VACCINE UPDATE

New Vaccines

New Knowledge on Old Vaccines

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PRESENTATION OVERVIEW:
A selected look at The New and the Old

- **Pneumococcal conjugate**
- **Acellular pertussis – Is switching to aP vaccine a mistake?**
- **Meningococcal vaccines**
- **Influenza vaccines**

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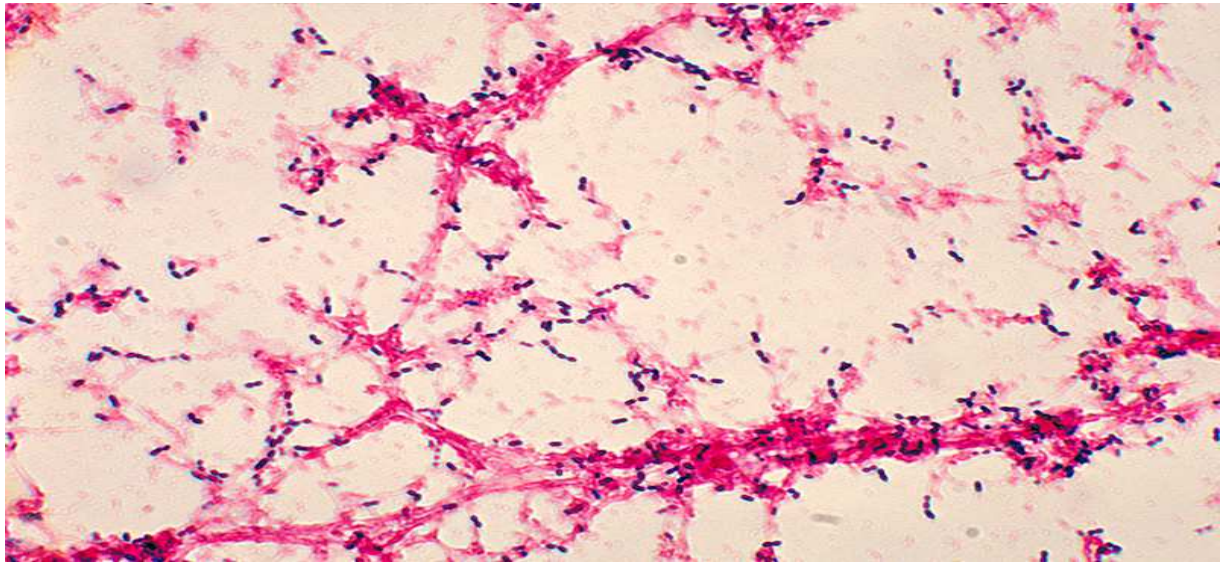
Pneumococcal Conjugate Vaccines



Pneumococci are common

Pneumococcal Carriage Rates

- Lowest in adults not in contact with children = 5%
- Average in children = 25-50%, highest in youngest
- In day care, >90% colonized

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Pneumococcal Disease Prior to PCV
Age Specific Incidence Invasive Disease Prior to PCV

AGE (mo)	Incidence (cases/100,000 py)
0-5	103
6-11	177
12-17	241
18-23	139
24-35	70
36-48	25

Overall, 70% higher than Hib risk prior immunization
Overall, 1:125 children under age four years old

[1] Black, S., Shinefield, H., Morozumi, P., Lavetter, A., et al. ICAAC Abstracts 1994

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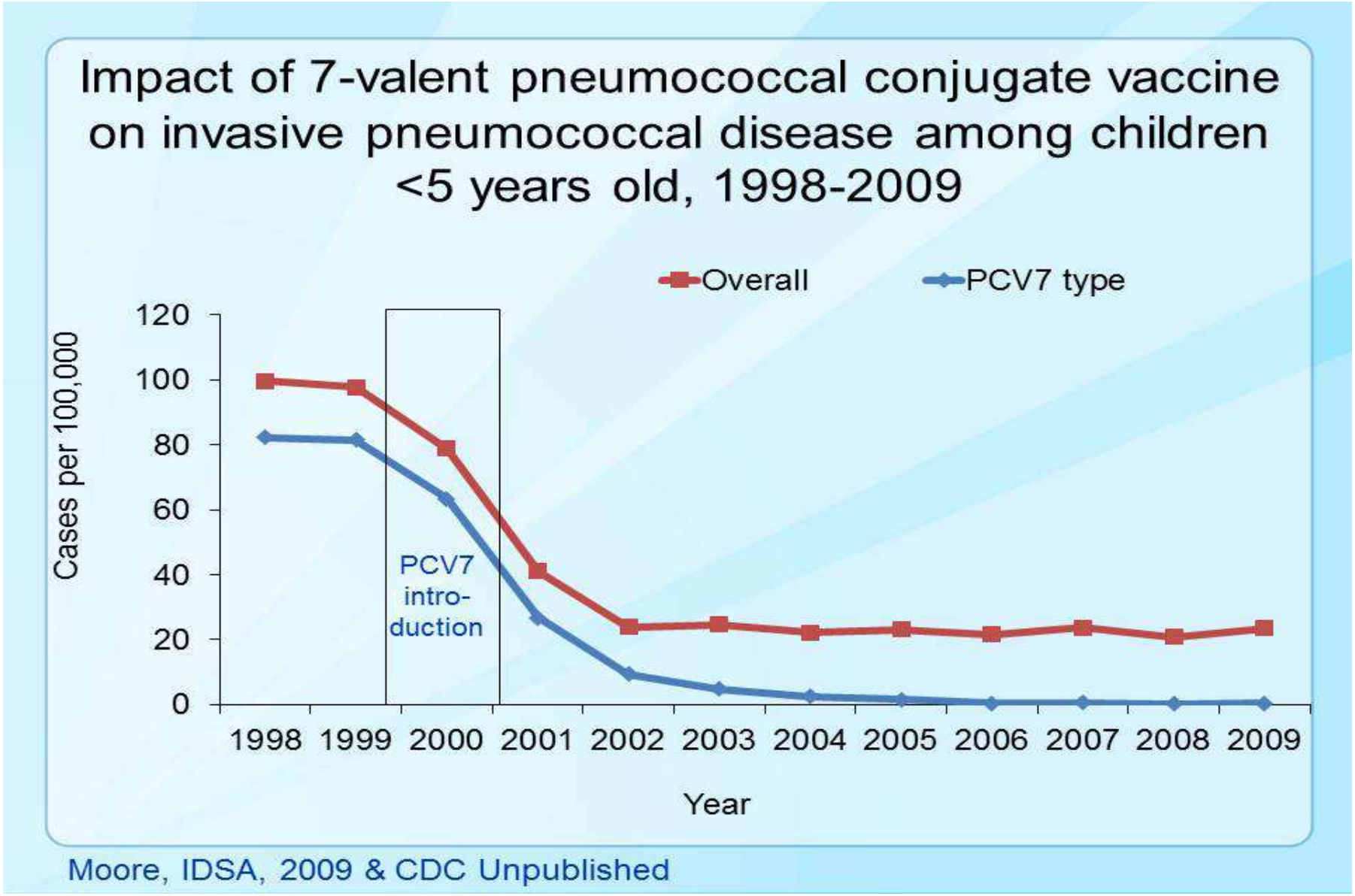
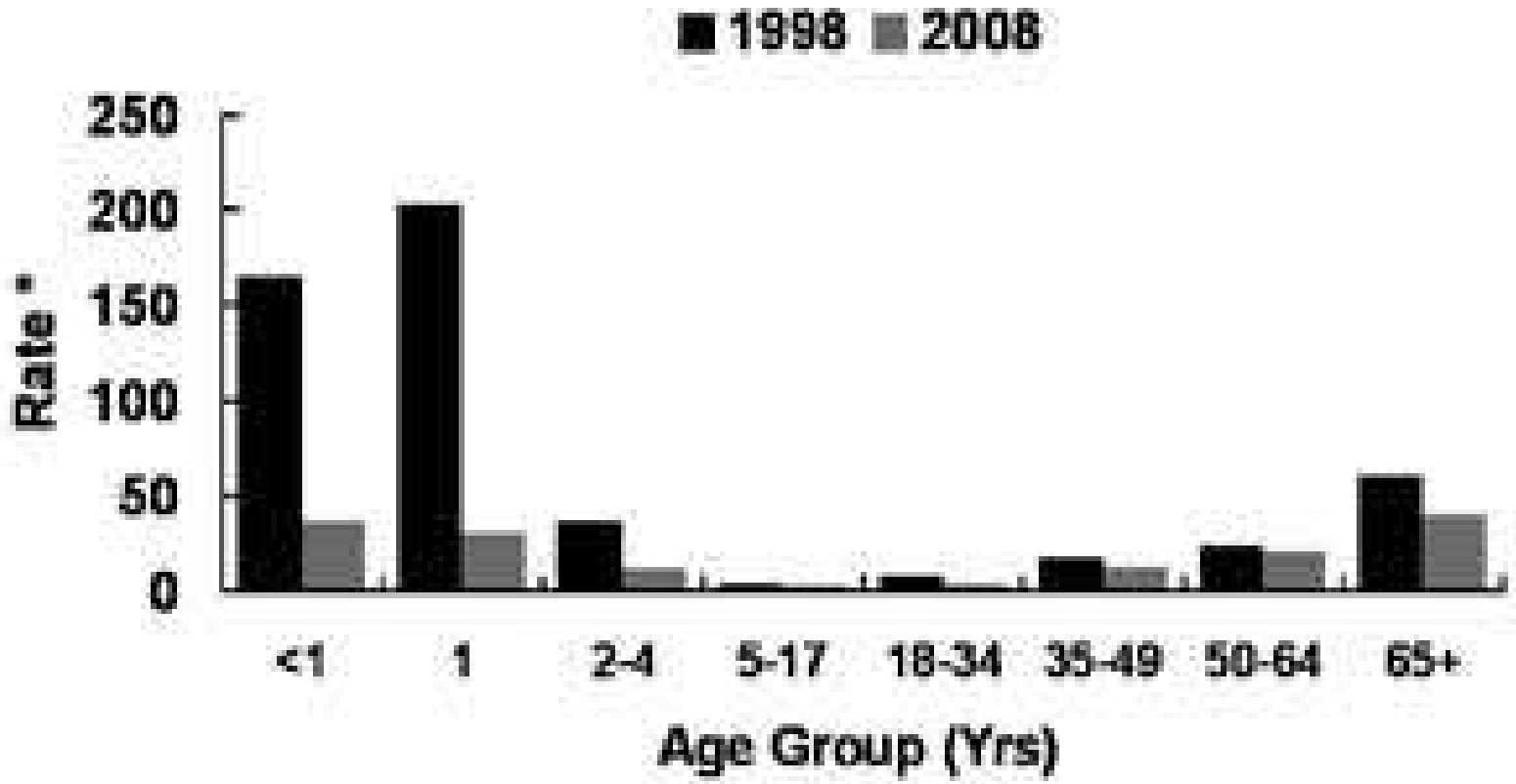
Impact of PCV7 Vaccine Use in Children in the US



Impact of PCV7 Vaccine Use in Children on Disease in all age groups



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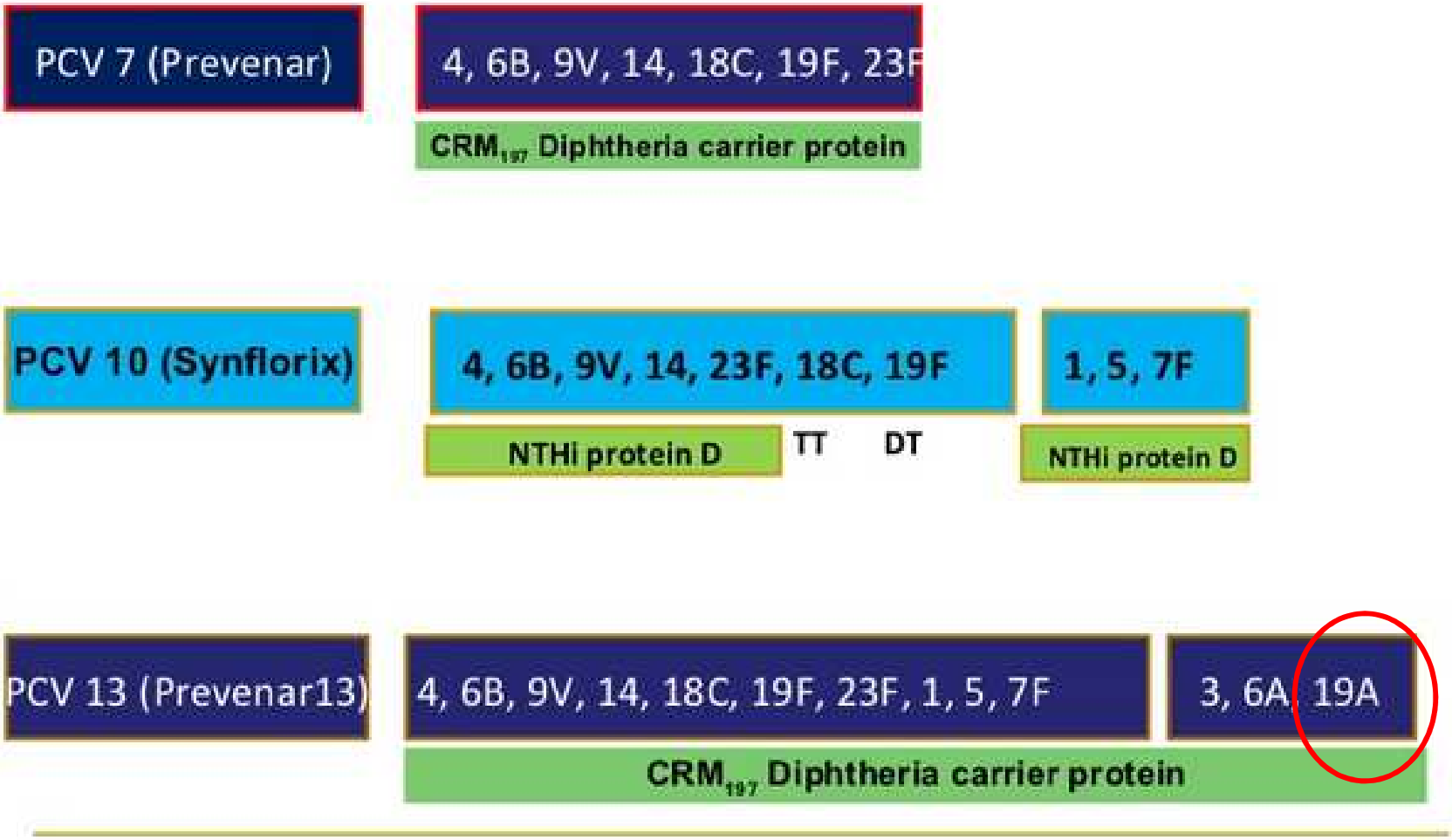
Currently licensed PCV vaccines



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The COMPAS Trial

- Large phase III trial in Argentina, Colombia, and Panama assessing protection against pneumonia, otitis media, invasive disease.
- Controversy during the trial in Argentina because of deaths in participants, but results show benefit:

Deaths in PHiD-CV N=11,798		Deaths in Control N=11,799		Vaccine efficacy
n	%	n	%	% (95% CI)
19	0.16	26	0.22	27.0 (-31.8; 59.6)

- Protection against consolidated pneumonia was 23% (95% CI=9-36) consistent with other vaccines.
- Invasive disease efficacy against vaccine serotypes was 100% (95% CI=83-100), 67% (CI=11-86) for all serotypes

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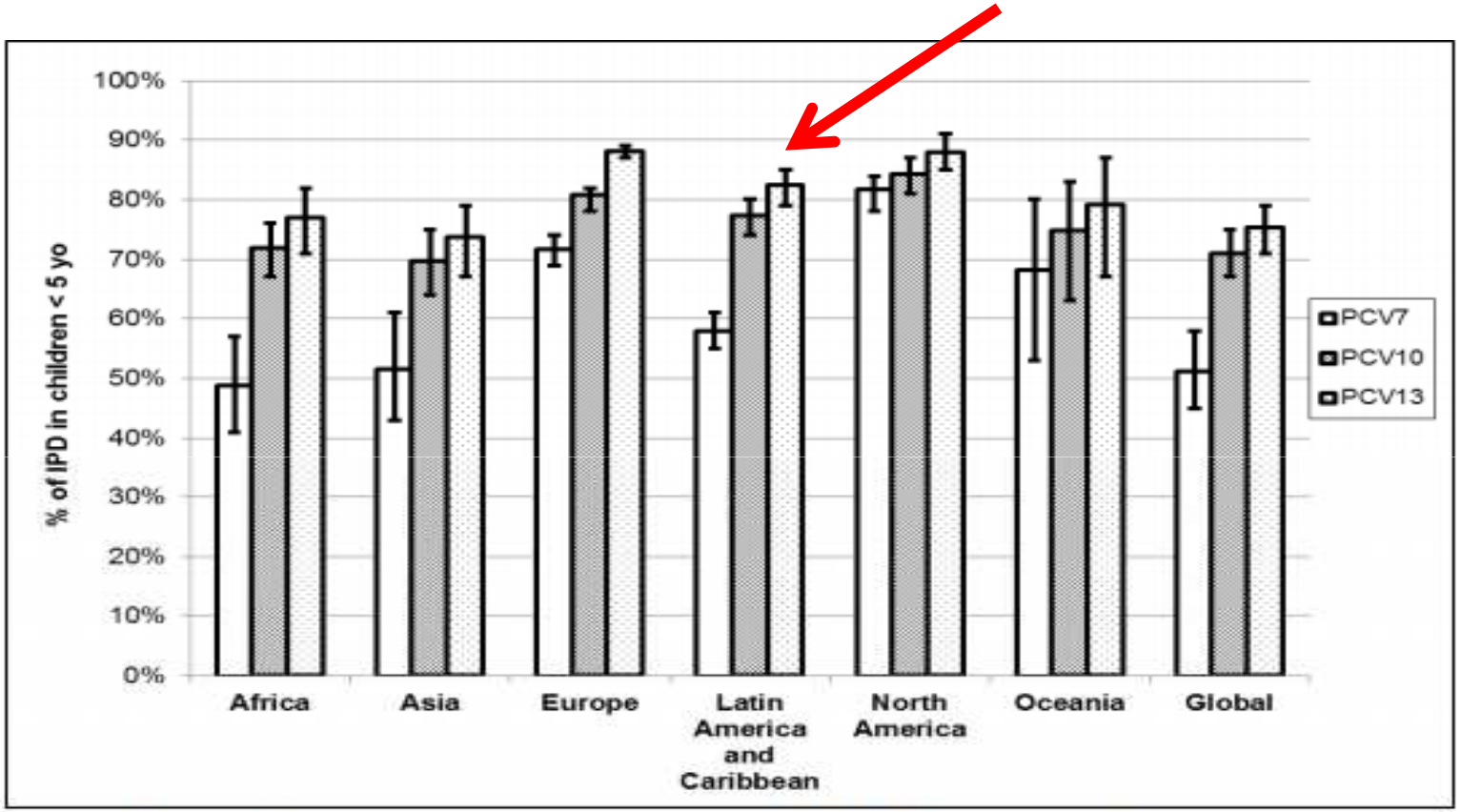
As presented at ESPID May 2013

Global Serotype coverage of available PCV vaccines



Source: Systematic Evaluation of Serotypes Causing Invasive Pneumococcal Disease among Children Under Five: The Pneumococcal Global Serotype Project

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What about dosing schedules?

- Possible dosing
  - 3+1 – original schedule used in US
  - 2+1 – used by many countries in Europe, also recommended by WHO for EPI
  - 3+0 – Recommended by WHO for EPI
- Immune responses higher with 2+1 vs 3+0.
- Post boost response for 6B higher with 3+1 vs 2+1.
- “ While one schedule may be preferred in a particular setting based upon local epidemiology or practical considerations, achieving high coverage with 3 doses is likely more important than the timing of doses”*
- Use of a booster in the second year of life is clearly of benefit.

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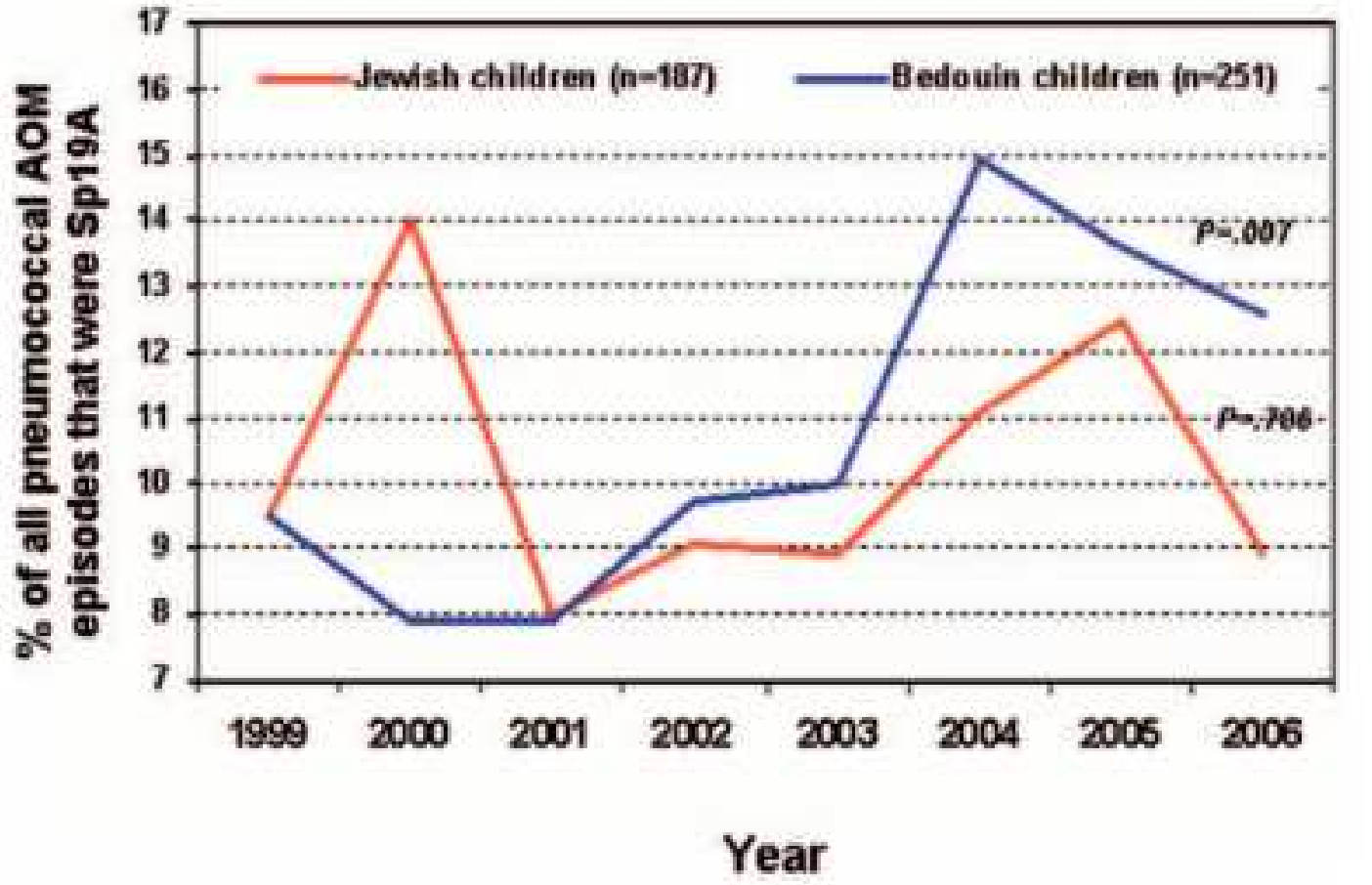
 * Whitney et al PIDJ supplement January 20, 2014 page S172

What about replacement?



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Data courtesy of R Dagan et al in JID 2009:199 (15 March)

Conclusions: PCV vaccines

- PCV vaccines have had a dramatic impact both because of their direct effect in children but also because of indirect effects in adults.
- Non-vaccine serotypes especially 19A became more common after PCV7 introduction in many countries
  - It remains to be seen if replacement will be a problem with newer generation vaccines
- Newer vaccines are in development
  - Mixed protein/PCV vaccines
  - Pure protein and whole organism vaccines

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Acellular Pertussis Vaccines:

The Road to Hell is paved with good intentions

What do we lose by switching to aP vaccines?

2010, 85, 385–400 No. 40

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

1ST OCTOBER 2010, 85th YEAR / 1ER OCTOBRE 2010, 85e ANNÉE
No. 40, 2010, 85, 385–400
http://www.who.int/wer

Contents

Pertussis vaccines: WHO position paper

Note de synthèse: position de l'OMS concernant les vaccins anticoquelucheux

in countries where the higher nonserious reactogenicity of wP would be an impediment to high vaccination coverage, the use of aP vaccine may be a mechanism to help improve acceptability. In these cases, aP vaccine should replace the wP vaccine in the national childhood immunization programme, either for the booster dose only or for the entire vaccination series.

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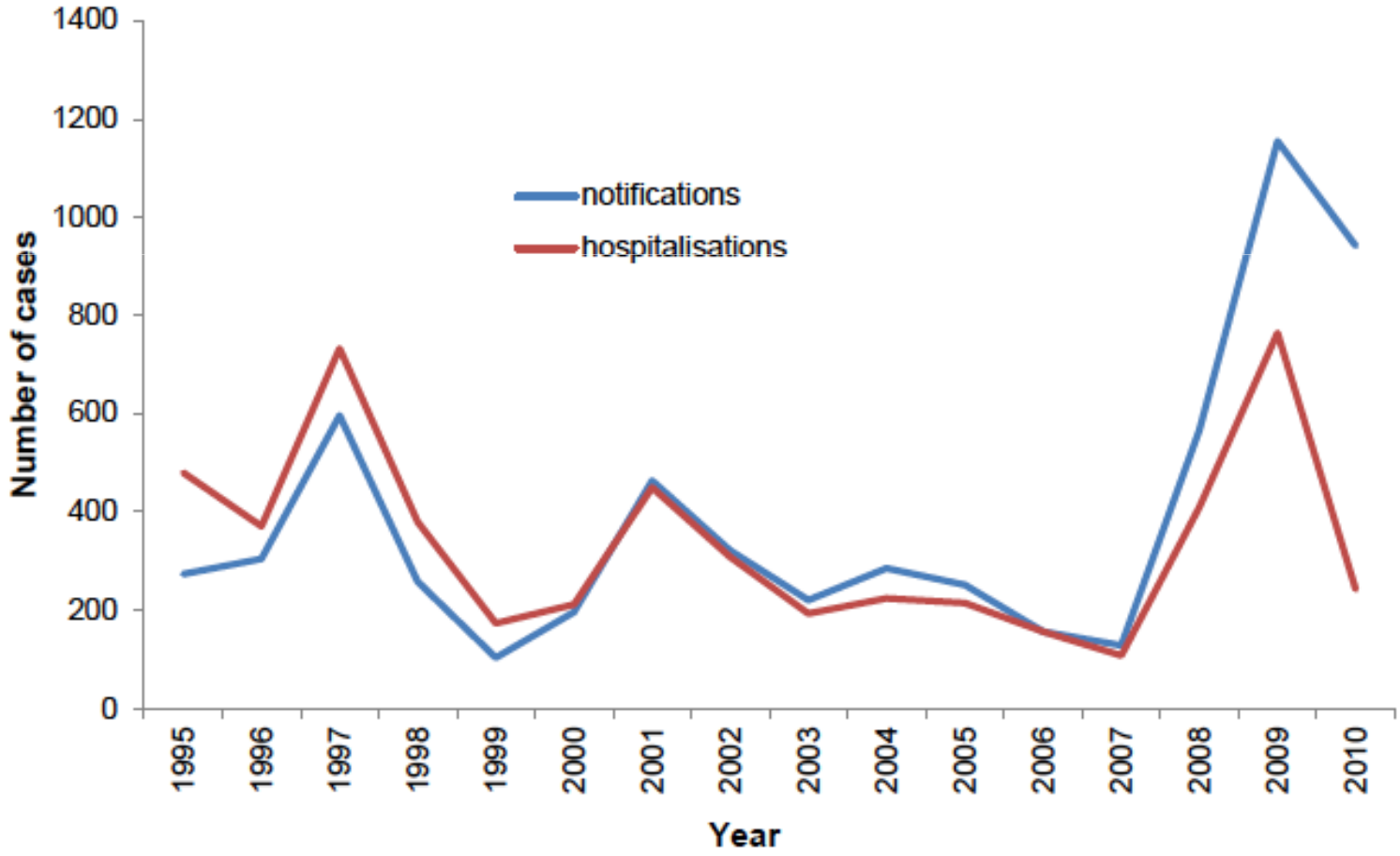
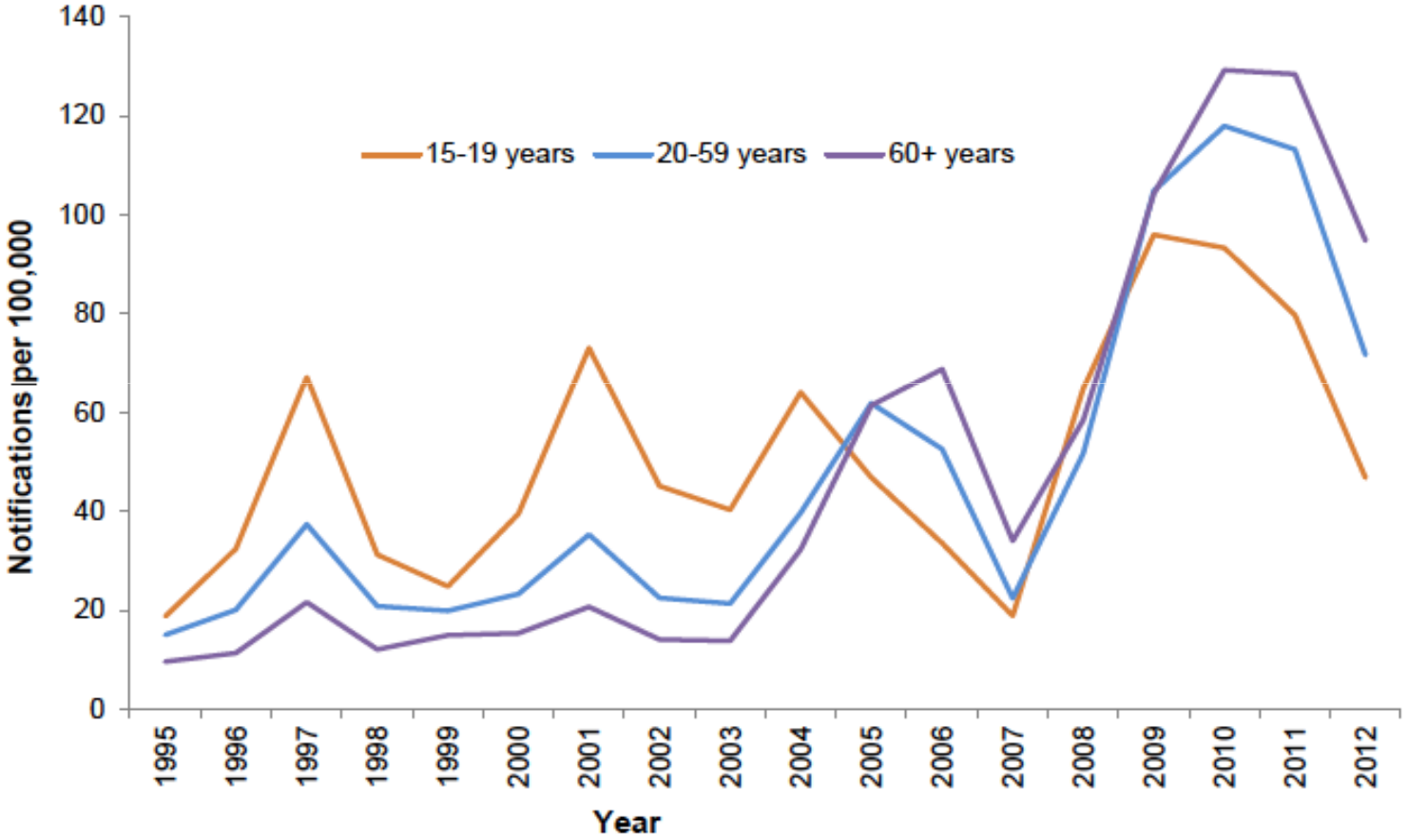
Australia

Trends in pertussis notifications and hospitalisations aged <1 year



Slide courtesy of Peter McIntyre

Incidence of reported pertussis cases* in Australia, persons aged ≥15 years



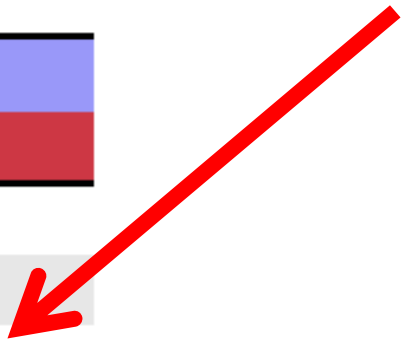
Slide courtesy of Peter McIntyre

Rapidly Falling Effectiveness with Time

Acellular pertussis vaccine
- effective from dose 1 but wanes by 3 years [1]

Age (months)	Doses*	Hospitalised VE (95% CI)#
2–3	1	55 (43 –65)
4-5	2	83 (70–90)
6–11	3	85 (75–91)

Age (years)	Doses*	Total cases VE (95% CI)#
1	3	79 (75–83)
2	3	71 (65–76)
3	3	59 (51–66)



Slide courtesy of Peter McIntyre

Factors Contributing to Surge in Pertussis Cases

- Waning of vaccine-induced immunity in older children
  - This was not apparent initially
    - Following introduction, older children had been primed with whole cell pertussis vaccine
    - Clinical trials did not have long term follow up
- Increased awareness and more frequent diagnostic testing
- aP vaccines are poor at preventing transmission
- There is evidence that vaccine selection pressure has induced pertussis toxins with “drifted” antigenicity.

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Next Steps

- Further studies to help us better understand why acellular vaccines are behaving differently than the older whole cell vaccines.
- Development of new vaccines
  - Use of adjuvants
  - Live attenuated vaccines.
  - Reintroduction of old whole cell vaccines into countries that have abandoned them is not likely
- Countries still using whole cell vaccines in their immunization program should delay consideration of switching to aP vaccines.

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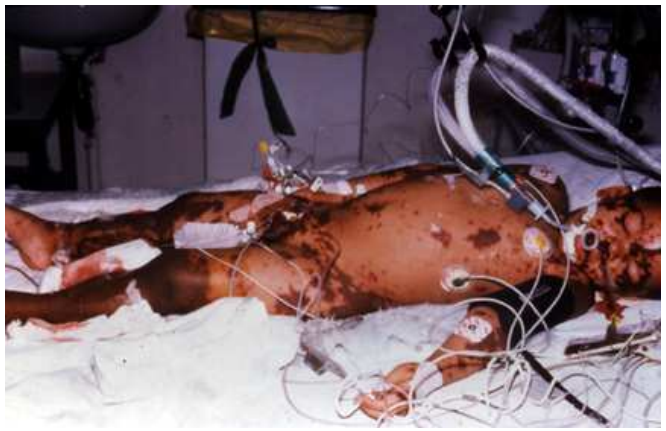
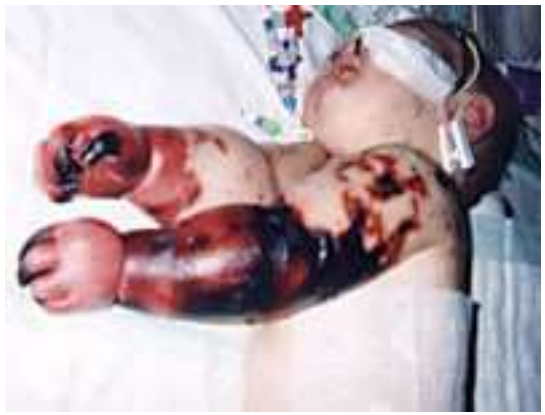
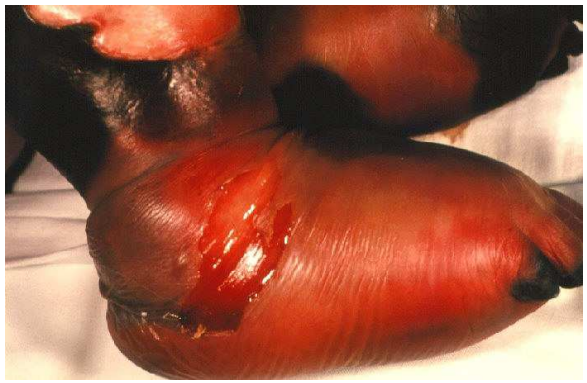
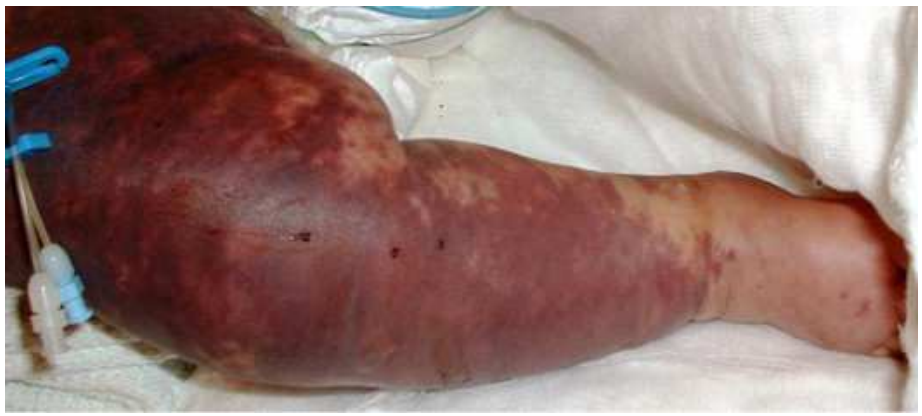
Meningococcal Vaccines









https://www.google.com/search?hl=en&site=&tbm=isch&source=hp&biw=1280&bih=915&q=meningococcal+disease&oq=meningococcal+disease&gs_l=img.3..0j0i24l9.6274.11235.0.11699.21.15.0.6.6.0.95.1078.15.15.0...0.0...1ac.1.4.img.O1miXv2l2Tg#imgrc=_

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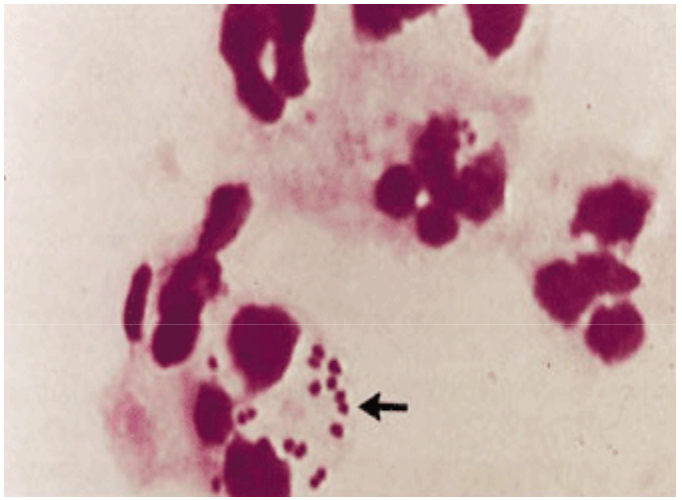
Neisseria meningitidis: The organism

- Encapsulated gram-negative diplococcus[1]
- Strictly human pathogen[1]
- Asymptomatic carriage common
  - Carrier prevalence: ~1%–35%[2]
  - <1% of carriers become symptomatic[3]
  - Duration of carriage is not fully understood
  - Stable in most cases for 5 to 6 months[4]
  - Factors that predict progression from carriage to invasive disease are unclear[4]
- Transmission[5]
  - Respiratory secretions
  - Incubation period: 2–10 days



Gram stain of *N meningitidis* in cerebrospinal fluid.[6]

1. van Deuren M, et al. *Clin Microbiol Rev*. 2000;13:144-166; 2. Brigham KS, et al. *Curr Opin Pediatr*. 2009;21:437-443; 3. Dull PM, et al. *J Infect Dis*. 2005;191:33-39; 4. Caugant DA, et al. *FEMS Microbiol Rev*. 2007;31:52-63; 5. *WHO*. Fact sheet: Meningococcal meningitis. 2010. http://www.who.int/mediacentre/factsheets/fs141/en/index.html; 6. Rosenstein NE, et al. *N Engl J Med*. 2001;344:1378-1388.

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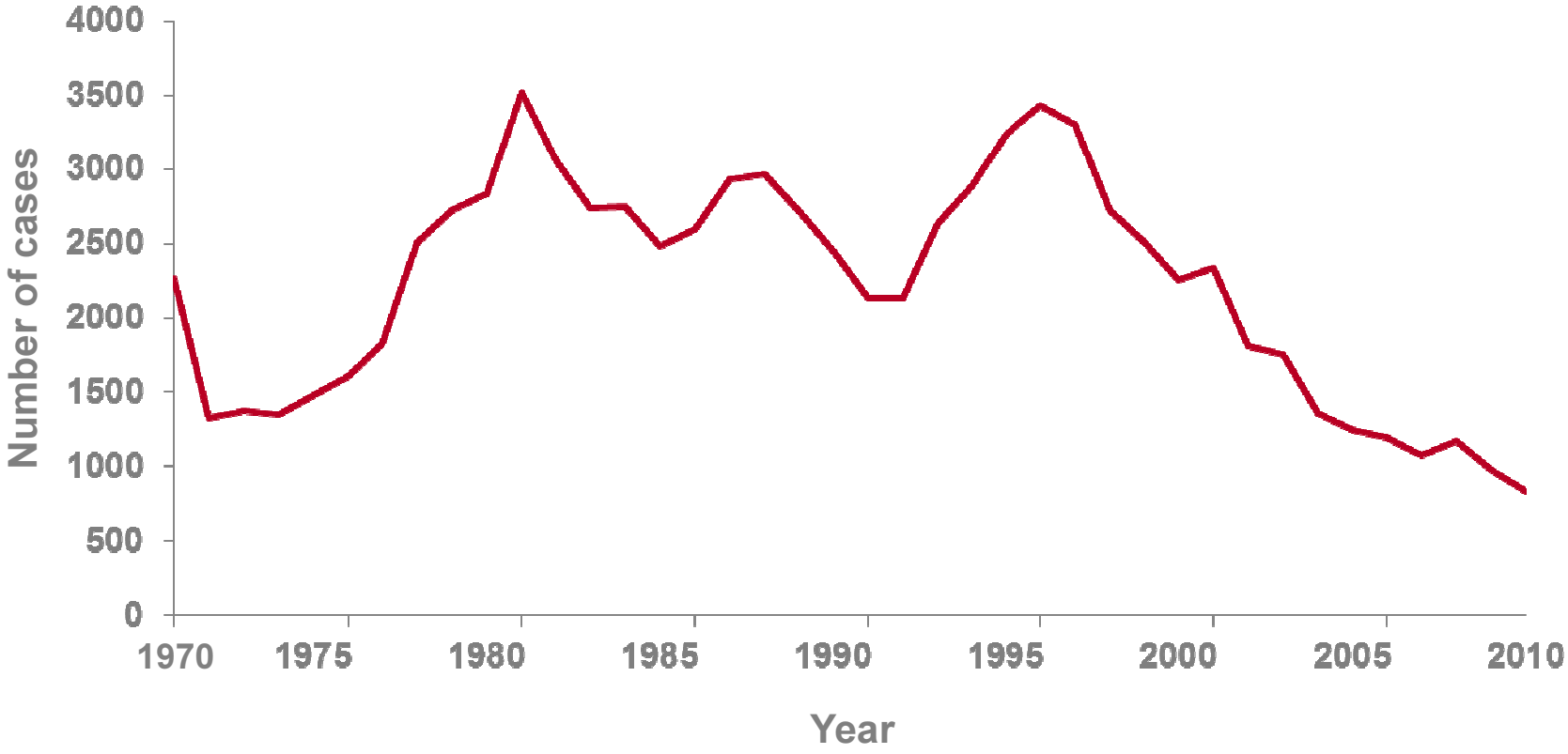
Historical Cases of Meningococcal Disease

All Ages in the *United States, 1970–2010*[1-4]



1. Centers for Disease Control and Prevention. *MMWR*. 2004;51:1-88; 2. Centers for Disease Control and Prevention. *MMWR*. 2010;57:1-100; 3. Centers for Disease Control and Prevention. *MMWR*. 2011;60:65-92; 4. Centers for Disease Control and Prevention. *MMWR*. 2011;60:1088-1116.

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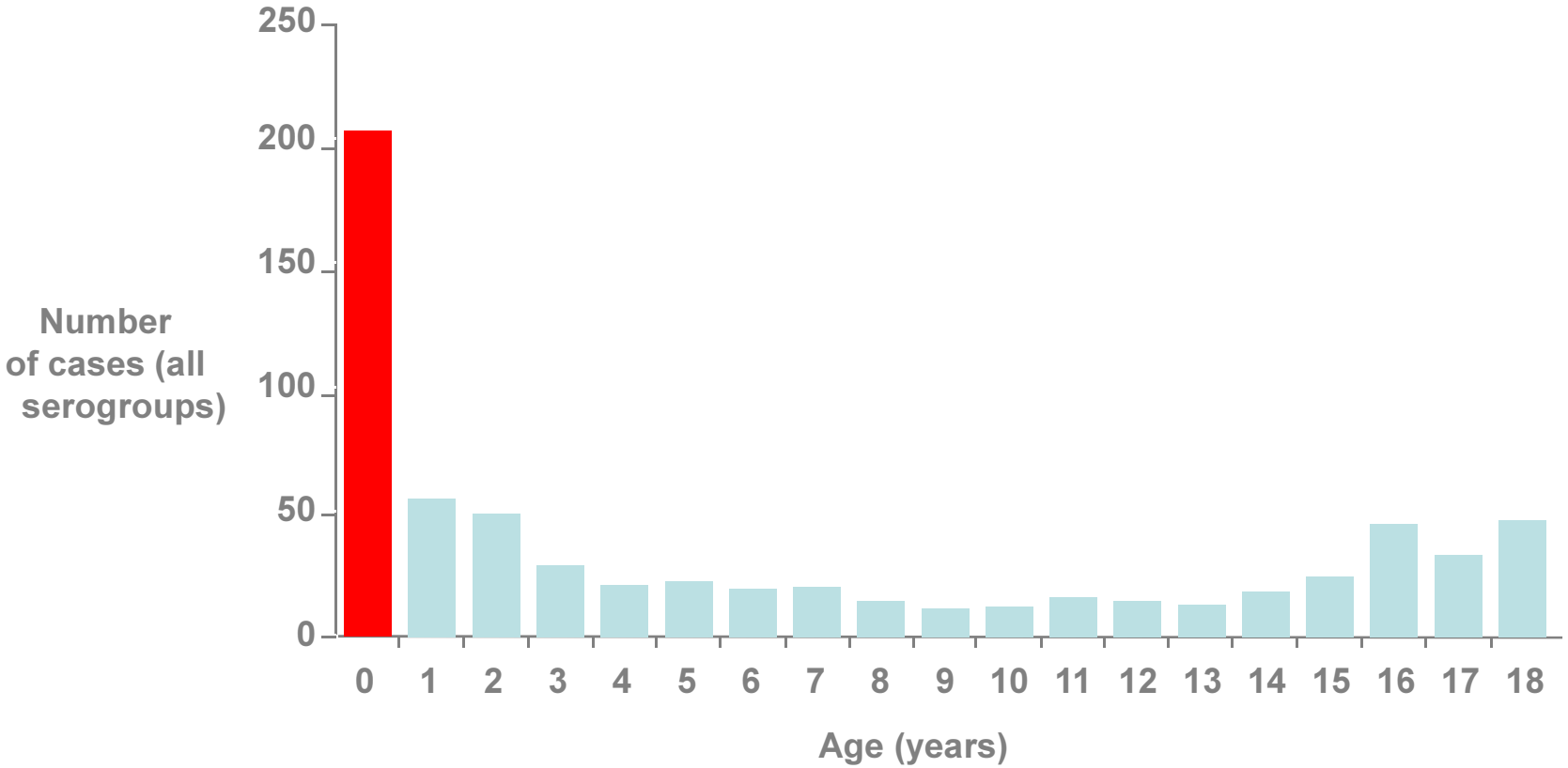
Estimated Annual Number of Cases of Meningococcal Disease by Age Group

United States, 1998–2007



NOTE: Active Bacterial Core surveillance cases from 1998–2007 projected to the US population.

CDC. Department of Health and Human Services. MacNeil J, et al for the Active Bacterial Core Surveillance (ABCs) Team and MeningNet Surveillance Partners. Presented at: National Immunization Conference; March 30–April 2, 2009; Dallas, TX.

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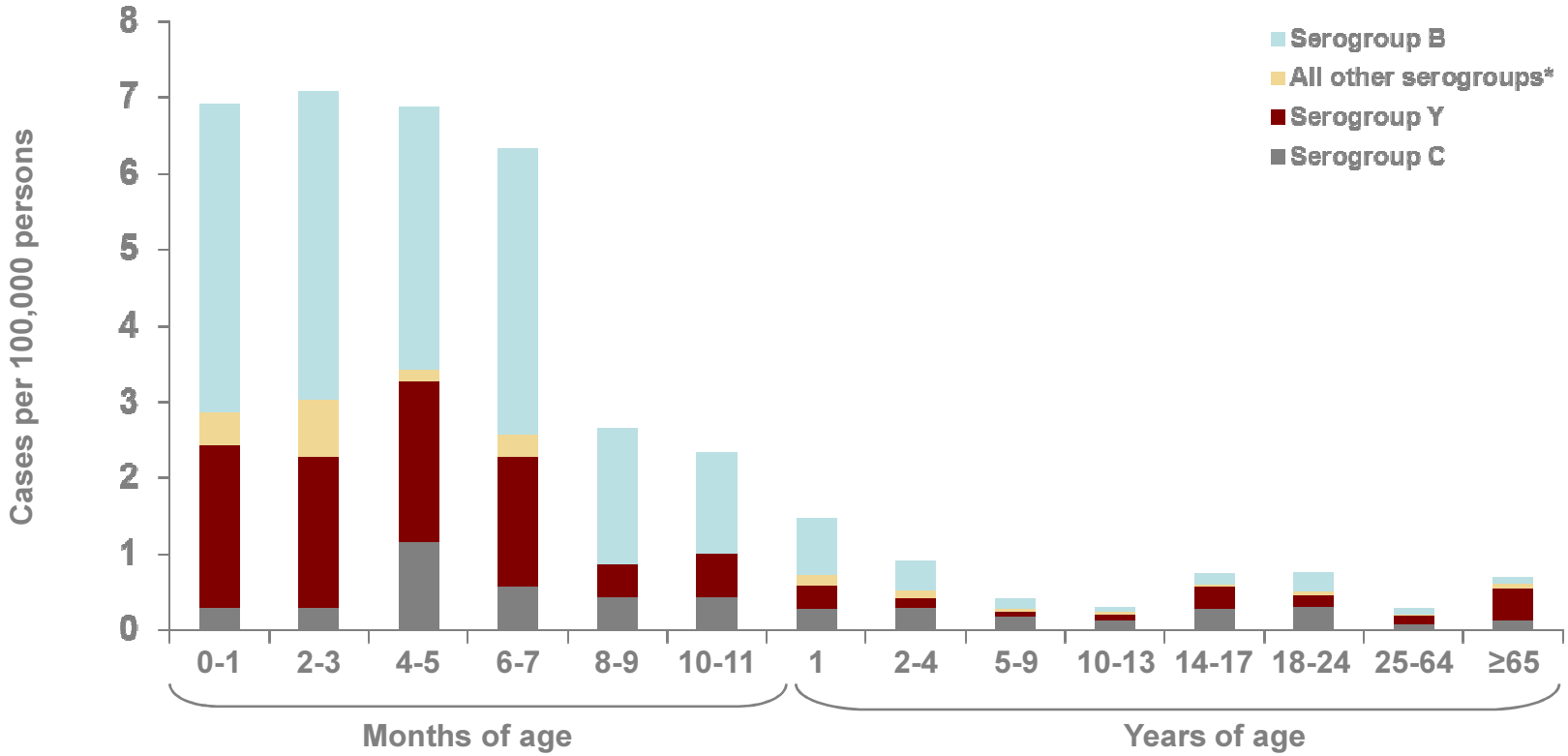
Three Different Serotypes are responsible for most disease

Rates of Culture-Confirmed Meningococcal Disease
United States, 1998–2007



*Includes serogroups A, W-135, and nongroupable strains.

Cohn AC, et al. *Clin Infect Dis*. 2010;50:184-191.

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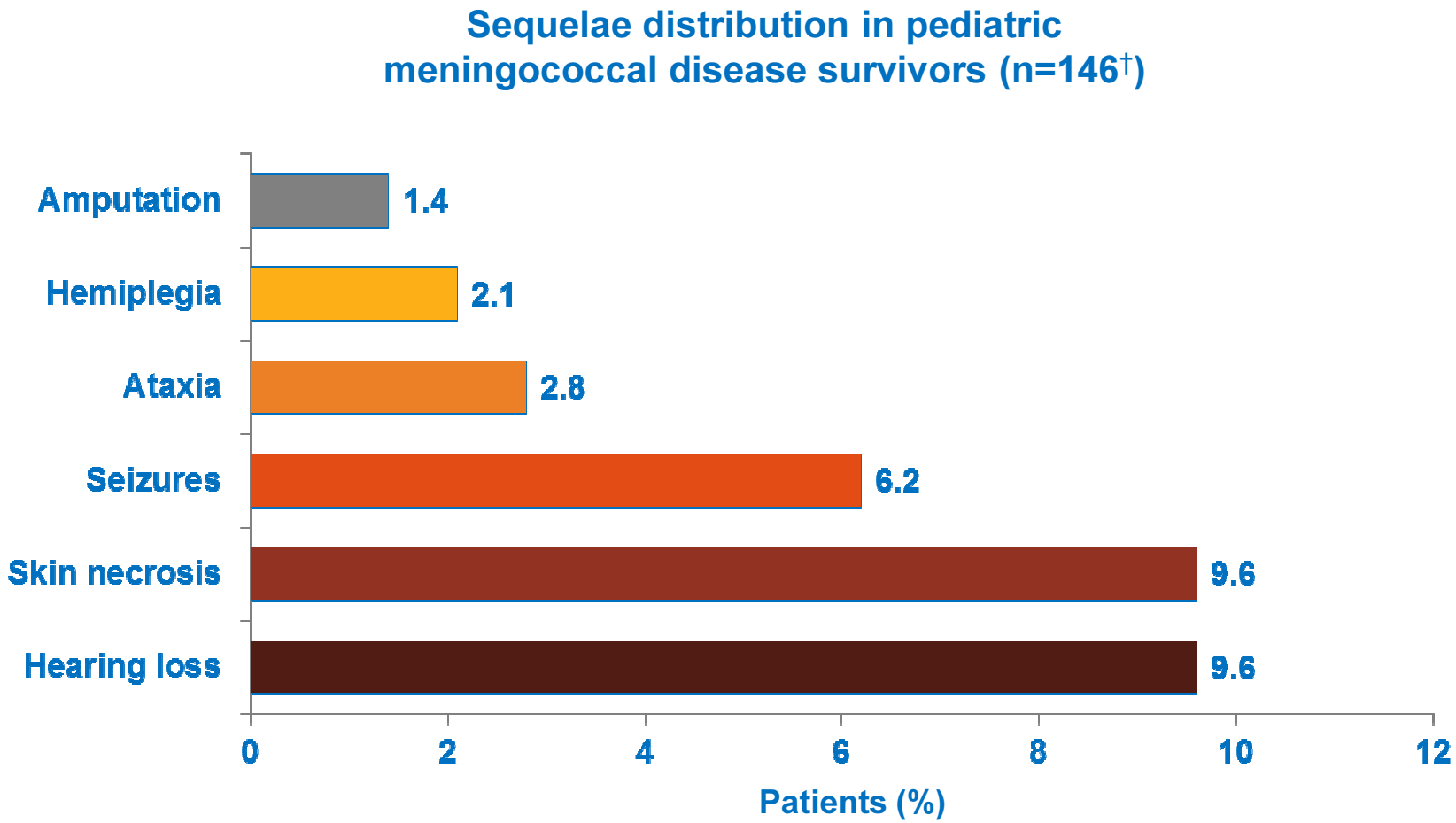
Infants and Children Suffer Significant Physical Sequelae From Meningococcal Disease

From 10 Children's Hospitals, United States, 2001–2005*



*Investigators from 10 children's hospitals in the United States identified all children from January 1, 2001, through March 15, 2005, who had systemic infections that were caused by *Neisseria meningitidis*.n=126 for <11 year olds; n=33 for ≥11 year olds.

Kaplan SL, et al. *Pediatrics.* 2006;118:e979-e984.

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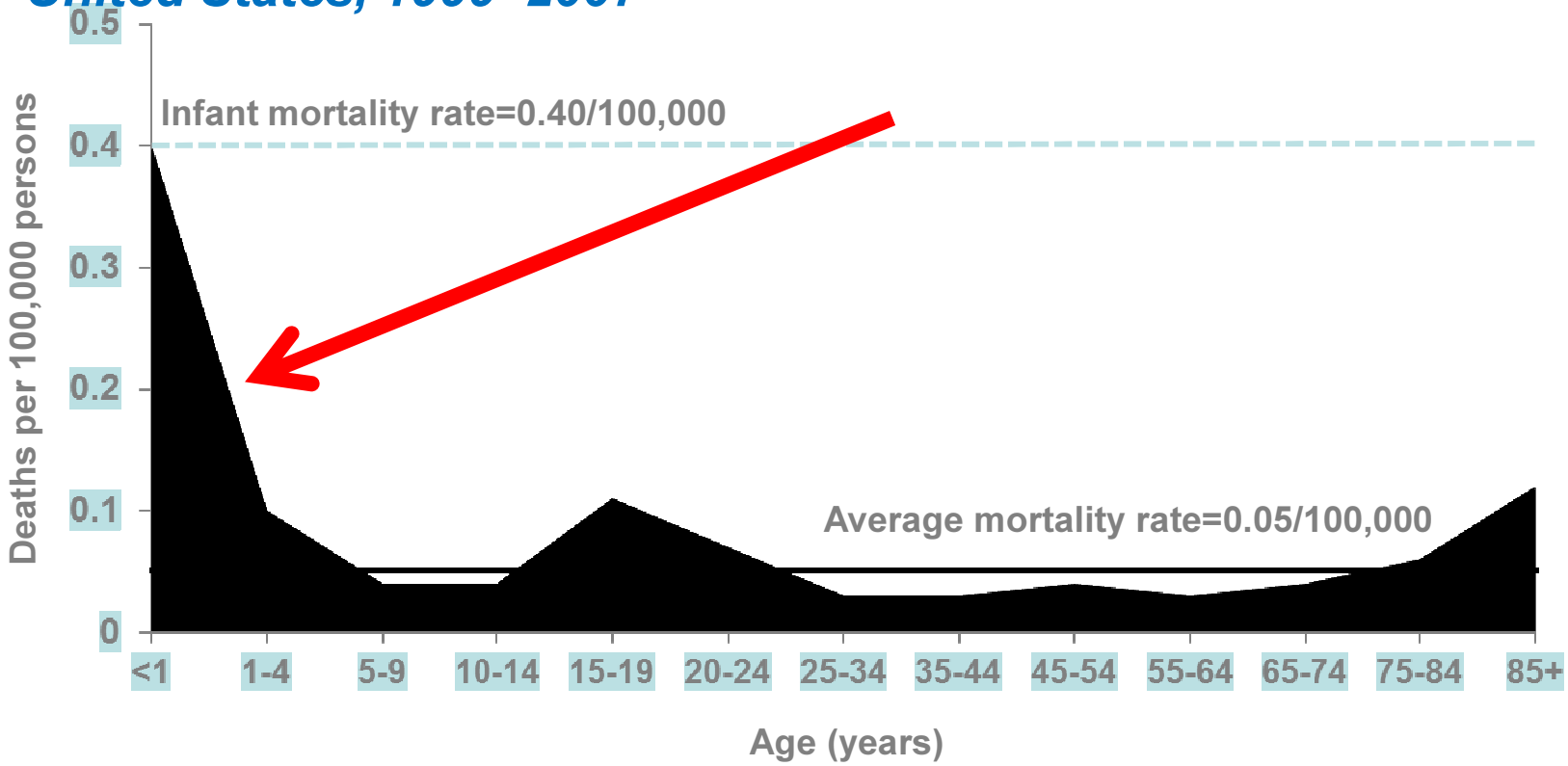
Rate of Mortality Due to Meningococcal Disease—by Age Group

United States, 1999–2007



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Centers for Disease Control and Prevention. Compressed Mortality File 1999-2007. http://wonder.cdc.gov/cmf-icd10.html.

Burden of Meningococcal Disease in Latin and South America, 2011

Slide courtesy of Angela Gentile

Number of Cases of Meningococcal Disease

- >201 cases
- 100 to 200
- 50 to 100
- 11 to 49
- 1 to 10
- No cases reported

Levels of surveillance vary across countries, which may limit direct comparisons of disease incidence.

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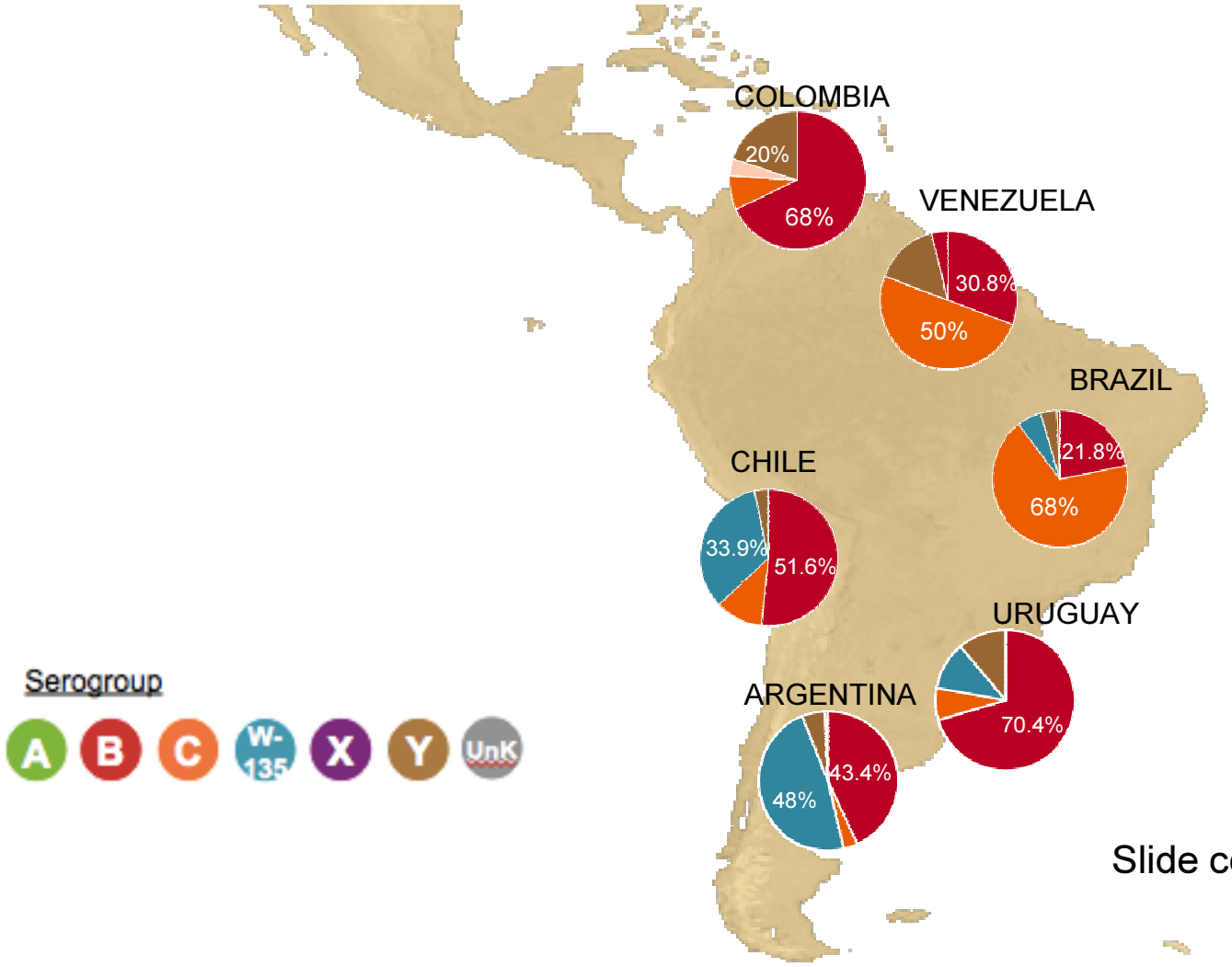
Informe Regional de SIREVA II, 2011, Washington, DC: Organización Panamericana de la Salud, 2012.

Neisseria meningitidis Serogroup Distribution Is Varied and Dynamic, Making Trends Unpredictable

2011



Slide courtesy of Angela Gentile

UnK=unknown.

Informe Regional de SIREVA II, 2011, Washington, DC: Organización Panamericana de la Salud, 2012.

Epidemiology: Overall Summary

- The incidence of meningococcal disease is higher in infants than any other age group
- Serogroup B disease is currently the most common serogroup in infants in many countries with complete surveillance
- The meningococcal mortality rate in infants of approximately 0.40/100,000 live births is about four times higher than that in adolescents

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Vaccines against Meningococcal Disease

- Meningococcal conjugate vaccines
  - GSK Hib/MenCY vaccine
  - Novartis ACYW-135 conjugate
  - Sanofi ACYW-135 conjugate (toddlers or older only)
- All effectively induce immunity
- None of these vaccines impact group B disease for which another approach is required

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Vaccines against Meningococcal Disease

- Meningococcal group B vaccines
- Conjugate vaccines for group B are not effective and run the risk of serious toxicity
  - Cross reactivity with heart and nervous tissue
- For this reason protein vaccines have been developed
  - Pfizer Men B recombinant factor H binding protein
    - In development
  - Novartis quadravalent protein/OMV vaccine
    - Approved for use in in Europe, Australia and other countries but not currently in USA

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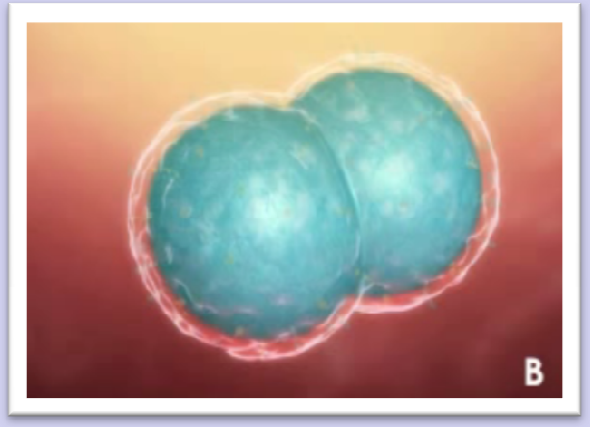
The Development of a Broad Coverage MenB Vaccine Has Been Challenging

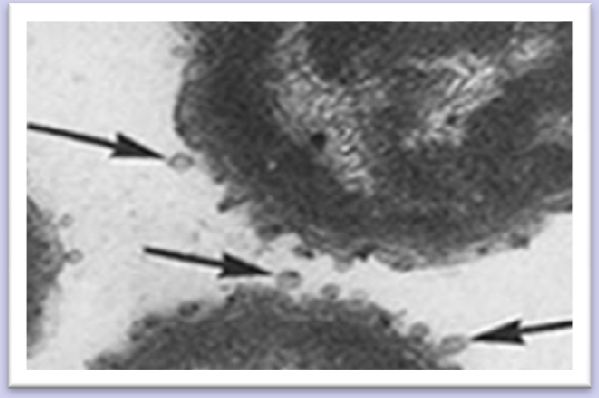
Capsular Vaccines

- Poorly immunogenic[1,2]
  - Structural homology between the B polysaccharide of the capsule and human tissue[1,2]



OMV-based Vaccines

- Serogroup B strains are highly diverse[3,4]
  - >80 different OMV types[5]
  - >8000 genetically different B strains[5]
- Immunogenic and proven effective for a **single** homologous serogroup B strain[3,4]
- Limited protection against heterologous meningococcal serogroup B strains[3,4]



Outer membrane “blebs” of *N meningitidis*[6]

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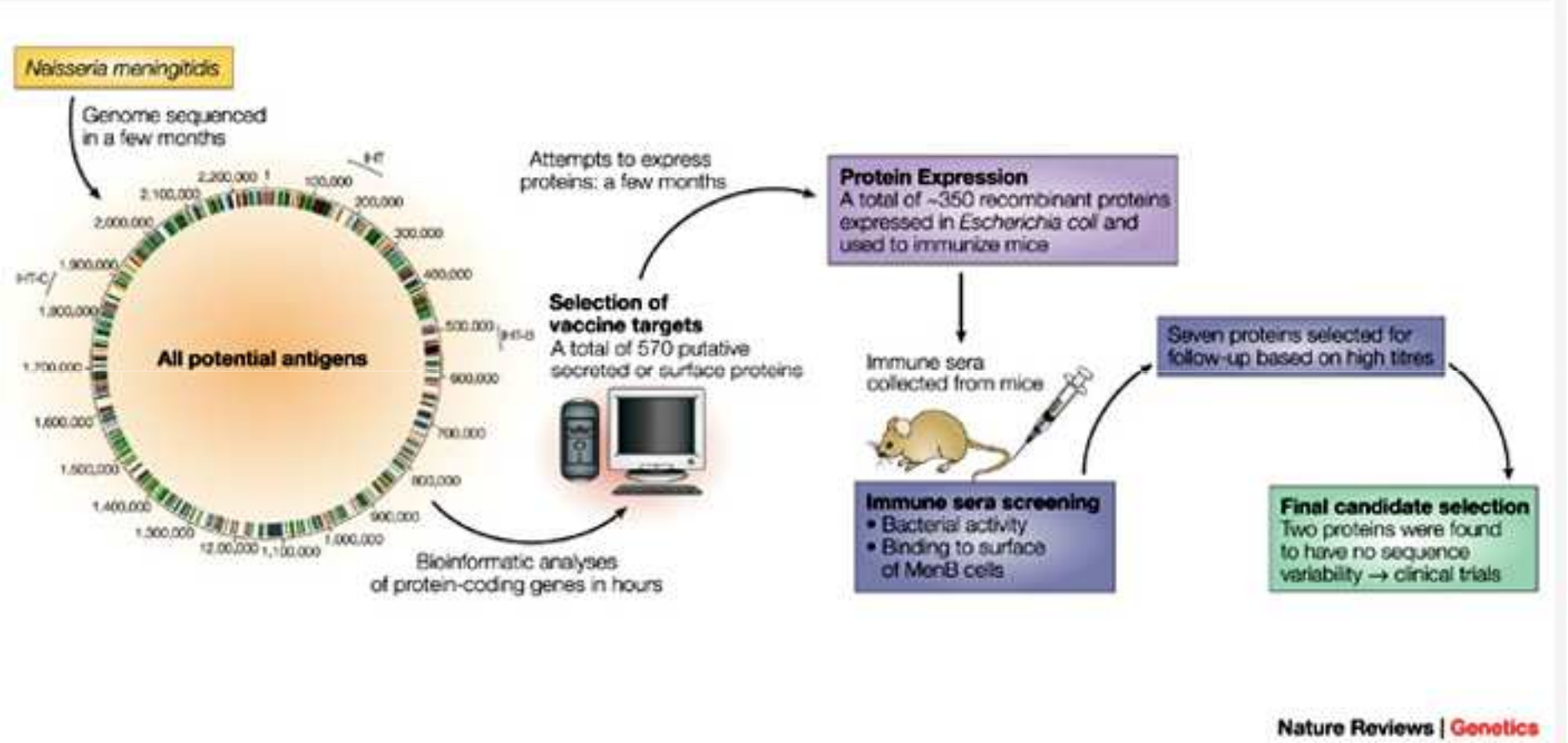
1. Finne J, et al. *J Immunol*. 1987;138:4402-4407; 2. Wyle FA, et al. *J Infect Dis*. 1972;126:514-522; 3. Sadarangani M, et al. *Lancet Infect Dis*. 2010;10:112-124; 4. Tan LK, et al. *N Engl J Med*. 2010;362:1511-1520; 5. Neisseria Multi Locus Sequence Typing website. http://pubmlst.org/neisseria/; 6. Devoe IW, et al. *J Exp Med*. 1973;138:1156-1167.

Reverse Vaccinology



Novartis BEXSERO® Consists of 4 Antigenic Components Chosen to Achieve Broad Protection

fHbp: factor H binding protein

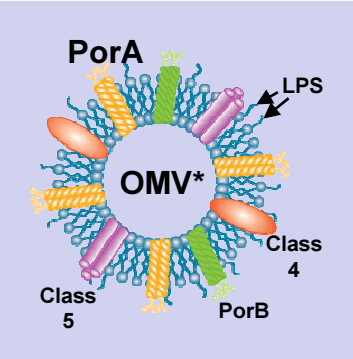
- Binds factor H, which enables bacterial survival in the blood[1,2]

NHBA: neisseria heparin-binding antigen

- Binds heparin, which may promote bacterial survival in the blood[7]
- Present in virtually all strains[6,7]

NadA: neisserial adhesin A

- Promotes adherence to and invasion of human epithelial cells[3-5]
- May be important for colonisation[4]



NZ PorA P1.4: porin A

- Major outer membrane vesicle protein—induces strain-specific bactericidal response[8]

Combining antigens that target different steps of meningococcal pathogenesis is likely to help optimize MenB vaccine effectiveness

*From *Neisseria meningitidis* serogroup B strain NZ 98/254 measured as amount of total protein containing the PorA P1.4.

1. Madico G, et al. *J Immunol*. 2006;177:501-510; 2. Schneider MC, et al. *Nature*. 2009;458:890-893; 3. Comanducci M, et al. *J Exp Med*. 2002;195:1445-1454; 4. Capecchi B, et al. *Mol Microbiol*. 2005;55:687-698; 5. Mazzon C, et al. *J Immunol*. 2007;179:3904-3916; 6. Serruto D, et al. *Proc Natl Acad Sci U S A*. 2010;107:3770-3775; 7. Bambini S, et al. *Vaccine*. 2009;27:1794-2803; 8. Martin DR, et al. *Clin Vaccine Immunol*. 2006;13:486-491.

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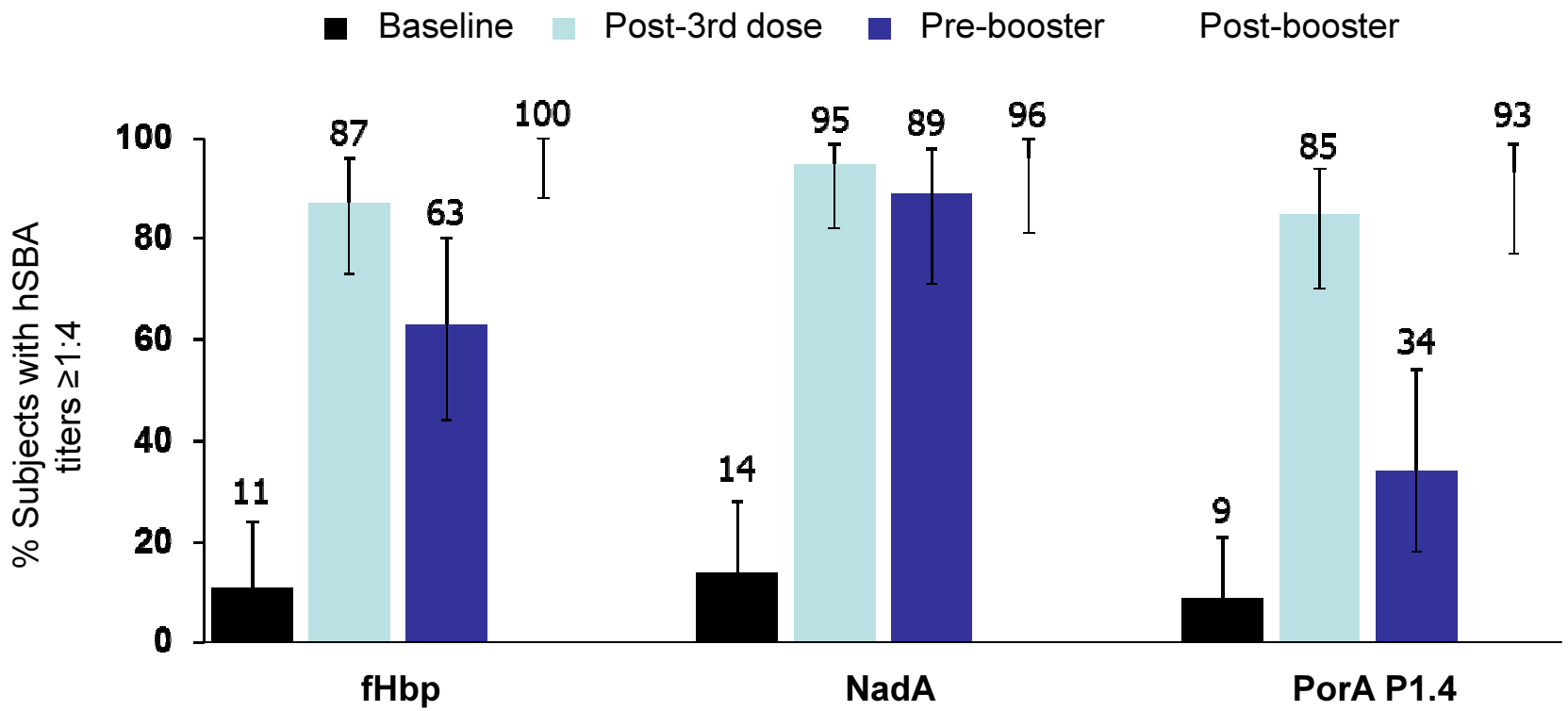
Novartis Four Component Meningococcal B Vaccine

Percentage of infants with bactericidal titers ≥1:4

- 4CMenB given in a 3-dose primary series at 2-4-6 plus a booster at 12 months of age - response for three of the four antigens



Findlow J, et al. *Clin Infect Dis*. 2010;51:1127-1137.

NHBA reference strain was not available in early development phase.

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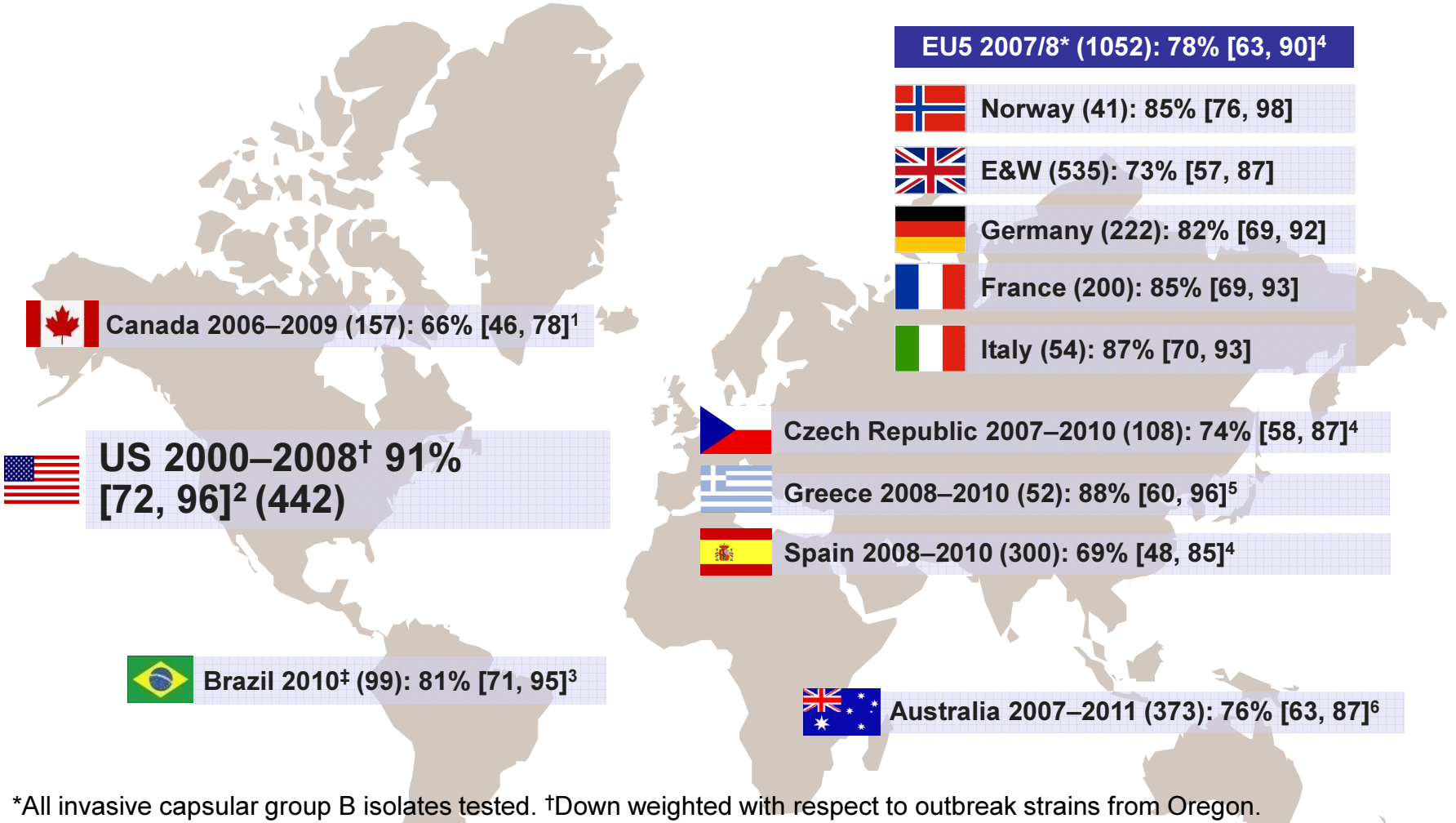
MATS Predicts the Country-Specific Estimated Strain Coverage of 4CMenB



*All invasive capsular group B isolates tested. †Down weighted with respect to outbreak strains from Oregon.
‡Represents about 53% of capsular group B cases.

1. Bettinger J, et al. Presented at: 5th Vaccine and International Society for Vaccines (ISV) Annual Global Congress; 2-4 October 2011; Seattle, WA; 2. Kim J, et al. Presented at: 19th International Pathogenic Neisseria Conference (IPNC). 9-14 September 2012. Würzburg, Germany. Poster P270; 3. Lemos AP, et al. Presented at: 19th International Pathogenic Neisseria Conference (IPNC). 9-14 September 2012. Würzburg, Germany. Poster P272; 4. Vogel U, et al. *Lancet Infect Dis*. 2012 [in press]; 5. Data on file, Novartis Vaccines and Diagnostics; 6. Nissen M, et al. Presented at: 19th International Pathogenic Neisseria Conference (IPNC). 9-14 September 2012. Würzburg, Germany. Poster P269.

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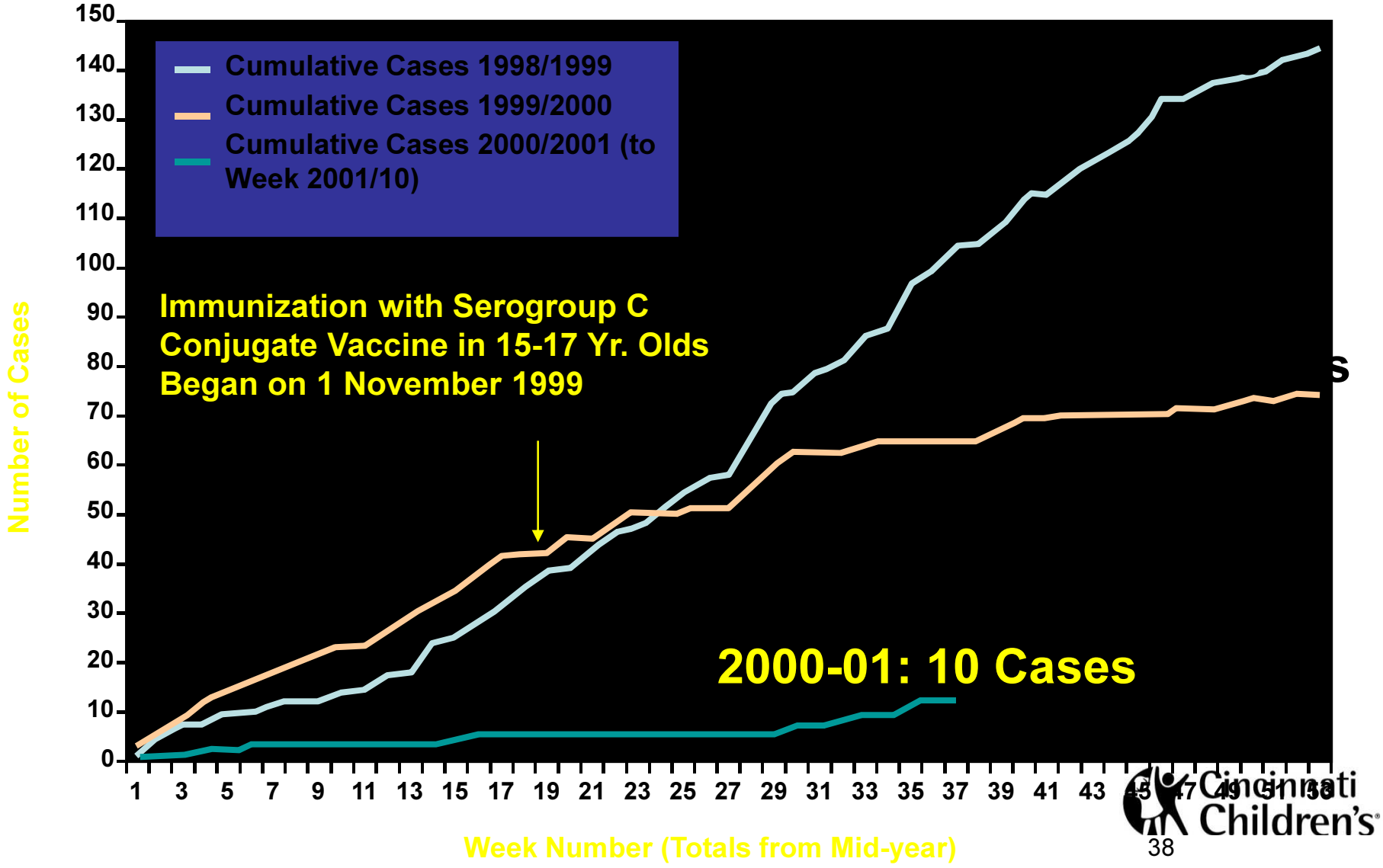
What Meningococcal Vaccine Programs can Achieve

MENINGOCOCCAL SEROGROUP C CASES IN U.K.



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Meningococcal Vaccines Conclusions

- Meningococcal disease is a disease of high morbidity and mortality even with state of the art therapy
- Group B disease is the most common serogroup in many countries especially in infants
- Several conjugate vaccines are available for serotypes A, C, W-135, and Y
- With a new 4 component protein vaccine for serogroup B now offers the potential to completely control this disease.

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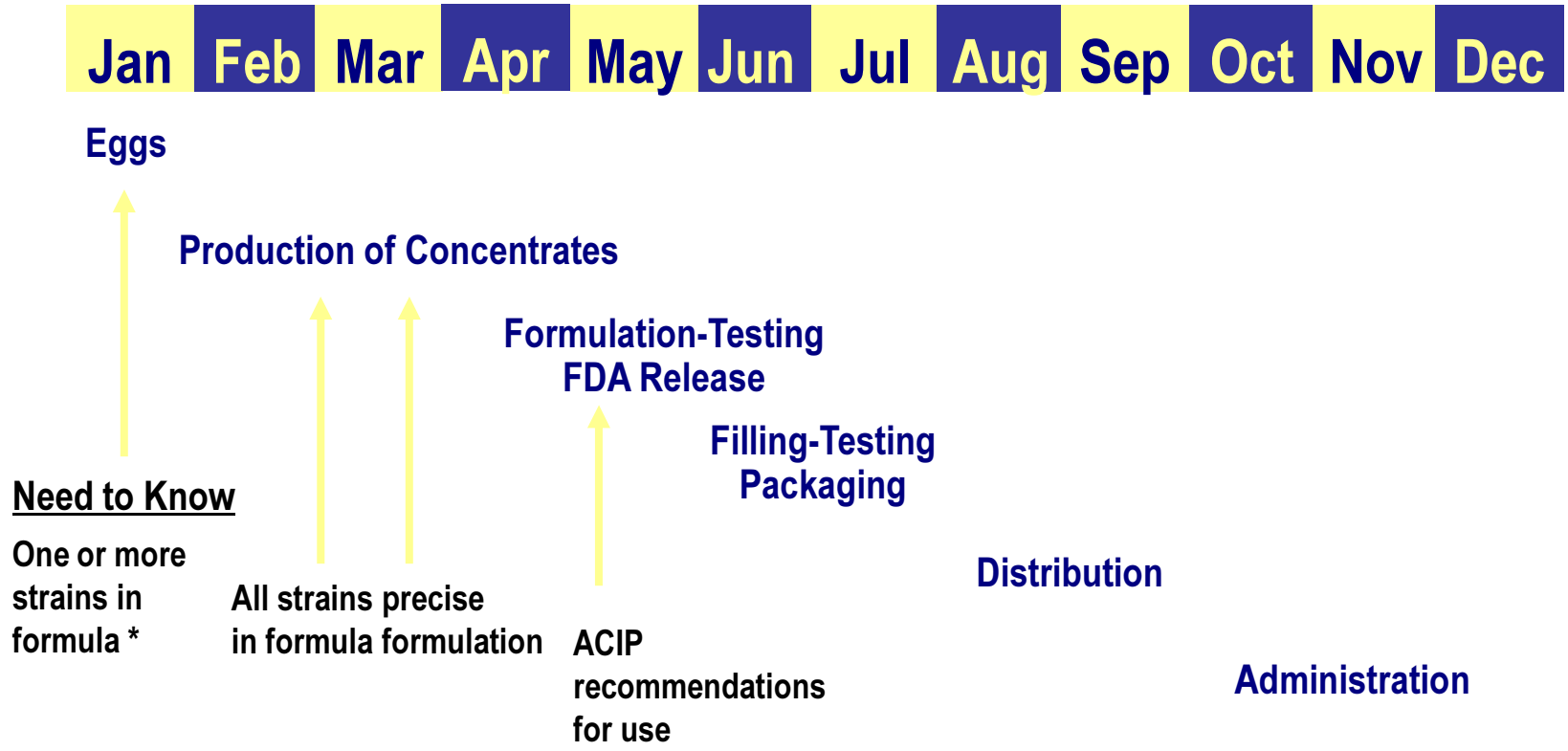
INFLUENZA

Timetable for Influenza Vaccine Production in the Northern Hemisphere



*The characteristics of the strains circulating the previous season provide the basis for selecting virus strains for the next year's vaccine. Courtesy of the Centers for Disease Control and Prevention.

Piedra PA, presented at SHEA symposium, Philadelphia, 2004; Malhotra A et al. *Pediatr Clin North Am* 2000;47:353-372; ACIP. *MMWR* 2003;52(RR-8):1-36; Cox NJ et al. 1999;354:1277-1282.

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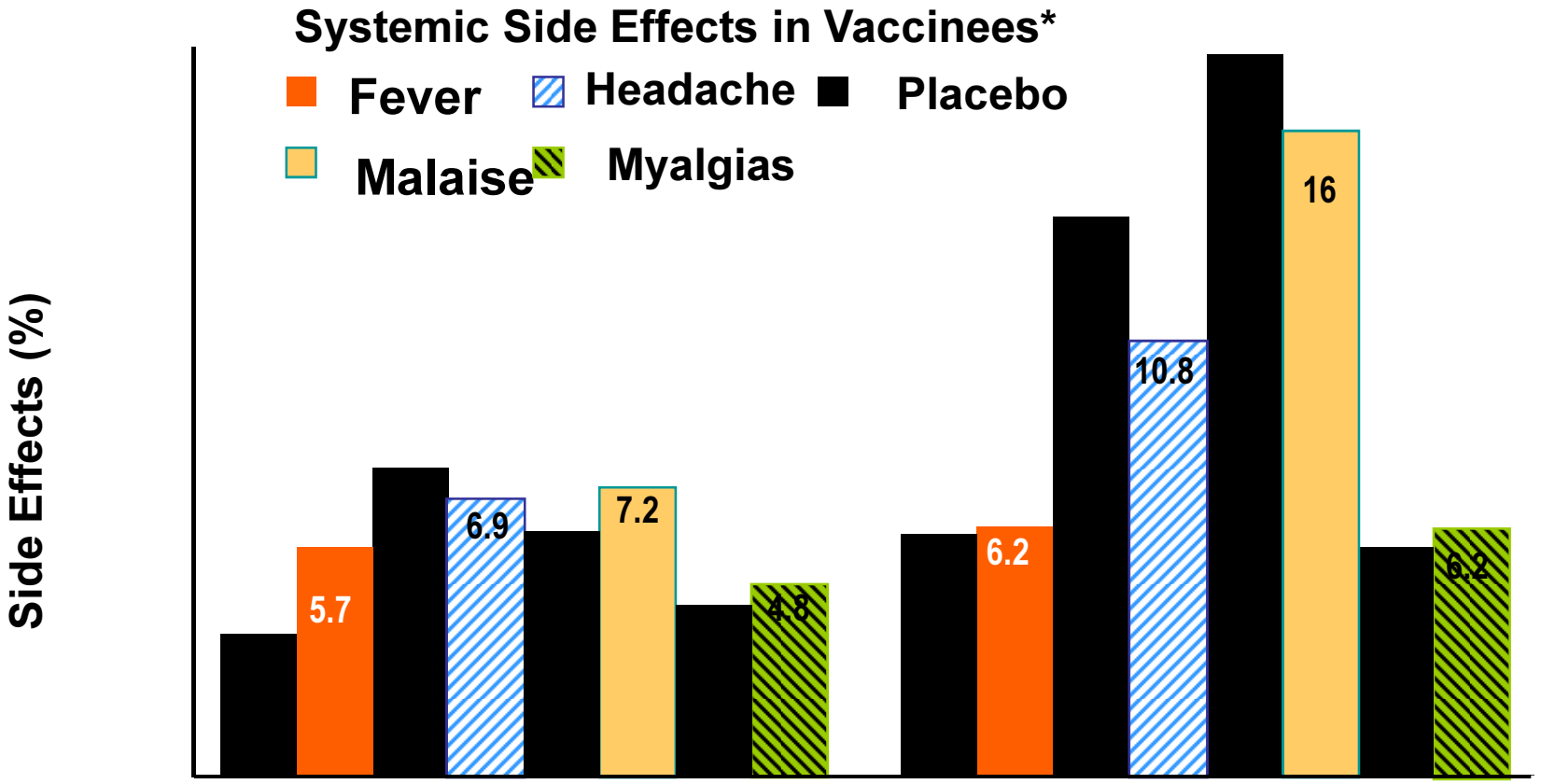
Safety of Influenza Vaccine



*Sore arms and injection-site reactions higher in vaccinated group.

1. Margolis KL et al. *JAMA*. 1990;264:1139-1141.
2. Nichol KL et al. *Arch Intern Med*. 1996;156:1546-1550.

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Target Groups for Influenza Vaccination in the US

- All persons who want to reduce their risk of becoming ill with influenza or of transmitting disease to others
- All persons 6 months of age and older
- Especially taregeting Individuals at high risk for influenza and its complications:
  - ≥50 years of age
  - Residents of nursing homes and chronic-care facilities
  - Persons with chronic pulmonary, cardiovascular, renal, hepatic, hematologic, or metabolic disorders
  - Immunocompromised persons
  - People with conditions that compromise respiration or increase risk for aspiration
  - Women who will be pregnant during influenza season

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CDC Recommendations 2013-2014

- Routine annual influenza vaccination of all persons aged 6 months and older continues to be recommended.
- 2013-14 U.S. trivalent influenza vaccines contain an A/California/7/2009 (H1N1)-like virus and a B/Massachusetts/2/2012-like virus. Quadrivalent vaccines will include an additional vaccine virus, a B/Brisbane/60/2008-like virus.
- Several new, recently-licensed vaccines will be available for the 2013-14 season, and are acceptable alternatives to other licensed vaccines indicated for their respective age groups when otherwise appropriate. No preference specified.
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Classes of New Influenza Vaccines

- Quadrivalent vaccines containing two A and two B strains
- Adjuvanted vaccines
- Vaccines not dependent on eggs for production
  - Cell culture based technology
  - Recombinant vaccines
- Live attenuated influenza vaccine

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Available Influenza vaccines 2013-2014 in the US

- A quadrivalent live attenuated influenza vaccine (LAIV4; Flumist® Quadrivalent [MedImmune]). For healthy, nonpregnant persons aged 2 through 49 years;
- A quadrivalent inactivated influenza vaccine (IIV4; Fluarix® Quadrivalent [GlaxoSmithKline]) in addition to the previous trivalent formulation. For persons aged 3 years and older;
- A quadrivalent inactivated influenza vaccine (IIV4; Fluzone® Quadrivalent [Sanofi Pasteur]) will be available in addition to TIV. For persons6 months and older;
- A trivalent cell culture-based inactivated influenza vaccine (ccIIV3; Flucelvax® [Novartis]), which is indicated for persons aged 18 years and older
- A recombinant hemagglutinin (HA) vaccine (RIV3; FluBlok® [Protein Sciences]), which is indicated for persons aged 18 through 49 years.
- No adjuvanted influenza vaccines currently in the US.

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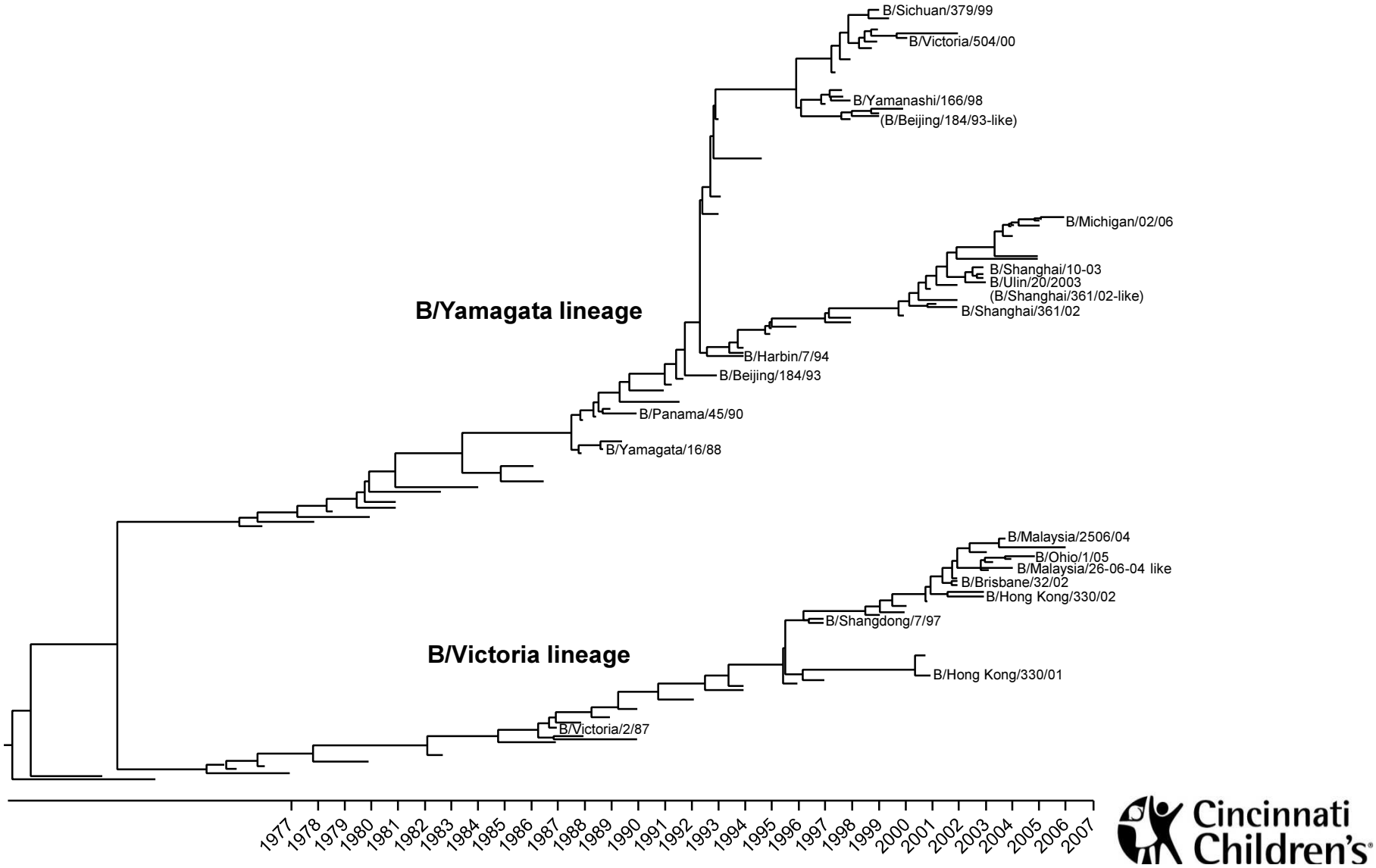
The two distinct lineages of influenza B



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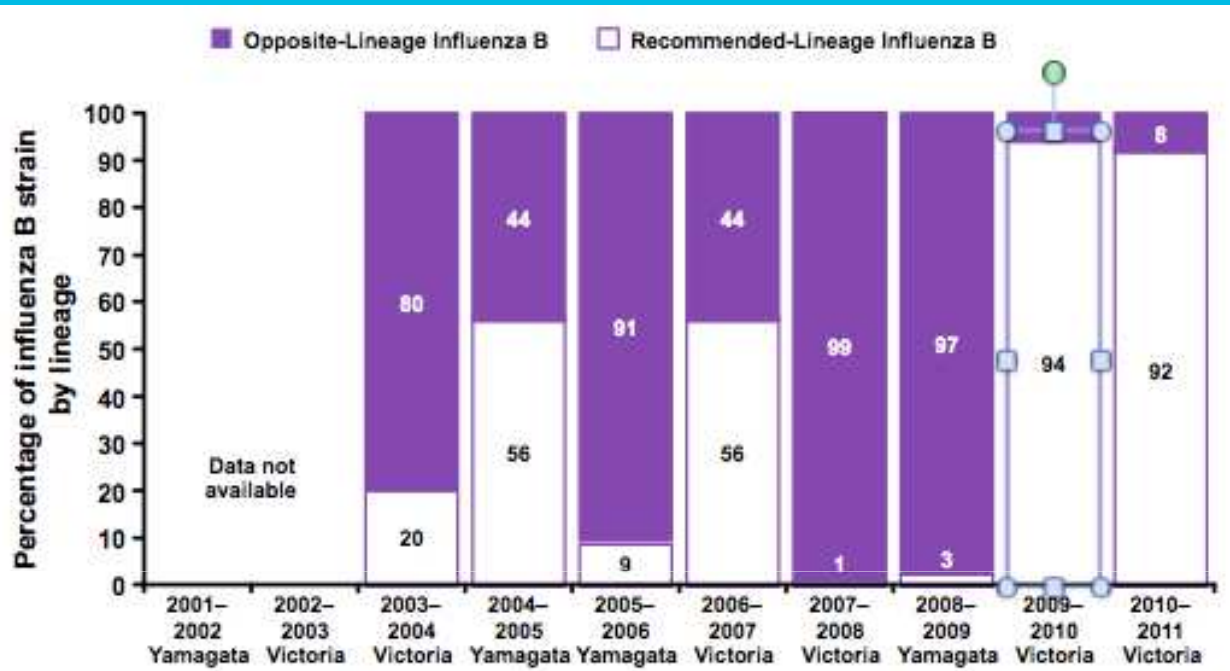
The rationale for quadrivalent vaccines



- Accuracy of selection for B strains has been very poor
- There are two strain lineages.
- Doubling the number of strains included increases the chance of obtaining a “correct” match

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How are influenza vaccines licensed each season?

- Although recommended now for children, each year vaccines are required to demonstrate achieving a 1:40 HAI titer or higher
  - This number is based upon old challenge trials which showed that a 1:40 titer protected **half** of challenged adults
  - Children are not tested each year
- Recent performance of a randomized trial in children allowed assessment of this correlate in children

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A/Brisbane/2007 (A/H3N2) HAI GMT
Subjects 6 to <72 Months of Age for Season 2008/09, Day 50 Results

	Adjuvanted TIV	TIV	Control
	N=311	N=313	N=153
GMT	746 (661–843)	92 (74–115)	12 (9.0–15.4)
Percent ≥1:40	98.7%	65.2%	20.9
Clinical Efficacy	89%	45%	–

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Vesikari T, *et al New Engl J Med* 2011;365:1406–1416

Antibody titer levels and associated protection rates in subjects 6 to <72 months of age for season 2008/09

Probability of Protection	H3N2 Antibody Titer Level
22%	1:40
50%	1:110
80%	1:330

Therefore, higher titers are needed in children to provide protection against influenza A

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Black S, *et al. Pediatr Infect Dis J* 2011;30:1081–1085

Potential benefits of adjuvanted influenza vaccine in children

- Increased immunogenicity against A strains versus TIV[1]
- Increased efficacy against clinical influenza in children[2]
- Broader protection against heterologous strains[1]
- Increased immunogenicity of B strains[1]
  - Currently available vaccines induce lower antibody titers against B strains versus A strains[1]
- Effectiveness against influenza B has not been documented

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1. Vesikari T, *et al. Pediatr Infect Dis J* 2009;28:563–571; 2. Vesikari T, *et al New Engl J Med* 2011;365:1406–1416

WHAT ABOUT NARCOLEPSY AND ADJUVANTED INFLUENZA VACCINES?

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What is narcolepsy?

- **Sleep disorder characterized by**
  - Excessive day time sleepiness
  - Cataplexy (not always) = loss of muscle tone triggered by emotion

- **Epidemiology**
  - Incidence below 1/100,000 PY
  - **Diagnosis usually often only after long lag time (5-10 years**) in adults
  - Age at onset peaks between 15-40 years of age

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What is narcolepsy?

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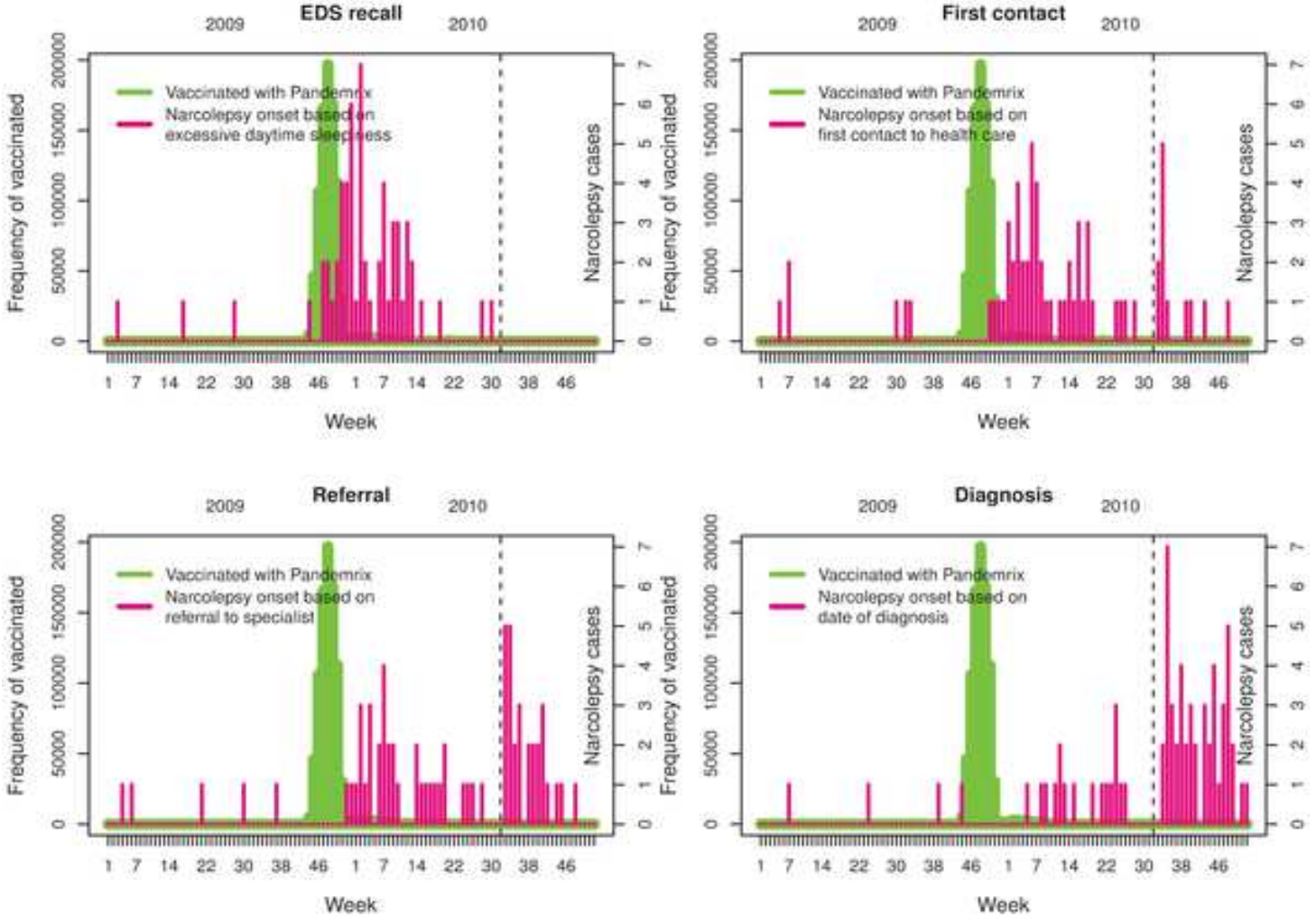
Figure 1. The temporal associations of pandemic vaccination, onset of narcolepsy (with four different definitions), and August 16, 2010, i.e. the date when the Swedish Medical Agency published the press release on the observation on the association between narcolepsy and Pandemrix vaccination (vertical dotted line).



Nohynek H, Jokinen J, Partinen M, Vaarala O, et al. (2012) AS03 Adjuvanted AH1N1 Vaccine Associated with an Abrupt Increase in the Incidence of Childhood Narcolepsy in Finland. PLoS ONE 7(3): e33536. doi:10.1371/journal.pone.0033536
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0033536

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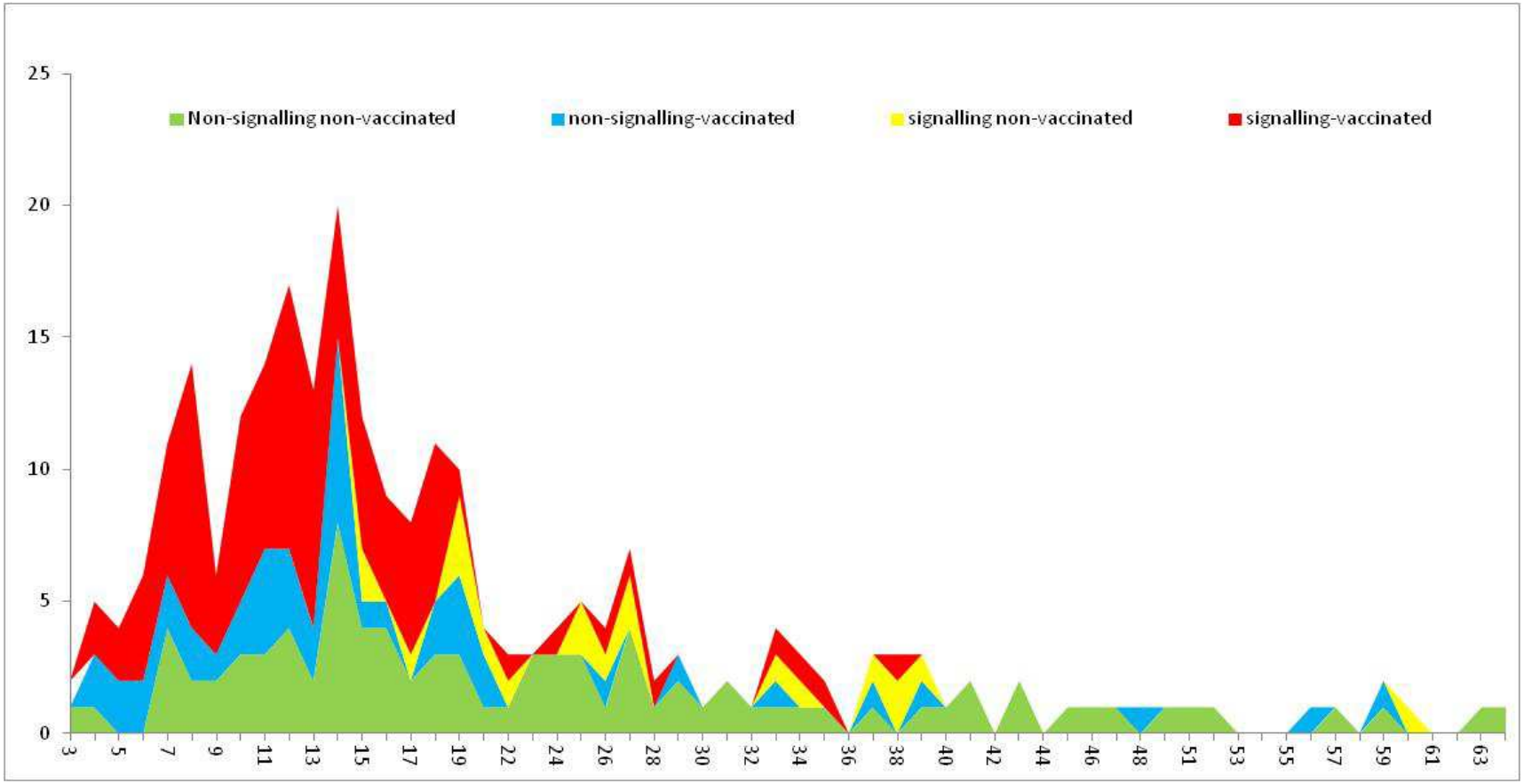
PLoS one

Age distribution of cases



Median age very young: 17 years

Also non- H1N1 vaccine exposed cases are young

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Narcolepsy Story Update

- There was an apparent increase in the risk of narcolepsy following AS03 adjuvanted 2009 pandemic H1N1 vaccine. Part of the apparent risk may be due to media attention and selective evaluation of vaccine cases.
- This has not been reported for MF-59 vaccine
- A multi country study SOMNIA is now ongoing in Latin America, Canada and Asia to further evaluate this.

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Vaccine Update: Conclusions

- New vaccines continue to become available to prevent disease in children and adults
  - Meningococcal B vaccine
  - Quadrivalent influenza vaccines
- Some newer vaccines may need rethinking
  - Acellular pertussis
- Other vaccines are on the horizon
  - Malaria
  - Norovirus
  - Dengue
  - Adjuvanted influenza vaccines

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