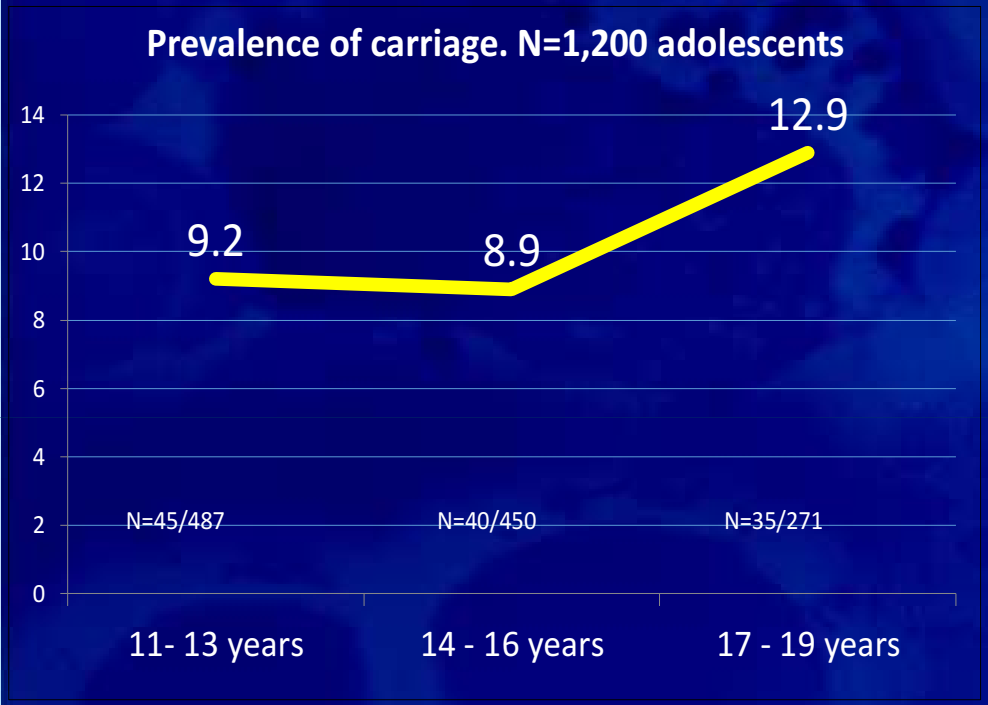
Incidence rates before and after Men C vaccination. Brazil, 2008-2014

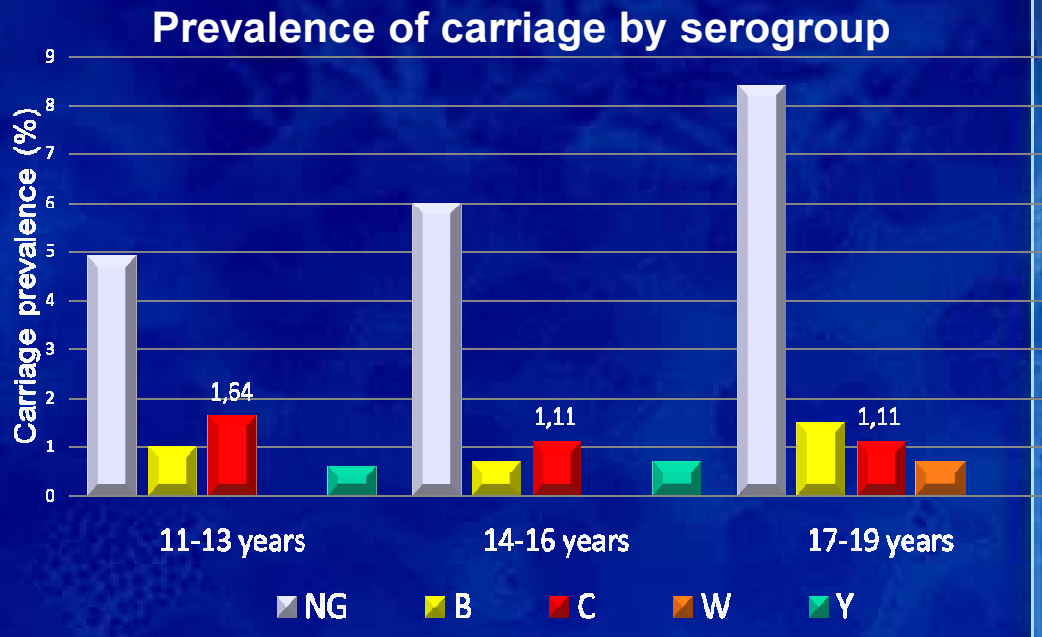


Early impact on incidence rates of meningococcal disease observed only in the age groups targeted for vaccination.

Safadi M, et al. *JPIDS*. 2014;3:91-93
SINAN, MS 2015.

Prevalence, Risk Factors and Molecular Characteristics of Meningococcal Carriage Among Brazilian Adolescents





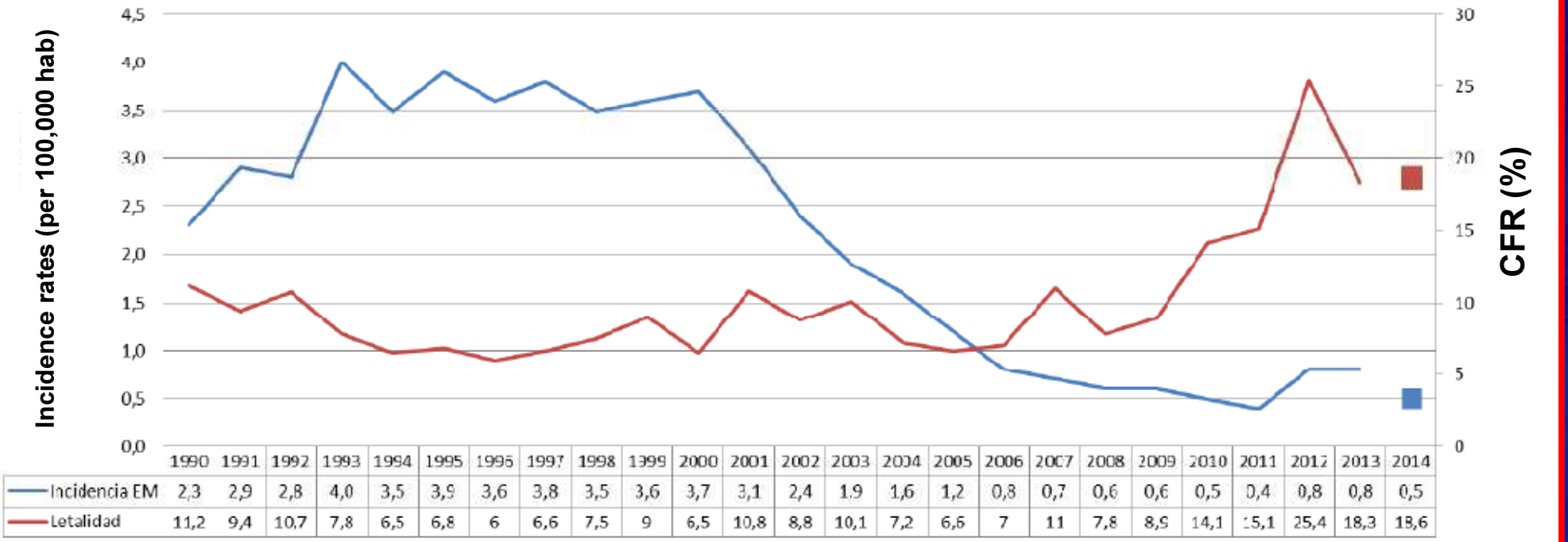
High carriage rates for serogroup C among adolescents of all age groups

Moraes JC; et al. Ped Infect Dis J, 2015

Decision for 2017 with MenC conjugate vaccine in Brazil:

- Booster doses in adolescents 9-13 years with MenC conjugate vaccine.

Incidence rates and CFR of Meningococcal Disease in Chile. 1990-2012

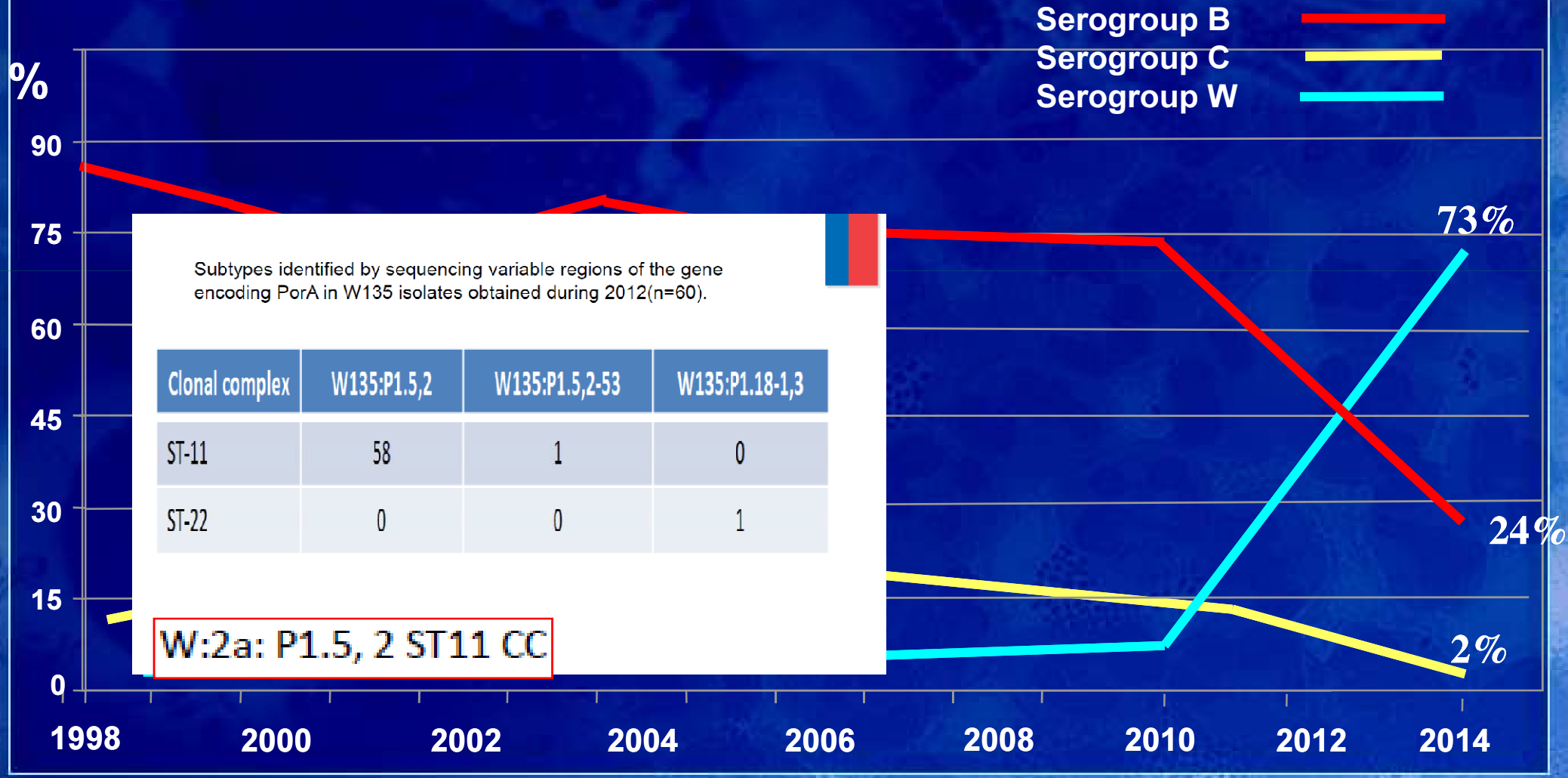


	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Incidencia EM	2,3	2,9	2,8	4,0	3,5	3,9	3,6	3,8	3,5	3,6	3,7	3,1	2,4	1,9	1,6	1,2	0,8	0,7	0,6	0,6	0,5	0,4	0,8	0,8	0,5
Letalidad	11,2	9,4	10,7	7,8	6,5	6,8	6	6,6	7,5	9	6,5	10,8	8,8	10,1	7,2	6,6	7	11	7,8	8,9	14,1	15,1	25,4	18,3	18,6

Increased incidence of MD in 2012 (from 0.4 to 0.8), associated to emergence of serogroup W (3 cases in 2010, 20 in 2011 and 60 in 2012).

http://epi.minsal.cl/epi/html/bolets/reportes/Meningitis/meningitis.pdf

Meningococcal Disease: Distribution by Serogroup. Chile, 1999 - 2014



Subtypes identified by sequencing variable regions of the gene encoding PorA in W135 isolates obtained during 2012(n=60).

Clonal complex	W135:P1.5,2	W135:P1.5,2-53	W135:P1.18-1,3
ST-11	58	1	0
ST-22	0	0	1

W:2a: P1.5, 2 ST11 CC

Fuente : Instituto de Salud Publica Lab. Referencia *Neisseria* Chile week 42, 2014.

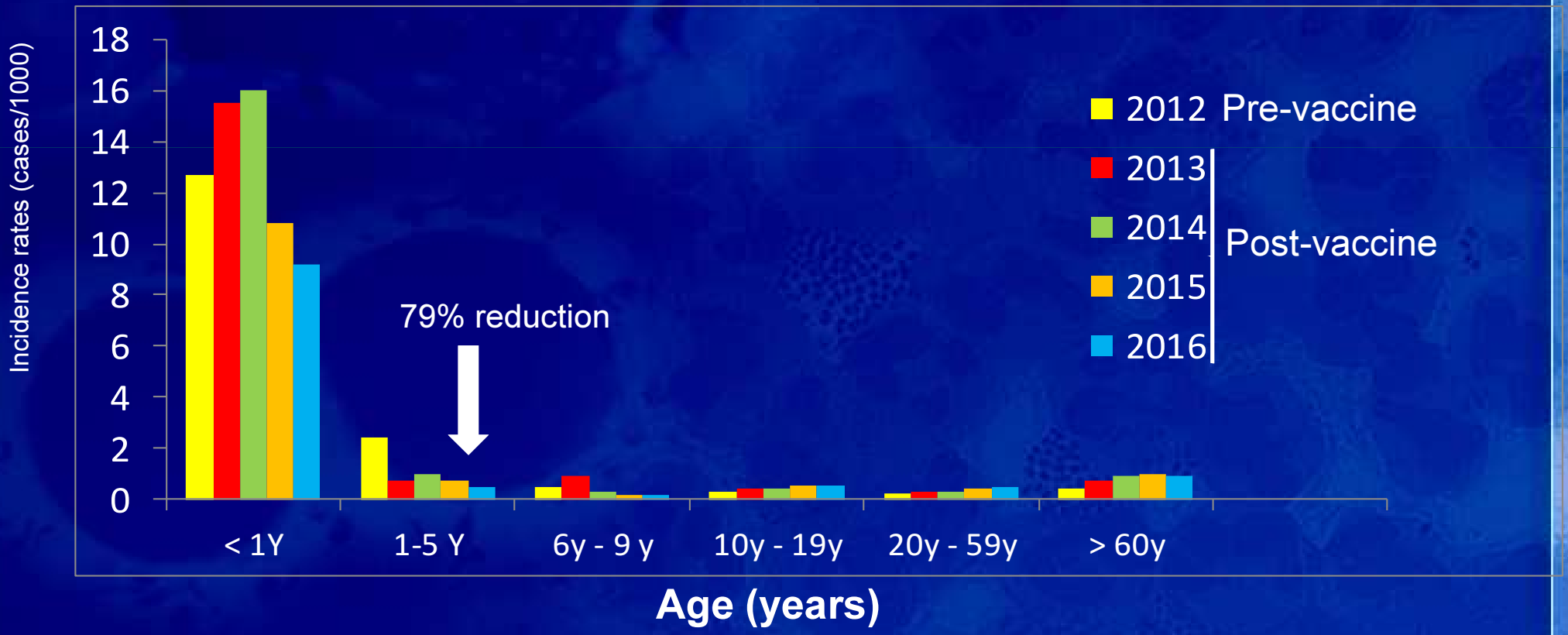
Reactive MenW Immunisation action in Chile

- An immunisation campaign started in 2012 with the tetravalent conjugate vaccine (Men ACWY), initially targeting children aged 9 months to < 5 years.
- 9 m to < 2 y: 2 doses (MenACWY-DT) and > 2 y: 1 dose (MenACWY-CRM).
- Approximately 1 million children vaccinated (Coverage >95%).
- From 2014: 1 dose (MenACWY-TT) in toddlers at 12 months.

http://epi.minsal.cl/epi/html/bolets/reportes/Meningitis/meningitis.pdf

Impact of the MenACWY immunisation campaign in Chile, 2012-2016

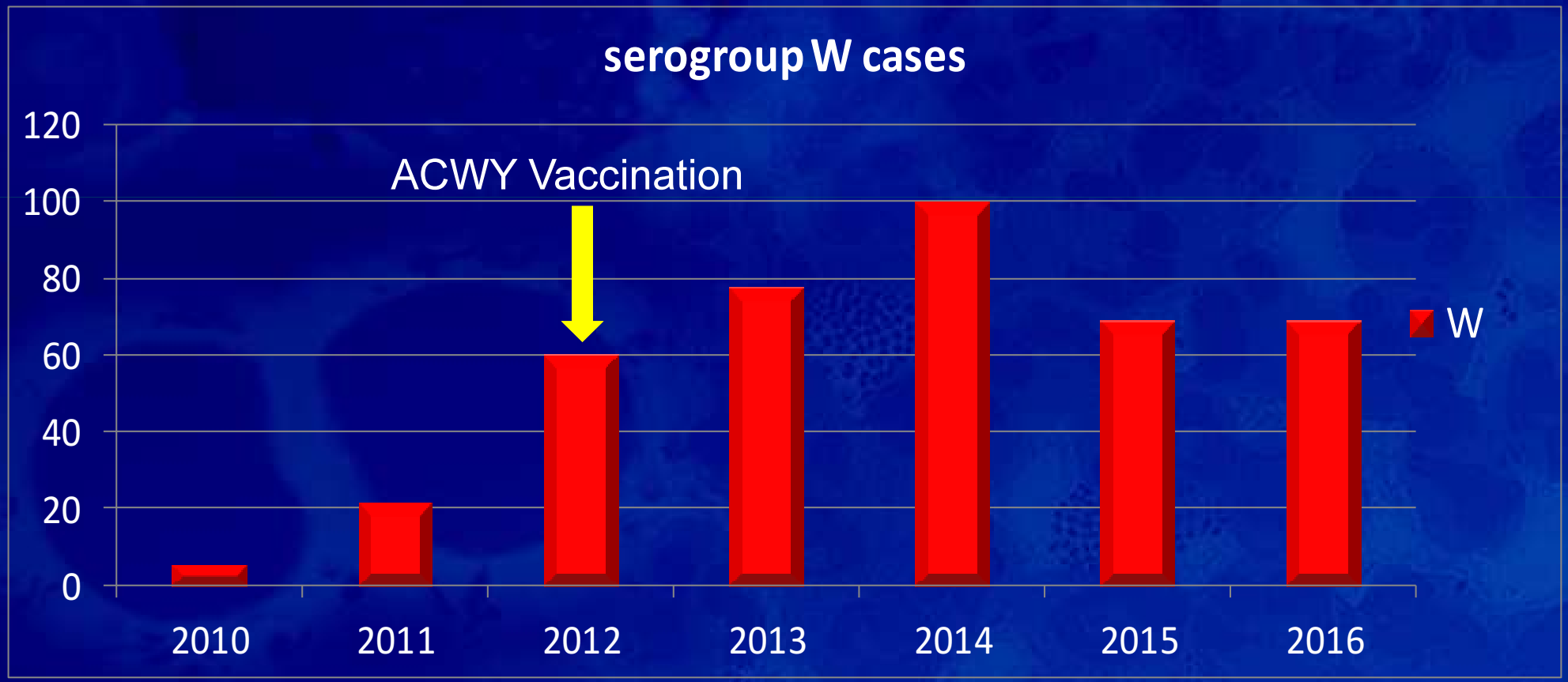
- **Reduction of 79% in the incidence rates of MD in children aged 1- 5 years**
- **No significant impact on incidence rates of other age groups**



ISP, Chile

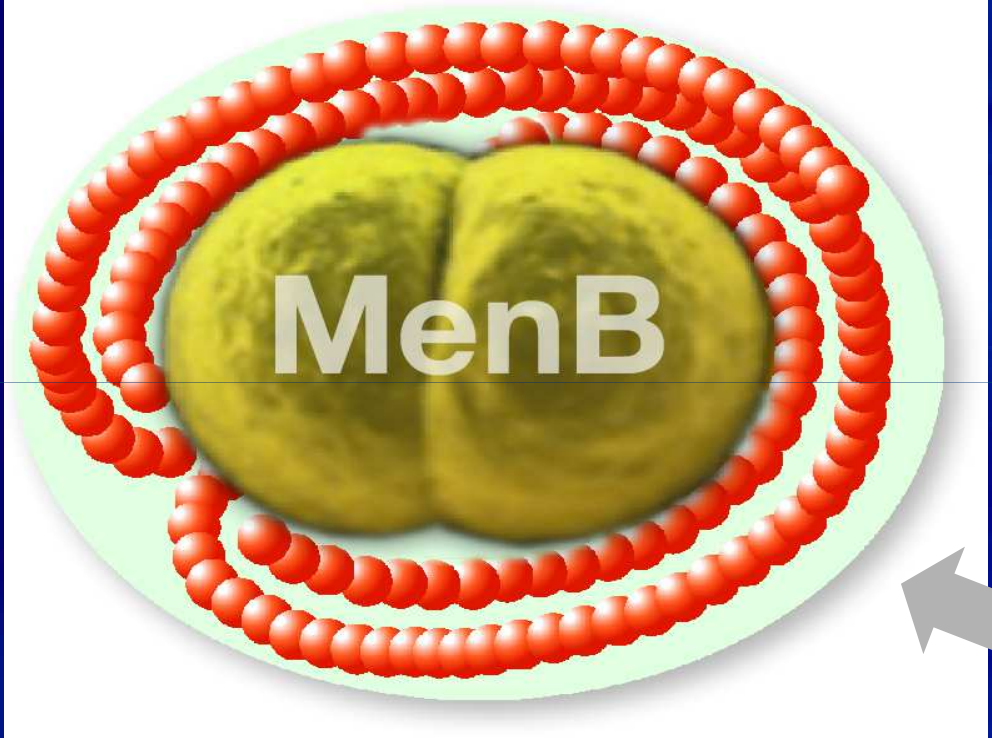
http://epi.minsal.cl/epi/html/bolets/reportes/Meningitis/meningitis.pdf. 2017

Number of cases of serogroup W cases. Chile, 2010 - 2016

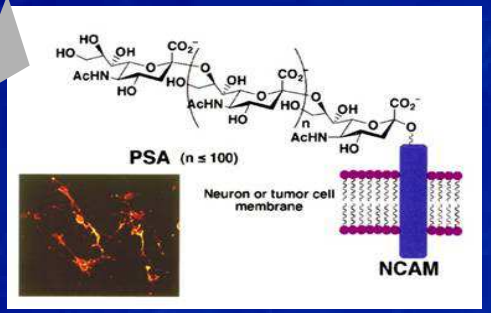


http://epi.minsal.cl/epi/html/bolets/reportes/Meningitis/meningitis.pdf. 2017

Meningococcus B capsule is a self antigen, poorly immunogenic and cannot be used for vaccination



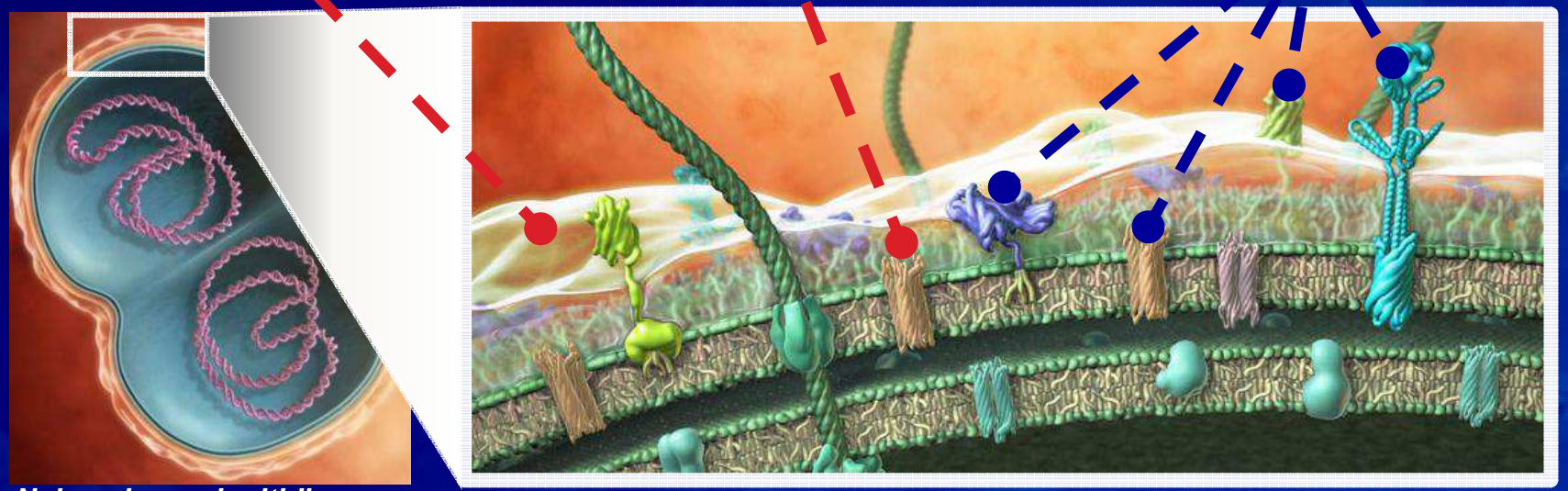
- Structurally identical polysialic acid units in fetal neural tissue
- Poorly immunogenic[1,2]
- No functional activity of vaccine-induced AB[3]



[1]Häyrinen J, et al. J Infect Dis. 1995;171:1481-1490; [2]Finne J, et al. J Immunol. 1987;138:4402-4407; [3]Bruge J, et al. Vaccine. 2004;22:1087-1096;

A Multicomponent Approach to MenB Vaccination

The polysaccharide capsule?	single subcapsular protein component	Multiple subcapsular components?
Poorly immunogenic[1]	Susceptible to antigenic variability[2,3]	Enables broad coverage across a number of strains[4]



Neisseria meningitidis

1. Häyrinen J, et al. *J Infect Dis*. 1995;171:1481-1490; 2. Sadarangani M, et al. *Lancet Infect Dis*. 2010;10:112-124;
3. Tan LK, et al. *N Engl J Med*. 2010;362:1511-1520; 4. Donnelly J, et al. *Proc Natl Acad Sci U S A*. 2010;107:19490-19495.

Cual de las siguientes opciones son características de las nuevas vacunas recombinantes contra serogrupo B?

1- No están licenciada en niños

2-Alto impacto en la prevención de la portación

3- la vacuna provee memoria inmunológica que da protección a largo plazo en vacunados

4-Vacuna segura y efectiva en el control de brotes a serogrupo B y en el uso rutinario.

5- Induce protección serogrupo específica.

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4CMenB Vaccine - GSK

MATS Concept

Are any of the 4CMenB components in the circulating strains:

(i) expressed to a sufficient degree, and

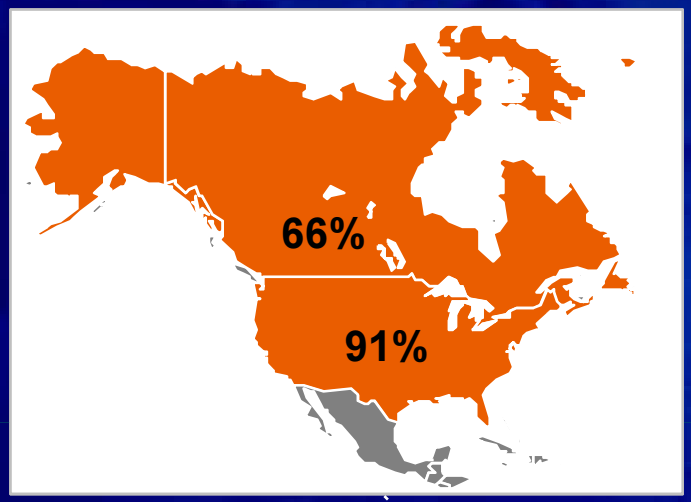
(ii) similar enough to the antigens in the vaccine such that the antibodies generated by 4CMenB will kill the bacteria?

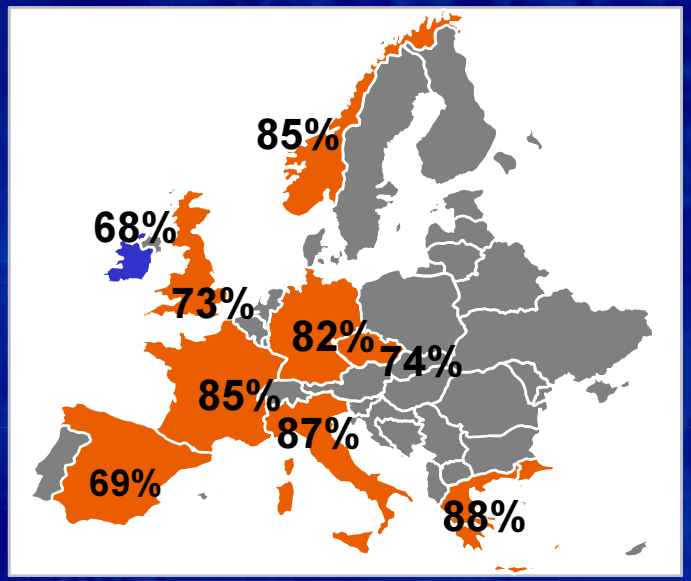
MATS can determine the minimum amount of recognizable antigen needed to result in bacterial killing, for <u>each</u> of the four components*

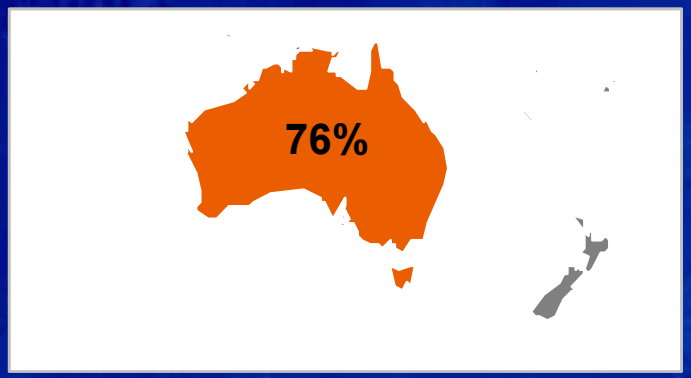
*individually

1. fHbp, NHBA and NadA assessments use ELISA → PHENOTYPIC
2. PorA assessment uses PCR sequencing → GENOTYPIC

Estimated Potential MenB Strain Coverage for specific countries based on MATS





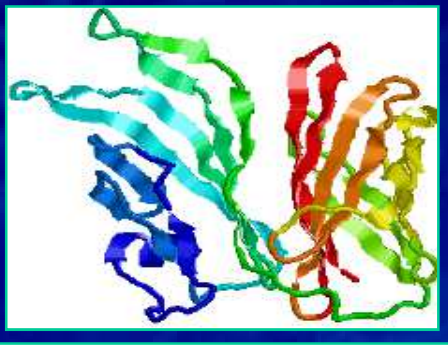


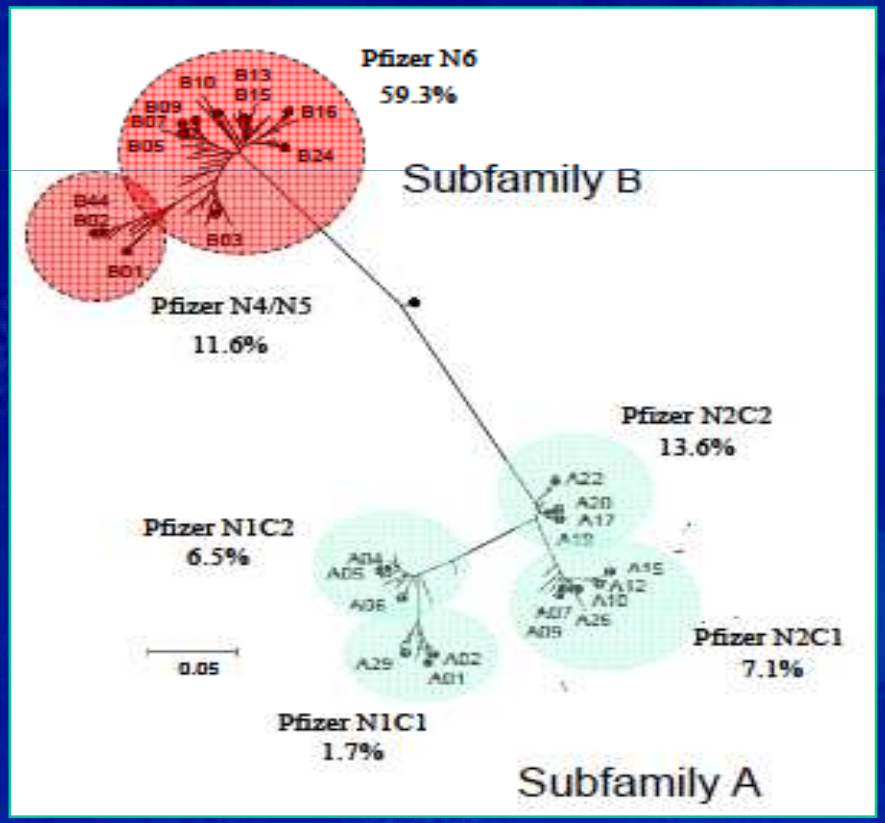
Canada (2006–2009): Bettinger JA, et al. *Vaccine*. 2013;32:124-130; **United States (2000–2008, data downweighted with Oregon outbreak strains)**: Kim E, et al. Presented at: 18th IPNC. September 9-14, 2012. Würzburg, Germany. Poster P270; **Brazil (2010)**: Lemos AP, et al. Presented at: 18th IPNC. September 9-14, 2012. Würzburg, Germany. Poster P272; **Norway, United Kingdom, Germany, France and Italy (July 2007–June 2008), Spain (2008–2010)**: Vogel U, et al. *Lancet Infect Dis*. 2013;13:416-425; **Greece (2008–2010)**: Data on file, Novartis Vaccines and Diagnostics; **Ireland (2009–2013)**: Data on file, Novartis Vaccines and Diagnostics; **Australia (2007–2011)**: Tozer SJ, et al. Poster presented at: 27th ICP; August 24-29, 2013. Melbourne, Australia.

Factor H (fH) binding protein (fHBP) vaccine - Pfizer

- **Virulence factor**

- Binds fH→ down regulates alternative complement pathway
- 3 variant groups:
- Variant 1 (family B),
- Variants 2 and 3 (family A).
- Two lipidated LP2086 variants in Pfizer vaccine were selected (one from each subfamily)
- 2 doses: 0 – 6 months or 3 doses: 0, 1-2 and 6 months (10 – 25 years of age)





First Use of a Serogroup B Meningococcal Vaccine in the US in Response to a University Outbreak

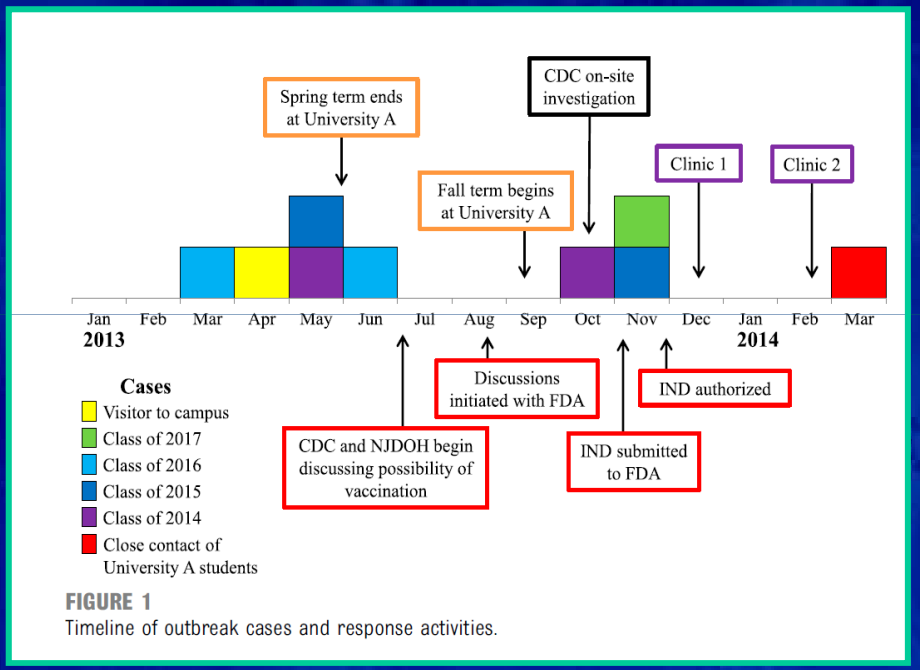


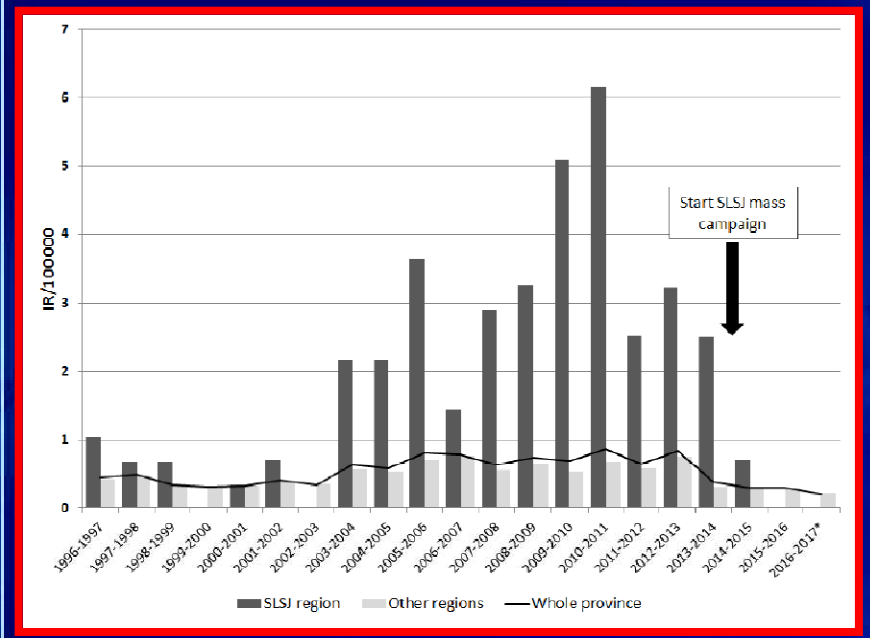
FIGURE 1
Timeline of outbreak cases and response activities.

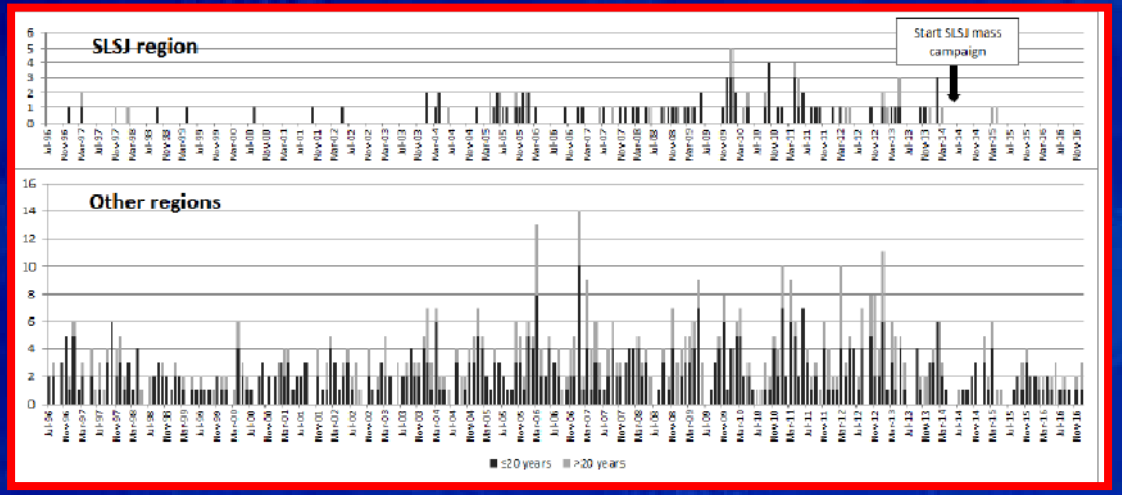
CONCLUSIONS: No serogroup B meningococcal disease cases occurred in persons who received 1 or more doses of 4CMenB vaccine, suggesting 4CMenB may have protected vaccinated individuals from disease. However, the ninth case demonstrates that carriage of serogroup B *Neisseria meningitidis* among vaccinated persons was not eliminated.

PEDIATRICS Volume 135, number 5, May 2015

Outbreak of serogroup B disease in Saguenay-Lac-Saint-Jean, Canada.

- Serogroup B (ST-269) clone emerged in Quebec, Canada.
- Incidence rate of 3.4/100,000 from 2006 to 2013.
- After vaccination of population (2 m-20 years) with 4CMenB decreases were, respectively 92% and 67%, in age-group ≤20 years and in those > 20 years





De Wals et al. CID, 2017

Serogroup B Meningococcal Disease Vaccine Recommendations at a University, New Jersey, USA, 2016

- In 2016 … sed with se…
- Sera of … analise…

Table. Molecular profile and flow cytometry analysis of the university outbreak strain with reference to MenB vaccine antigens, New Jersey, 2016*

Antigen	Outbreak strain	MenB-4C vaccine (Bexsero)	MenB-FHbp vaccine (Trumenba)	Interpretation
FHbp	A22†/2.19‡	B24†/1.1‡	A05†, B01†	The 2 FHbp subfamilies (A and B) are not expected to be cross-reactive. The outbreak strain has a subfamily A FHbp. MenB-FHbp contains FHbp from subfamilies A and B. Although the subfamily A FHbp contained in MenB-FHbp (A05) is not the same peptide allele as that in the outbreak strain (A22), some level of cross-reactivity is expected based on prior testing by the manufacturer (*2*). However, based on flow cytometry, the strain had relatively low expression of FHbp, which would be expected to decrease susceptibility to anti-FHbp bactericidal activity (*4*). MenB-4C contains a subfamily B FHbp, which is not expected to provide protection against the outbreak strain FHbp.
PorA	P1.5–1,10–1	P1.7-2.4	Not included	The PorA present in MenB-4C and in the outbreak strain are 2 different PorA variable region sequence types and are not expected to be cross-reactive; therefore, no protection based on PorA is expected for either vaccine.
NHba	p0020	p0022	Not included	The NHba present in MenB-4C and in the outbreak strain are 2 different peptide alleles. The extent of cross-reactivity is not known. By flow cytometry, low binding to the outbreak strain was observed by using
				on NadA is expected for either vaccine.

Immune responses were observed with both vaccines. However, due to the rapid fall of hSBA antibodies (4 months after the second dose) the option was to use a 3-dose series of Trumenba* to vaccinate 35,000 students.

Emerg Infect Dis. 2017;23(5):867-869

Impact of 4CMenB on carriage.

4CMenB secondary

Carriage prevalence and calculated efficacy for carriage of combined capsular groups BCWY or all *N. meningitidis* strains across cumulative later timepoints (Visits 4–6)

		Vaccine Groups		Efficacy % (95% CI)
		4CMenB	Control	
B, C, W, Y Capsular group	Number	449	539	**26.6%** (10.5 – 39.9)
	%	**18.0%**	**20.9%**	
	N	2489	2576	
Any *N. meningitidis*	Number	797	885	**18.2%** (3.4 – 30.8)
	%	**32.0%**	**34.4%**	
	N	2489	2576	

4CMenB reduces nasopharyngeal carriage of *N. meningitidis* capsular group BCWY strains

Non-significant trends for virulent B strains (12.6%; p=0.350) and all ST B strains (15.6%; p=0.225)

Analyses adjusted for baseline carriage, treatment group, centre and significant risk factors as identified within the multivariate model.

Read R et al. ESPID 2013

Meningococcal Carriage Evaluation in Response to a Serogroup B Meningococcal Disease Outbreak and Mass Vaccination Campaign at a College—Rhode Island, 2015–2016

- Four cross-sectional surveys were conducted: in conjunction with the 3-dose series MenB-FHbp vaccination campaigns and the fourth round examined MenB-FHbp impact 1 year post

Conclusions: Carriage prevalence on campus remained stable, suggesting MenB-FHbp does not rapidly reduce meningococcal carriage or prevent serogroup B carriage acquisition.
This reinforces the need for high vaccination coverage to protect vaccinated individuals and chemoprophylaxis for close contacts during outbreaks.

Meningococcal serogroup				
By real-time polymerase chain reaction[a]				
A	0 (0)	0 (0)	0 (0)	0 (0)
B	31 (4)	36 (4)	26 (4)	22 (4)
C	8 (1)	3 (0.3)	0 (0)	0 (0)
W	0 (0)	0 (0)	1 (0.2)	1 (0.2)
X	1 (0.1)	2 (0.2)	0 (0)	5 (1)
Y	3 (0.4)	4 (0.5)	1 (0.2)	2 (0.3)
Nongroupable	132 (18)	166 (19)	95 (15)	100 (16)

CID 2017:64 (15 April)

UK Immunization Recommendations for Meningococcal Vaccines

AGE	Immunisation (Vaccine Given)
2 months	• **MenB**
4 months	• **MenB**
Between 12 - 13 months	• Hib/MenC (combined as one injection); plus: • **MenB**
13-18 years	• **Men ACWY - given to 17-18 year olds and first time students up to 25 years.**

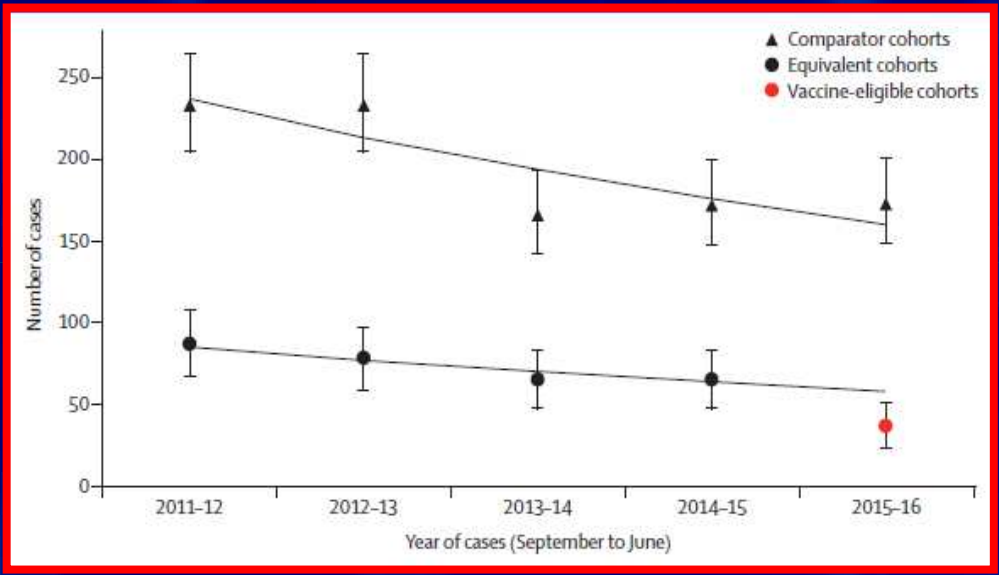
MenACWY – recommended for travelers to Mecca for religious festivals of *Hajj* or *Umrah*

http://www.nhs.uk/conditions/vaccinations/pages/vaccination-schedule-age-checklist.aspx

Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study

Sydel R Parikh, Nick J Andrews, Kazim Beebeejaun, Helen Campbell, Sonia Ribeiro, Charlotte Ward, Joanne M White, Ray Borrow, Mary E Ramsay, Shamez N Ladhani

UK introduced the MenB vaccination in September 2015 for infants at two and four months of age, with a booster dose at 12-13 months (high coverage)



Impact:

Comparing with the pre-vaccine period, a 50% reduction in MenB incidence rates was observed in the cohorts eligible for vaccination (p=0·0001).

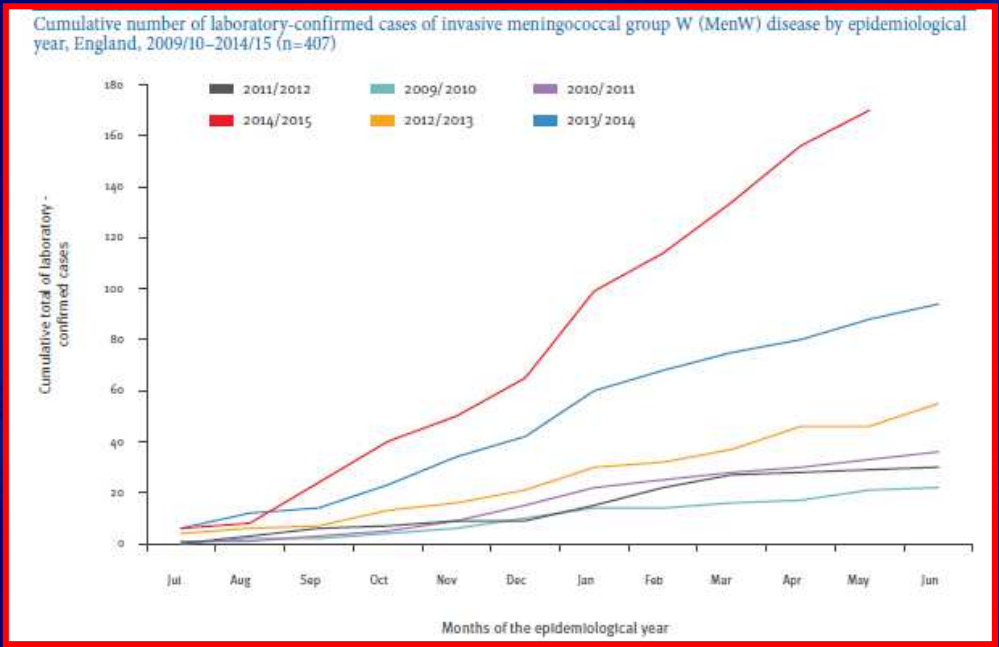
Effectiveness:

- One dose of the vaccine: 22% (95% CI –105 to 67,1).
- Two doses of the vaccine: 82,9% (95% CI 24,1–95,2).
- At least one dose of the vaccine: 64% (95% CI 8,9–84).

Lancet, online 27 October 2016

Emergence of serogroup W in UK

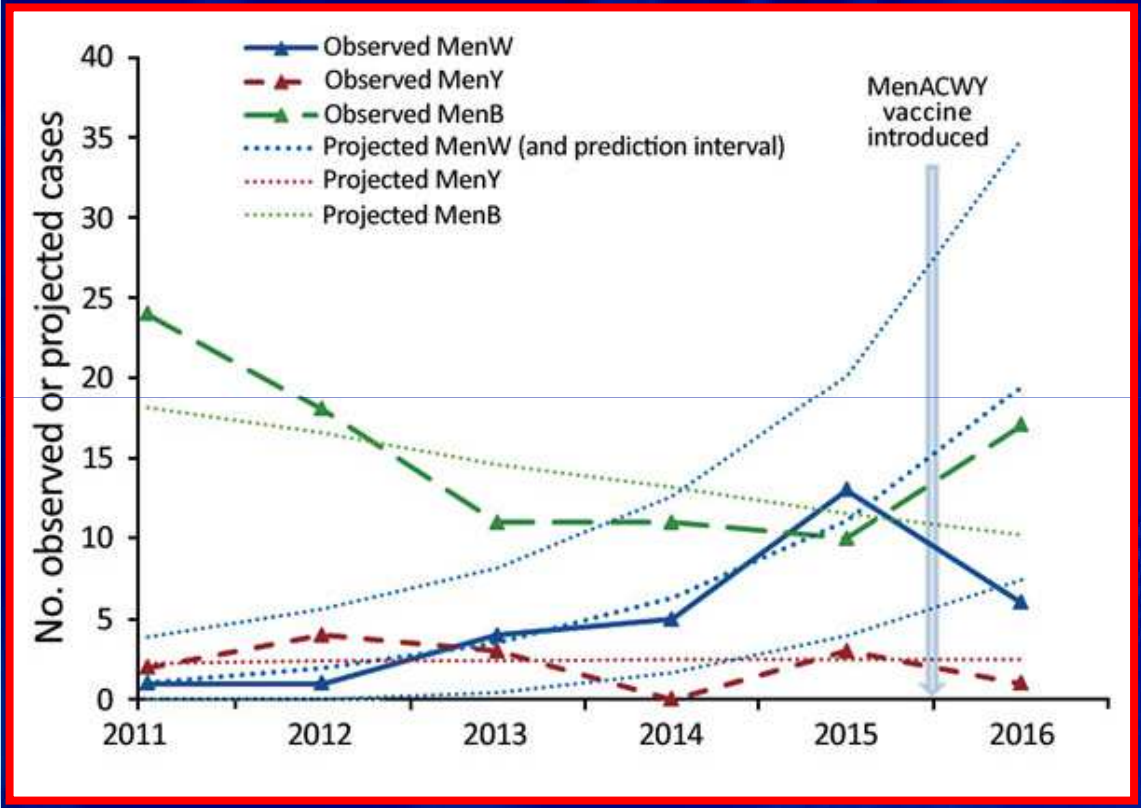
- In the light of the rapidly increasing W (cc11) disease from 2009/10 to 2014/15, ACWY conjugate vaccine was introduced in late 2015 for 13-18 years teenagers and university freshers and is intended to induce herd protection.



- A quarter of cases occurred in children aged <5 years, and half the cases in adults aged ≥45 years.
- 49% of the cases presenting with septicemia[1]
- CFR of 33% in a subgroup of adolescentes 15-19 years, with higher CFR among patients with GI symptoms[2]

Campbell H et al, Euro Surveill. 2015; Campbell H et al, Euro Surveill. 2016

Observed and projected cases of W, Y, and B MD in England among persons who left school



- Coverage of 36,6% among persons who left school.
- During the first 12 months of the MenACWY vaccination program for teenagers, a 69% decrease (18%–88%) was observed.

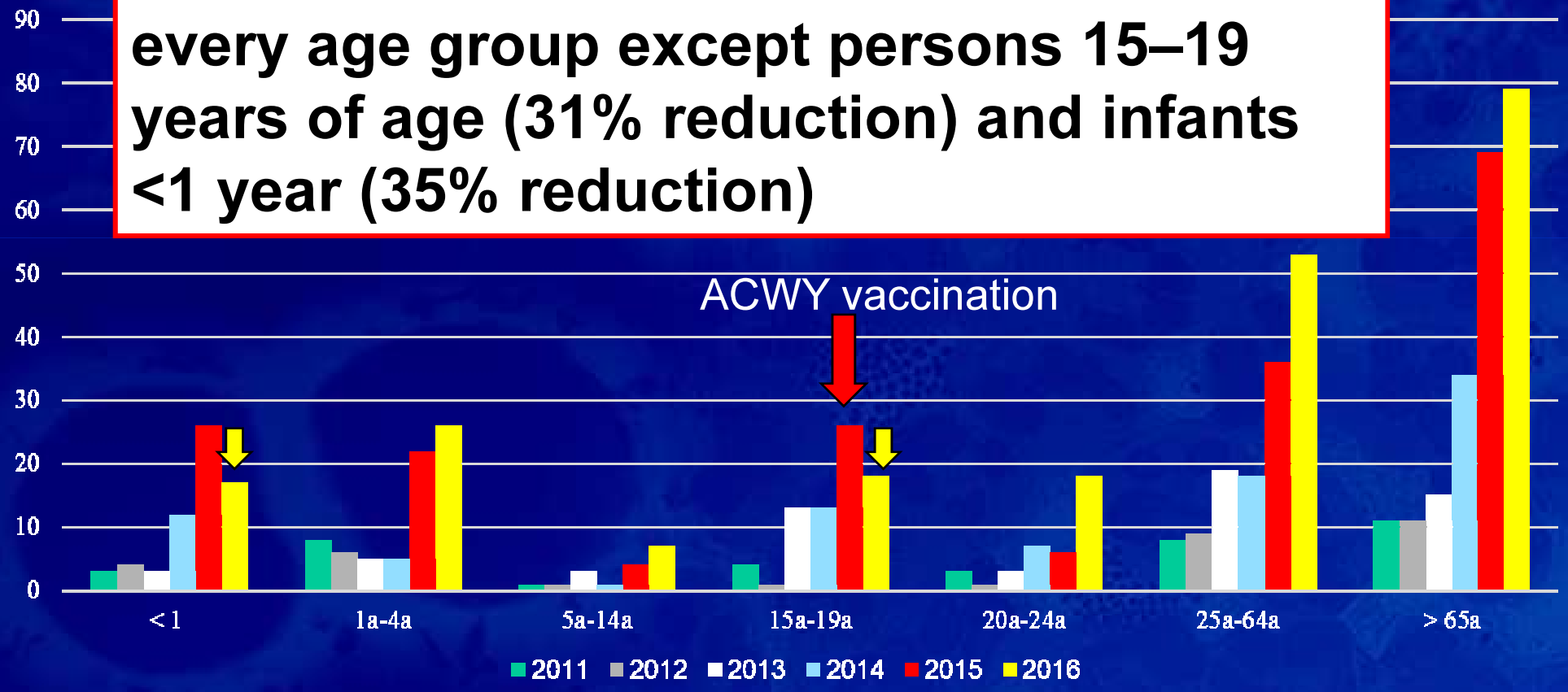
No cases in vaccinated adolescents.

Early estimated vaccine effectiveness was 100% (−47% to 100%)

Campbell H et al. Emerg Infect Dis. 2017 Jul

Age distribution of group W cases, by academic year, England, 2011 – 2016.

Cases and incidence rates increased in every age group except persons 15–19 years of age (31% reduction) and infants <1 year (35% reduction)



Campbell H et al. Emerg Infect Dis. 2017 Jul

Un año después de la implementación del nuevo programa de vacunación del Reino Unido (vacuna Men B en niños y vacuna ACWY conjugada en adolescentes) se observo una significativa reducción de casos de meningococo W en niños y adolescentes.

Cual fue el probable mecanismo que logró la reducción de casos en niños?

1- Flutuación natural de casos

2- El efecto rebaño de la aplicación de la vacuna tetravalente conjugada ACYW en adolescentes.

3- La protección cruzada inducida por la vacuna de Meningococo B.

4- La introducción de la vacuna influenza en niños pequeños.

5- Vigilancia epidemiológica inadecuada.

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Effectiveness of Meningococcal B Vaccine against Endemic Hypervirulent *Neisseria meningitidis* W Strain, England

Table. Bactericidal antibody titers in pooled serum samples from infants vaccinated with Bexsero and adolescents immunized with Menveo against 6 invasive clinical *Neisseria meningitidis* serogroup W isolates in England and Wales, UK, during 2011–2012*

	Adolescents receiving Menveo			Infants receiving Bexsero			
	Positive control†		Negative				
Isolate	Before	After	control‡	Pool 1§	Pool 2¶	Pool 3#	Pool 4**
M11–240417	<16	256	<2	64	128	>128	>128
M11–240427	<16	128	<2	32	32	64	64
M11–240802	<16	512	<2	32	>64	>64	>64
M12–240016	<16	256	<2	32	32	64	128
M11–240798	<16	512	<2	>64	>64	>64	>64
M12–240754	<16	256	<2	64	64	>64	>64

- Samples of infants vaccinated with Bexsero presented hSBA > 1/32 against W cc11 meningococcal strains.

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 22, No. 2, February 2016

Considerations for the future with meningococcal vaccines:

- Booster doses in adolescents with conjugate vaccines.
- Use of the protein-based Men B vaccines