

Meningokok Hastalıkları ve MenACWY- TT Aşısı



Prof. Dr. Zafer Kurugöl



**61. Türkiye Milli Pediatri Kongresi
15-19 Kasım 2017, Antalya**

Bakteriyel Menenjit Etkenleri

Likely pathogens

<1 month

Group B streptococci, *Escherichia coli*, *Listeria monocytogenes* (neonatal pathogens)

1-3 months

No immunisation or one dose of primary immunisation

Neonatal pathogens, *S pneumoniae*, *N meningitidis*, Hib

3-6 months

No immunisation

S pneumoniae, *N meningitidis*, Hib

At least two doses of primary immunisation (with Hib-Omp vaccine)

S pneumoniae, *N meningitidis*

>7 months to 5 years

No immunisation

S pneumoniae, *N meningitidis*, Hib

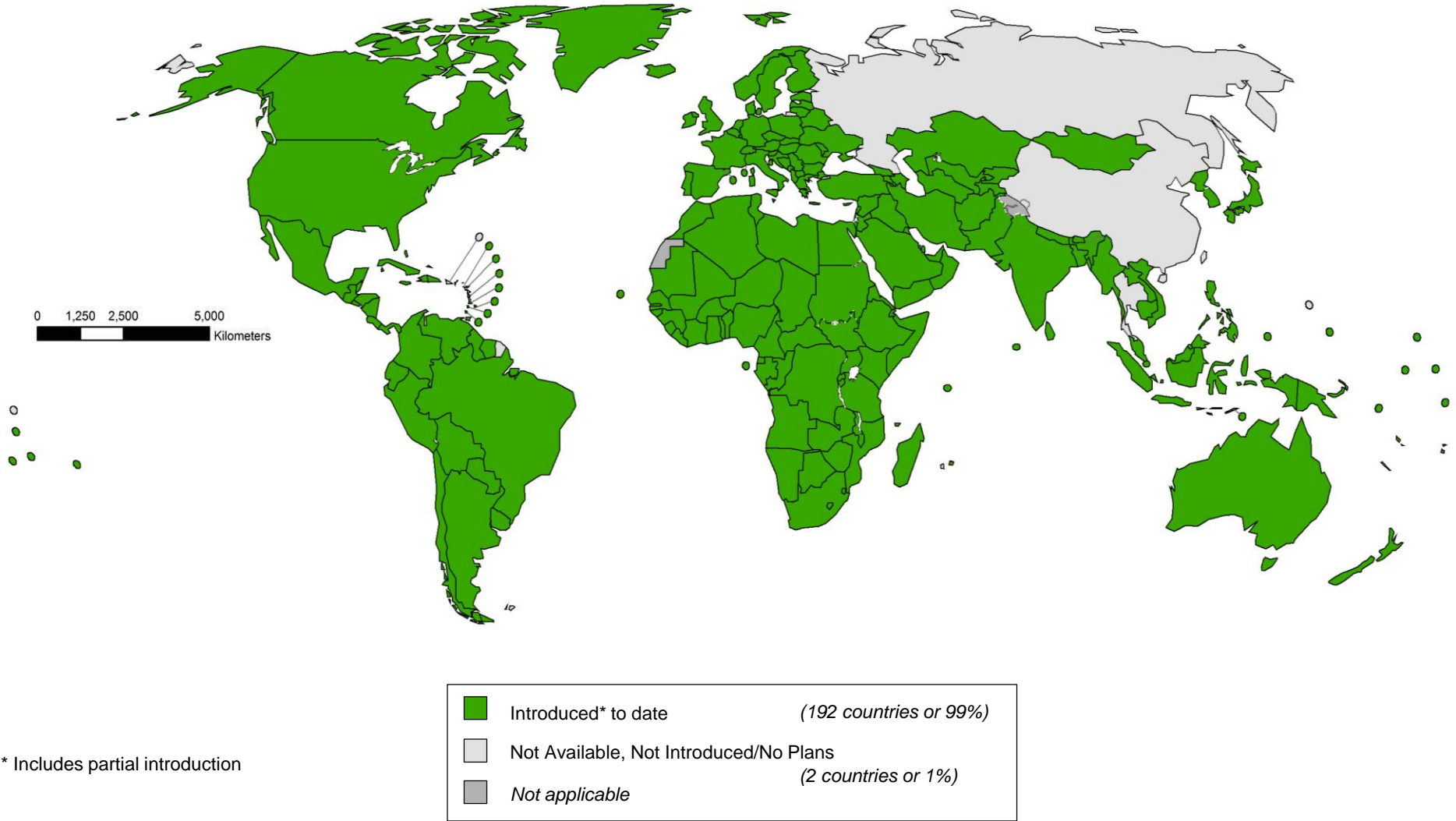
Primary immunisation completed

S pneumoniae (non-PCV serotypes), *N meningitidis*

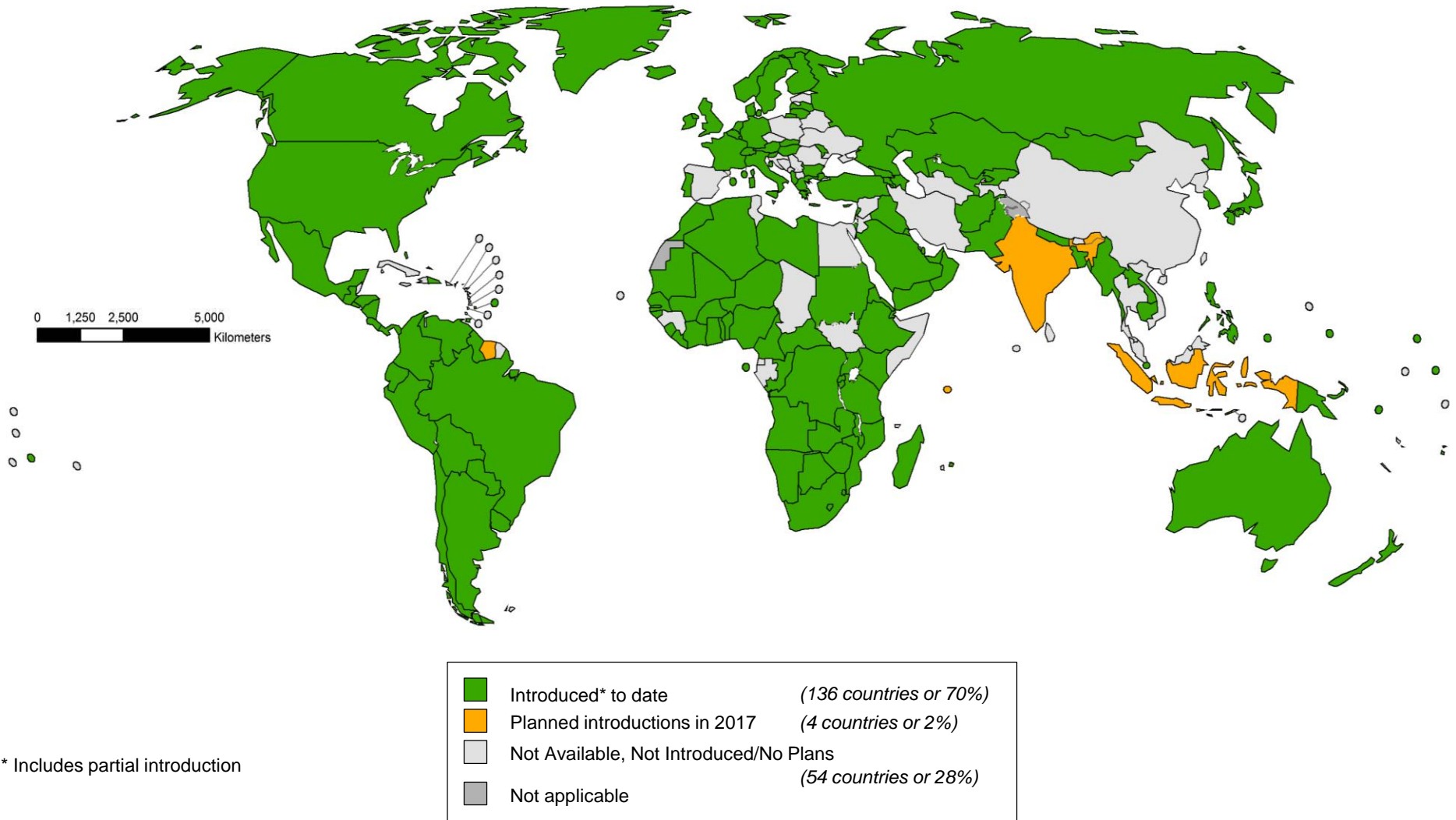
6-21 years

S pneumoniae, *N meningitidis*

Hib aşısını ulusal aşı şemasına ekleyen ülkeler (2017)



Konjuge Pnömokok aşısını aşı şemasına ekleyen ülkeler (2017)



Effect of vaccines on bacterial meningitis worldwide

Peter B McIntyre, Katherine L O'Brien, Brian Greenwood, Diederik van de Beek

Lancet 2012; 380: 1703–11

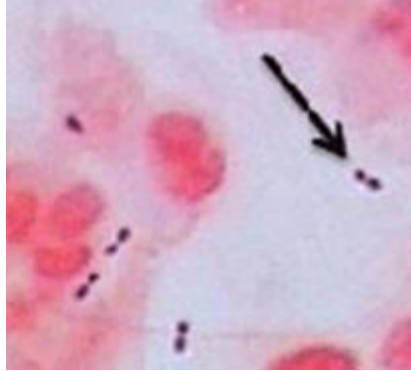
	<i>Haemophilus influenzae</i> type b ²²	<i>Streptococcus pneumoniae</i> ²¹	<i>Neisseria meningitidis</i> ^{12,23}
Cases			
Highest incidence region (Africa)	46 (31–52)	38 (11–48)	>100 (endemic)* >1000 (epidemic)*
Lowest incidence region (Europe)	16 (12–22)	6 (5–9)	1–2 (endemic)† 2–10 (epidemic)†
Deaths			
Highest mortality region (Africa)*	31 (20–35)	28 (7–36)	..
Lowest mortality region (Europe)†	4 (3–6)	3 (1–7)	..
Morbidity			
Proportion of survivors with major long-term sequelae ¹	9.5% (7.1–15.3)	24.7% (16.2–35.3)	7.2% (4.3–11.2)

Data are n per 100 000 population per year (95% CI) unless otherwise specified. Mean proportion of survivors with major long-term sequelae for all organisms combined in the highest incidence regions is 25% (95% CI 19–32), and in the lowest incidence regions is 9% (7–12).¹ *African meningitis belt. †Low incidence regions for invasive meningococcal disease—Europe, USA, and Australia.

Table 2: Estimates of global disease burden for meningitis attributable to *Haemophilus influenzae* type b, *Streptococcus pneumoniae* (children younger than 5 years), and *Neisseria meningitidis* (all ages), by organism and region

Neisseria meningitidis

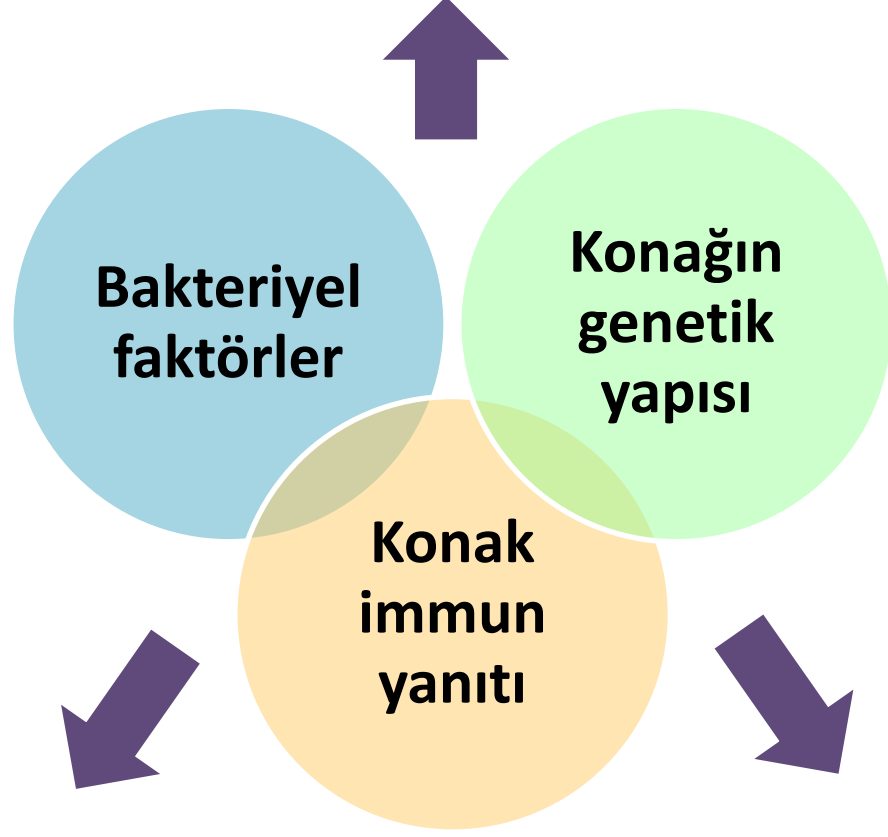
Gram-negatif
Aerobik
diplokok



Polisakkarid
kapsül

- Kapsüler antijenlere göre 12 serogrup
 - Klinik olarak 5 serogrup önemli (A, B, C, Y, W)
 - Serogrup X, Afrika'da küçük epidemiler
- Kapsüler antijenler uzun süreli immunolojik hafıza oluşturmazlar

Gizli bakteriyemi
Etkili immün yanıt



Menenjit ± Meningokoksemi
Kan-beyin bariyerini geçiş

Meningokoksemi
Vasküler hasar, DIK
Doku hasarı, şok

Etiology of Childhood Bacteremia and Timely Antibiotics Administration in the Emergency Department

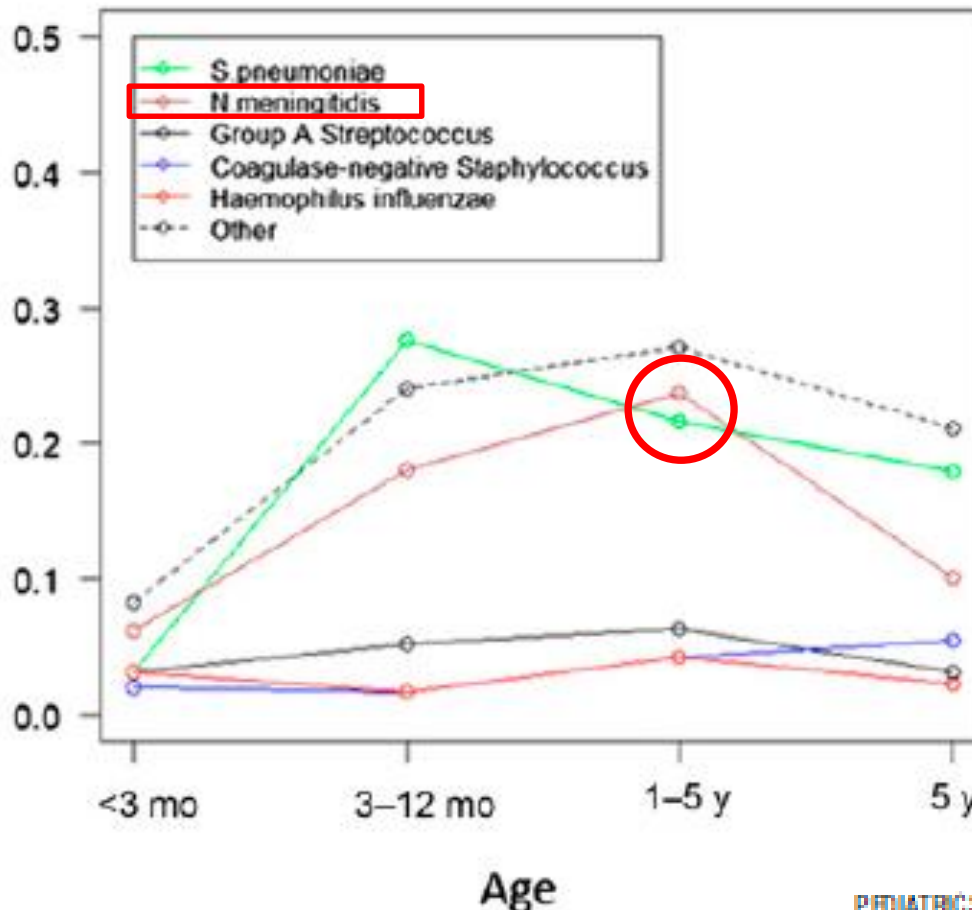
Adam D. Irwin, MRCPC^a, Richard J. Drew, MD FRCPATH^b, Philippa Marshall, MBChB^a, Kha Nguyen, MRCPC^a, Emily Hoyle, MBChB^a, Kate A. Macfarlane, MBChB^a, Hoying F. Wong, MBChB^a, Ellen Mekonnen, MBChB^a, Matthew Hicks, MBChB^a, Tom Steele, MBChB^a, Christine Gerrard, BSc^c, Fiona Hardiman, BSc^c, Paul S. McNamara, PhD FRCPCH^a, Peter J. Diggle, PhD^d, Eitan D. Carroll, MD FRCPCH^a

BACKGROUND: Bacteremia is not associated with significant mortality. Timely antibiotic administration is associated with improved outcomes.

METHODS: A retrospective study of children aged 0-5 years with bacteremia in the ED between 2001 and 2011. Susceptibility to common pathogens was recorded.

RESULTS: A total of 575 clinical isolates were identified. *S. pneumoniae* (n = 96) and *N. meningitidis* (n = 142) were the most common pathogens. The incidence of bacteremia was 1.42 per 1000 ED attendances (6.6%–14.5%) in vaccine-preventable infections. The pneumococcal bacteremia was significantly associated with ED attendances (P = .002). Susceptibility to common pathogens was 2.3–5.8%. Median time to antibiotic administration was 27–97 minutes longer in Group A Streptococcus.

CONCLUSIONS: Changes in the epidemiology of bacteremia are associated with changes in antibiotic treatment. Increasingly pediatric antibiotic resistance is associated with delayed antibiotic administration. Prompt, effective antimicrobial therapy is essential for improved outcomes. Continued etiological surveillance is essential.



Meningococcal pneumonia



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Pneumonia

Invasive meningococcal disease

ABSTRACT

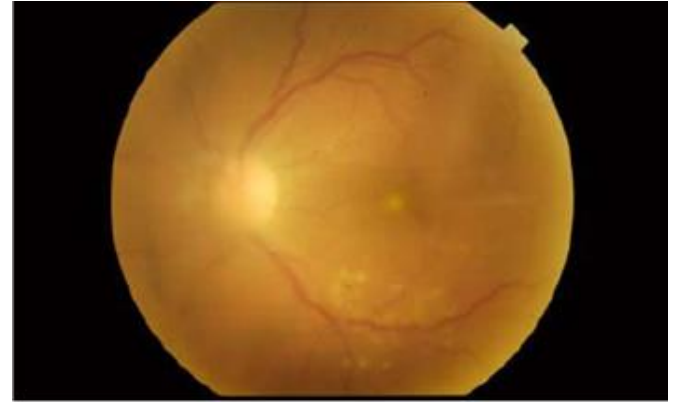
Neisseria meningitidis remains the most important cause of bacterial meningitis worldwide, particularly in children and young adults. The second most common and a potentially severe end-organ manifestation of invasive meningococcal disease (excluding systemic sepsis) is meningococcal pneumonia. It occurs in between 5% and 15% of all patients with invasive meningococcal disease and is thus the second most common non-systemic end-organ manifestation. To establish the diagnosis requires a high level of clinical awareness – the incidence is therefore very likely underreported and underestimated. This review of 344 meningococcal pneumonia cases reported in the Americas, Europe, Australia, and Asia between 1906 and 2015 presents risk factors, pathogenesis, clinical manifestations, diagnostic approaches, treatment, and prognosis of meningococcal pneumonia.

- Vakaların %5-15 pnömoni
- Özellikle >65 yaş, çocuklarda da görülebilir
- En sık Y, W
- Radyoloji diğer bakteriyel etkenlerle benzer

Meningokok hastalığı

Klinik bulgular

- Artirit
- Otitis media
- Epiglottit
- Perikardit
- Konjunktivit
- Endoftalmit
- Uretrit
- Postenfeksiyöz inflamatuvar sendrom
- Kronik meningokoksemi





Late Sequel of Meningococccemia: Skeletal Dysplasia

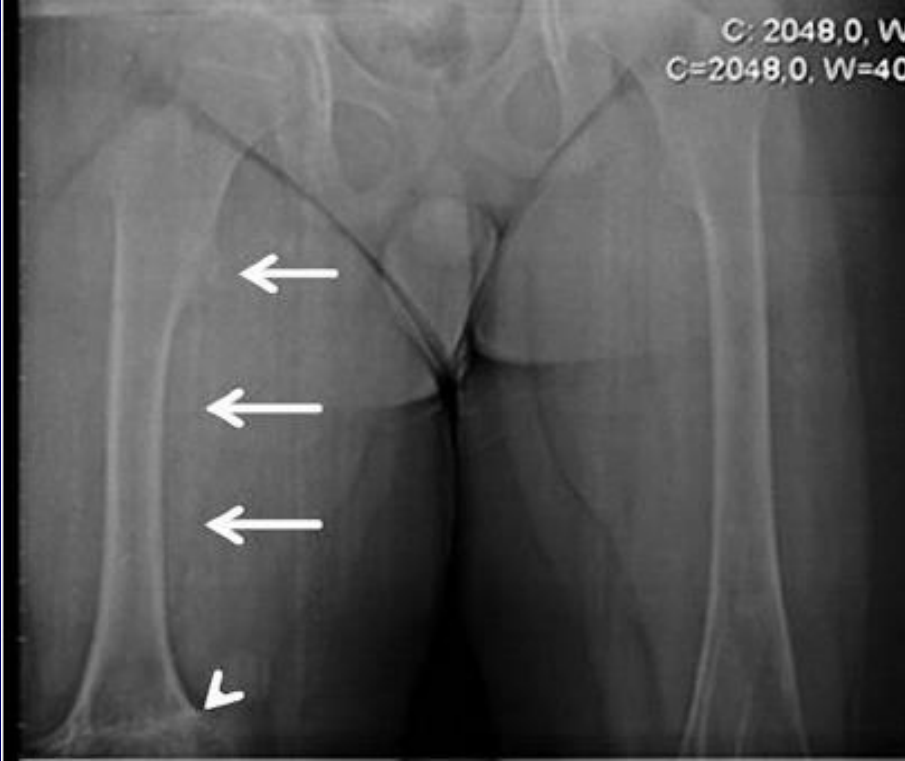


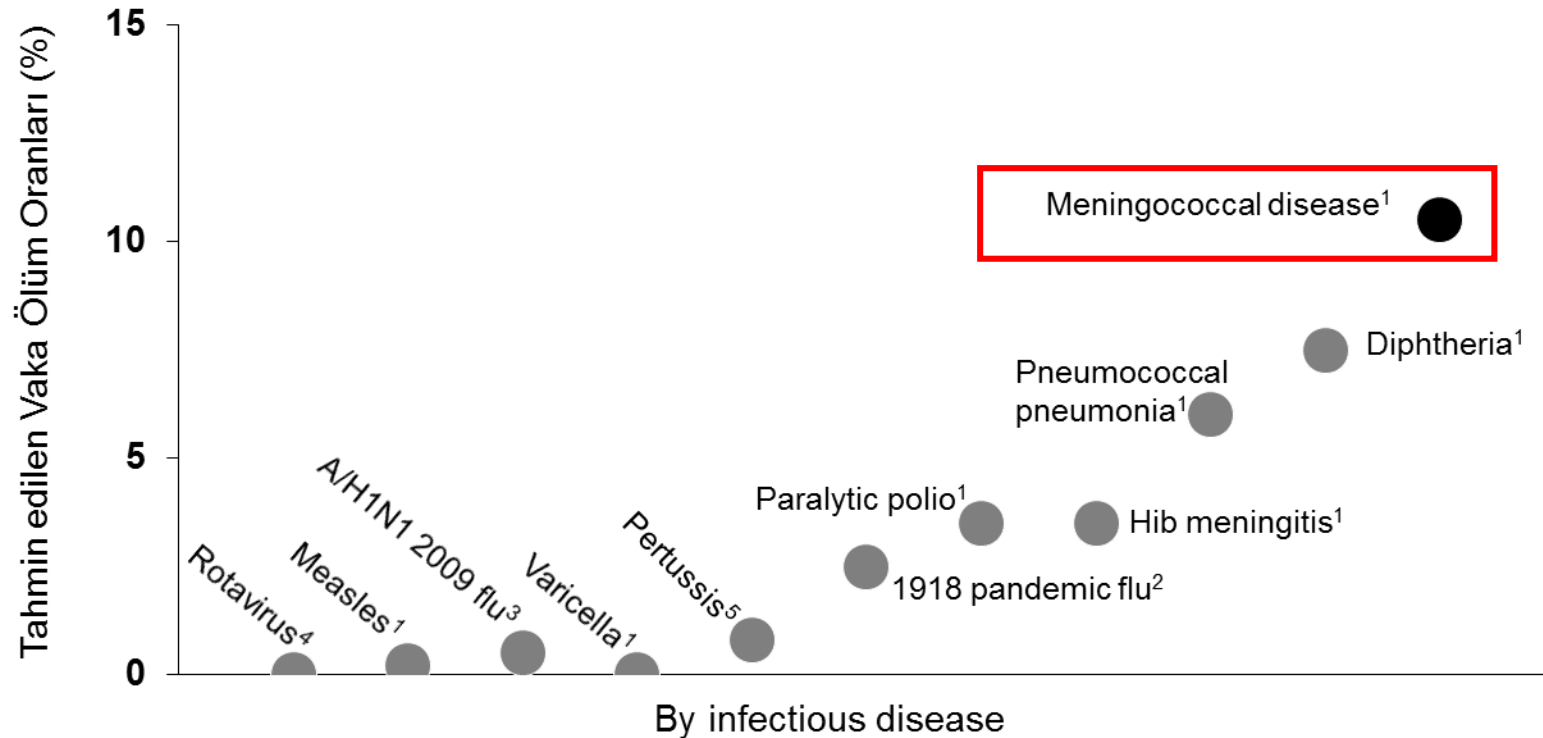
Figure 1. Limb length discrepancy and angulation of legs.

İnvaziv meningokok hastalığı (IMH)

1.200.000 vaka
135.000 ölüm

- Hızlı progresyon gösteren (meningokoksemi),
 - Tedavi nedene
 - En yaygın enfeksiyon
- Meningokokal menenjitte fatalite oranı %10-20,
 - meningokoksemi vakalarında %40

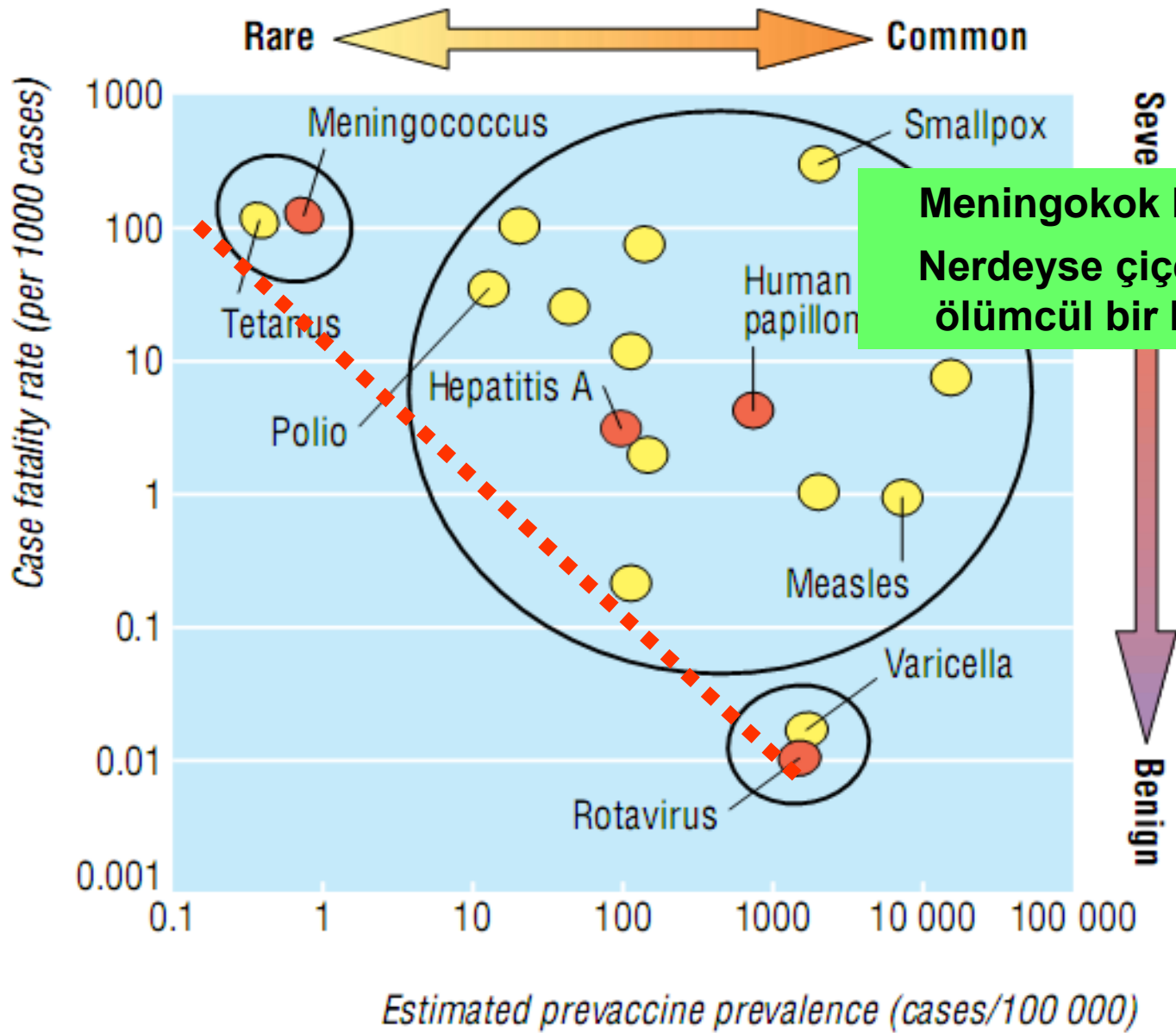
Vaka/Ölüm Oranları

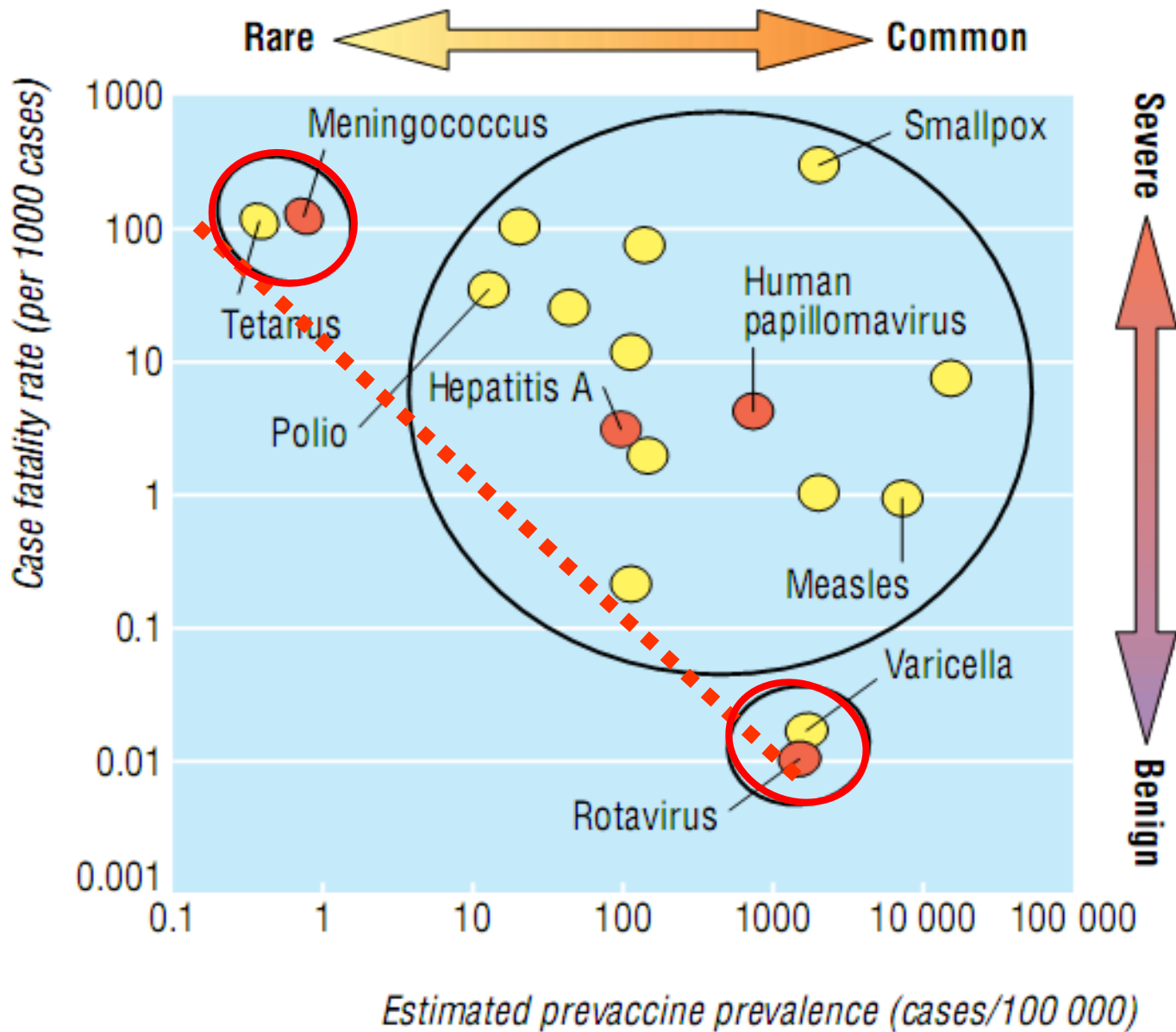


Notes: Meningococcal disease and Hib meningitis: despite appropriate antimicrobial therapy; paralytic polio: in children; 1918 pandemic flu: in young adults; varicella: in children and adolescents; A/H1N1 2009 flu: worldwide; measles: US, 1985–1992; rotavirus: US general population; pertussis: infants <6 months of age, US, 2001–2003.

Hib=*Haemophilus influenzae* type b.

1. Centers for Disease Control and Prevention (CDC). *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 12th ed. Atkinson W, et al, eds. Washington, DC: Public Health Foundation; 2012. <http://www.cdc.gov/vaccines/pubs/pinkbook/index.html#chapters>; 2. Taubenberger JK, et al. *Emerg Infect Dis*. 2006;12:15-22; 3. Pandemic H1N1 2009 Overview. CIDRAP website. http://www.cidrap.umn.edu/cidrap/content/influenza/swineflu/biofacts/h1n1_panview.html; 4. Gerba CP, et al. *Wat Res*. 1996;30:2929-2940; 5. Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep*. 2005;54:1283-1286.





SEKELLER

Long-term sequelae (any) %10-20

Hearing impairment

Hearing loss (any) 8 (7%)

Severe hearing loss 4 (3.5%)

Hearing aid 2 (1.7%)

Cochlear implant 1 (0.9%)

Neurologic, behavioral, developmental and motor impairment

Learning-academic difficulties (any) 26 (22.6%)

Behavioral and emotional problems 17 (14.8%)

Chronic headaches 16 (14%)

Neuro ... 4 (12.9%)

Çalışma yaptırıyorum aşı takvimine alacağız

Hürriyet Haber

03.08.2005 - 00:00 | Son Güncelleme : 03.08.2005 - 00:01

Makbule Başboğa'nın kollarının ve bacaklarının kesilmesine yol açan menenjit aşısının bulunmayışıyla ilgili olarak Hürriyet'in sorularını yanıtlayan Sağlık Bakanı Recep Akdağ, şunları söyledi:'Bu aşı plan dahilinde çocukluk çağı rutin aşılarının içine girecek. Biz

İnvaziv meningokok hastalığı (IMH)

- Semptomlar başlangıçta (ilk 12 saatte) nonspesifiktir →

0–12 saat
Nonspesifik

Ateş, baş ağrısı, bulantı,
kusma, ishal, nezle, kırıklık,
iştah azalması, irritabilite

İnvaziv meningokok hastalığı (IMH)

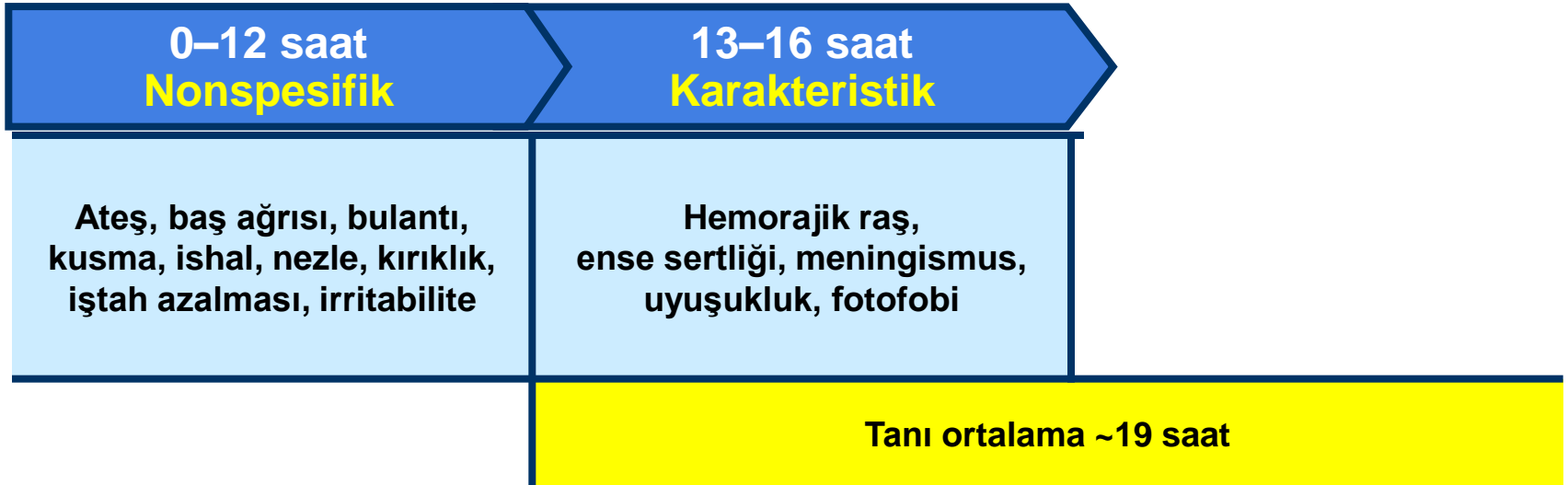
- Semptomlar başlangıçta (ilk 12 saatte) nonspesifiktir → yanlış tanı (ÜSYE, gastroenterit)

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İnvaziv meningokok hastalığı (IMH)

- Semptomlar başlangıçta (ilk 12 saatte) nonspesifiktir → yanlış tanı (ÜSYE, gastroenterit)
- Hızlı progresyon gösterir, 24 saat içinde ölüm

0–12 saat Nonspesifik	13–16 saat Karakteristik	16–~24 saat Geç
Ateş, baş ağrısı, bulantı, kusma, ishal, nezle, kırıklık, iştah azalması, irritabilite	Hemorajik raş, ense sertliği, meningismus, uyuşukluk, fotofobi	Konfüziyon veya deliryum, konvülsiyon, bilinç kaybı; ölüm
Tanı ortalama ~19 saat		

- Önceden sağlıklı bebek
- Saat 10.00 ⇒ Ateş, huzursuzluk
- Aile hekimi ⇒ ÜSYE
- Oral antibiyotik (am-Klavunat)
- Saat 15.00 ⇒ Konvülsiyon,
vücutta döküntü (kol ve gövdede
birkaç adet)

- Önceden sağlıklı bebek
- Saat 10.00 ⇒ Ateş, huzursuzluk
- Aile hekimi ⇒ ÜSYE
- Oral antibiyotik (am-Klavunat)
- Saat 15.00 ⇒ Konvülsiyon, vücutta döküntü (kol ve gövdede birkaç adet)
- Saat 16.00 ⇒ Ege Üniversitesi Çocuk Acil başvurusu



- Önceden sağlıklı bebek
- Saat 10.00 ⇒ Ateş, huzursuzluk
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- Saat 17.00 ⇒ Exitus



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- Saat 16.00 ⇒ Ege Üniversitesi Çocuk Acil başvurusu
- Saat 17.00 ⇒ Exitus
- Kan Kültürü ⇒ N. Meningitidis
- PCR ⇒ Seroprup W



Purpura fulminans in a child due to *Neisseria meningitidis*

H. Özdemir · T. Kendirli · E. Çiftçi ·
E. İnce



Fig. 1 Petechiae on the chest and quickly replaced bullous and purpuric lesions



Fig. 2 Purpura fulminans (PF) and necrosis all over the body

4. saatte

was positive for *Neisseria meningitidis*. Despite the appropriate medical and supportive treatment, disseminated vascular coagulation (DIC) and multi-organ failure developed and the patient died during the 58th h of hospitalization.

24. saatte



Kanuni SS Has Başvuruda



Okmeydanı Hastanesi birkaç saat sonra



İngiltere


- **2015 Temmuz-2016 Ocak**
- **15-19 yaş grubunda GIS bulguları ile başvuran 103 vaka**
- **%64 olguda yalnızca karın ağrısı**
- **%23 olguda gastroenterit (%11 sadece ishal)**
- **8 olguda apandisit, 8 olguda peritonit**
- **%19 olguda abdominal cerrahi**
- **İlk 24 saat içinde ölümler**



İngiltere

- 2015 Temmuz-2016 Ocak
- 15-19 yaş grubunda GIS bulguları ile başvuran 103 vaka
- %64 olguda yalnızca karın ağrısı
- %23 olguda gastroenterit (%11 sadece ishal)
- İlk 24 saat içinde ölümler
- Yüksek fatalite ile seyreden
- Hipervirulan ST-11 serogrup W suşu

İnvaziv hastalık risk faktörleri

Yaş	Konağa ait	Sosyal faktörler	Nazofaringeal irritasyon
✓İnfant ✓Ergen	✓(✓(bo ✓F ✓(TL ✓(<p>PEDIATRICS[®] OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS</p> <p>An underlying condition was present in only 9 (5.6%) patients (complement deficiency detected as a result of the meningococcal infection [2], sickle cell dis-</p>	
	✓/meöy	Sheld B. Ha	sha llen
		patient (19 years of age) received the meningococcal polysaccharide vaccine 1.5 years before onset of this infection (serogroup B). Three secondary cases of meningococcal disease were identified in the daughter of a baby-sitter, a household contact, and a patient in close proximity in the ICU.	

Previous pathology in cases of invasive meningococcal disease in children under 5 years old

Raquel Abad ^a, Rosa Cano ^b, Israel John Thuissard ^c, Julio A. Vázquez ^a.   

- **İspanya**
- **5 yaşından küçük 1255 IMH vakası**
 - **1209 hastada (%96.5) altta yatan hastalık bulunmadığı,**
 - **Sadece 46 (%3.5) hastada altta yatan hastalık saptanmış.**

Previous pathology in cases of invasive meningococcal disease in children under 5 years old

Raquel Abad ^a, Rosa Cano ^b, Israel John Thuissard ^c, Julio A. Vázquez ^{a,d}.✉.✉

- **46 hastada altta yatan hastalık saptanmış.**

- Hematolojik malignitesi hasta : 0

**SADECE RİSK GRUBUNUN
AŞILANMASI DURUMUNDA
1255 VAKANIN YALNIZCA
BİRİNDE KORUNMA
SAĞLANACAKTIR.**

- SSS patolojileri, kafa fraktürü: 3 hasta
- Minör konjenital anomaliler: 34 hasta

İnvaziv hastalık risk faktörleri



Table 1. Statistically significant risk factors for invasive meningococcal disease (univariate analysis).

Variables	Cases (%)	Controls (%)	p-value*
Immigrant	18/44 (40.9%)	20/84 (23.8%)	0.044
Monitoring child's health by the same pediatrician	29/42 (69%)	72/84 (85.7%)	0.027
Father smoker	30/42 (71.4%)	36/82 (43.9%)	0.004
Number of cigarrets per day (fathers)			
(≥20)	26/42 (61.9%)	30/82 (36.6%)	0.004**
(1–19)	4/42 (9.5%)	6/82 (7.3%)	
Density: number of people/ house dimensions (100 m ²) median value (IQR)	5.3 (4.0–6.7)	4.2 (3.2–5.6)	0.019***
Density: ≥ 4.4 (number of people per 100 m ² house)	25/37 (67.6%)	33/73 (45.2%)	0.026
Contact with cases of IMD	4/41(9.8%)	0/84 (0%)	0.010
History of viral respiratory infection	22/43 (51.2%)	27/84 (32.1%)	0.037
Sore throat	8/43 (18.6%)	4/84 (4.8%)	0.021
Church attendance	12/43 (27.9%)	40/82 (48.8%)	0.024
Relocation or vacation during the previous month	10/43 (23.3%)	6/83 (7.2%)	0.010

*Chi-square test or Fisher's exact test

** Chi-square test for trend

***Mann-Whitney test.

Hadjichristodoulou C, et al. PLoS One. 2016;11(6):e0158524.

REVIEW ARTICLE

Risk factors for community-acquired bacterial meningitis

Lene Fogt Lundbo & Thomas Benfield

Table 1. Summary of risk of bacterial meningitis in all age groups.

Pathogen	Age groups with highest rates of colonization	Ages groups with highest rates of invasive disease	Site of entry	Most important risk factors
<i>Streptococcus pneumoniae</i>	The youngest children	The elderly and young children	Nasopharynx, through skull fracture or from contiguous or distant foci of infection	Crowding, smoking , splenectomy, HIV infection, B-cell dysfunction, complement deficiencies, hematological cancer, cochlear implants
<i>Neisseria meningitidis</i>	Older children, adolescents and young adults	Infants, adolescents/young adults and the elderly >65	Nasopharynx or blood. Possibly via n. Olfactorius	Crowding, smoking , late complement deficiency, complement inhibitor treatment, asplenia, HIV infection
<i>Haemophilus influenzae</i>	Unvaccinated individuals	Adults; infants and children if not vaccinated	Nasopharynx, contiguous spread from local infection	Crowding, smoking , HIV infection, splenectomy, diminished humoral immunity

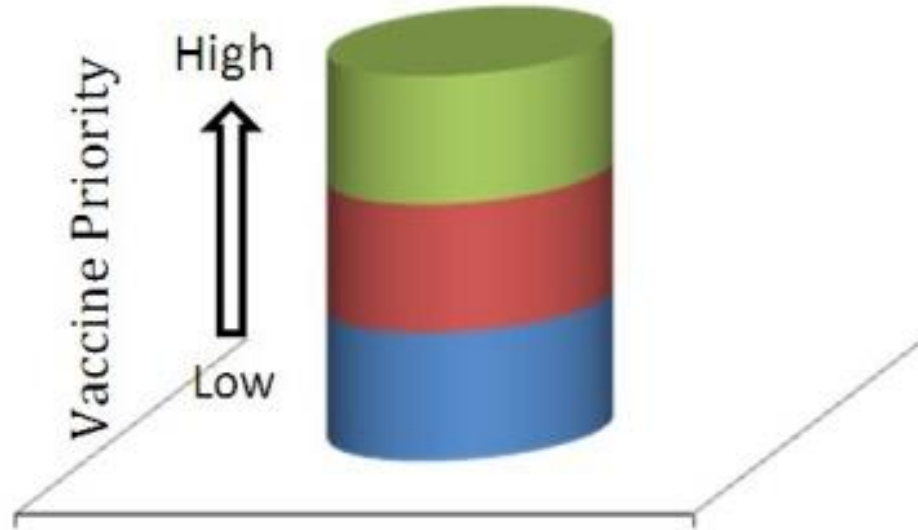
İnvaziv hastalık risk faktörleri

Yaş	Konağa ait	Sosyal faktörler	Nazofaringeal irritasyon
✓İnfant ✓Ergen	✓C5-C9 kompleman defekti ✓Opsonizasyon ve fagositoz bozuklukları ✓Properdin eksikliği ✓Genetik polimorfizm (MBL, TLR4 gen) ✓Splenektomi veya fonk aspleni ✓Hipogamaglobulinemi ✓HIV ✓Ailede daha önce geçirilmiş meningokokal enfeksiyon öyküsü ✓ Astım ya da akciğer enfeksiyonu nedeniyle hospitalizasyon öyküsü ✓ Eculizumab kullanımı ✓ Prematüre doğum	✓ Hac ziyaretinde bulunma ✓ Toplu yaşam (yurt, askeri birlik) ✓ Fakirlik ✓ Küçük-kalabalık yerlerde yaşam ✓ Sağlık çalışması olma ✓ Endemik bölgeye seyahat ✓ Aşırı alkol tüketimi	✓ Sigara ✓ Solunum yolu enfeksiyonları

IMH- Epidemiyoloji

- **İnvaziv meningokok hastalığı epidemiyolojisi (insidansı, yaş dağılımı, serogrup dağılımı) ülkeden ülkeye değiştiği gibi zaman içinde de önemli değişiklikler gösterir.**

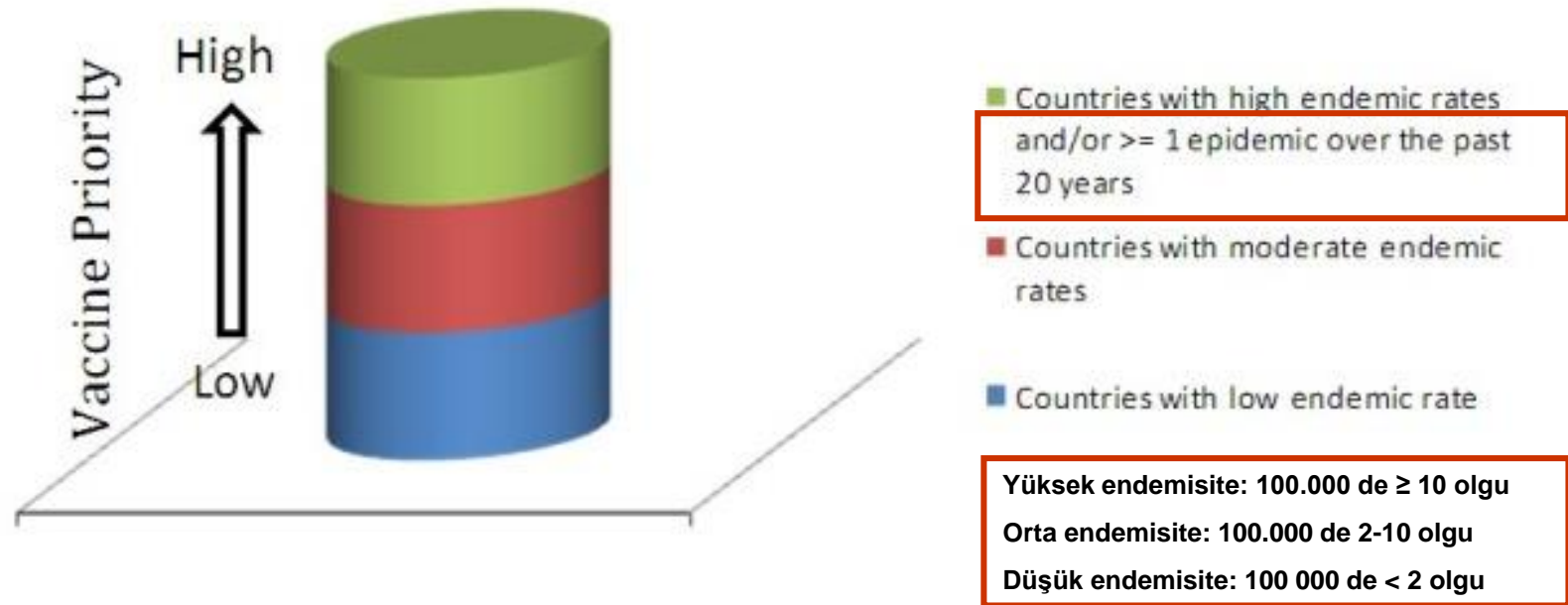
IMH- Epidemiyoloji



Yüksek endemisine: 100.000 de ≥ 10 olgu
Orta endemisine: 100.000 de 2-10 olgu
Düşük endemisine: 100 000 de < 2 olgu

A categorization of countries according to IMD attack rates.

IMH- Epidemiyoloji



A categorization of countries according to IMD attack rates.

Table 2. Organizations with population size $\geq 5,000$ persons

1 case	<ul style="list-style-type: none"> • Serogrouping of isolate or clinical specimen performed • Isolate typed or stored for future molecular typing, or sent to CDC, but not discarded • Case investigation • Chemoprophylaxis of close contacts
2 cases in 6 months	Same response as after 1 case with the following additions:

[CDC](#) > [Meningococcal Home](#)

Meningococcal Outbreaks



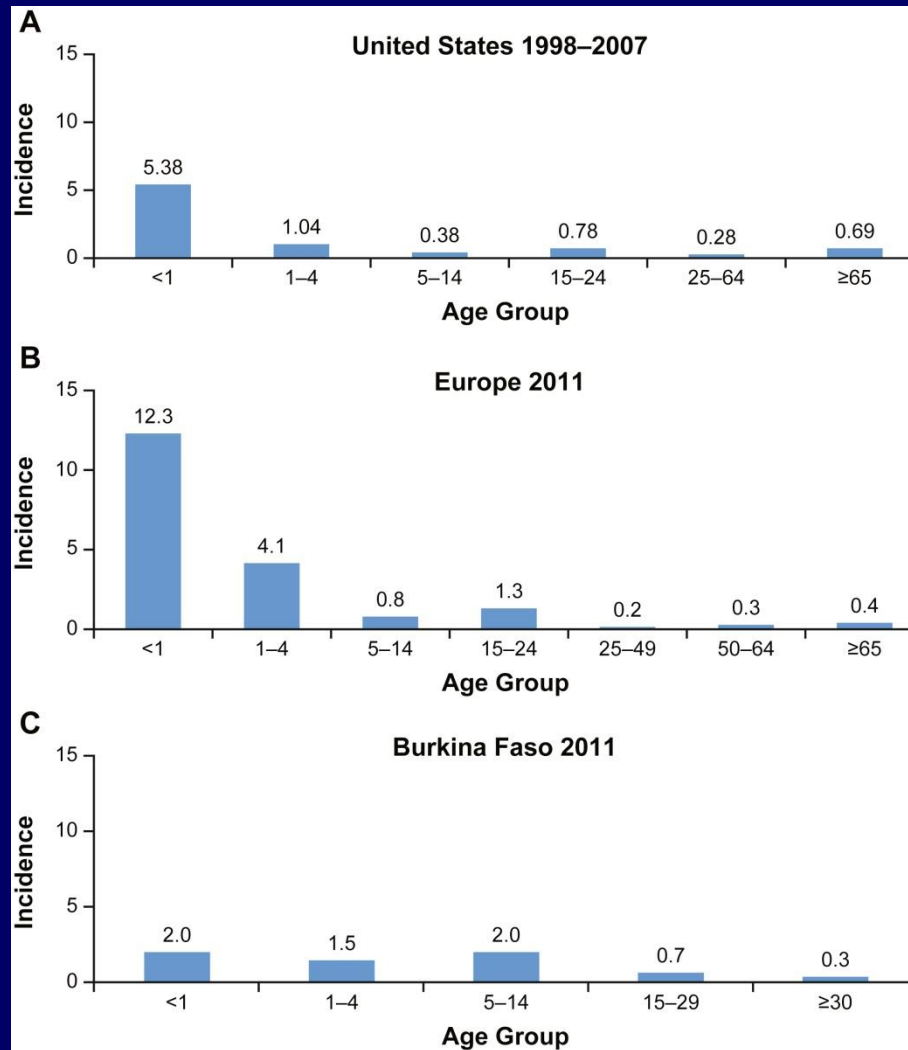
Outbreak Definition

An outbreak occurs when multiple cases of the same serogroup (types) happen in a population over a short time period. Outbreaks can occur in communities, schools, colleges, prisons, and other populations. Depending on the population size and specific circumstances, [health officials may declare an outbreak after just two cases.](#)

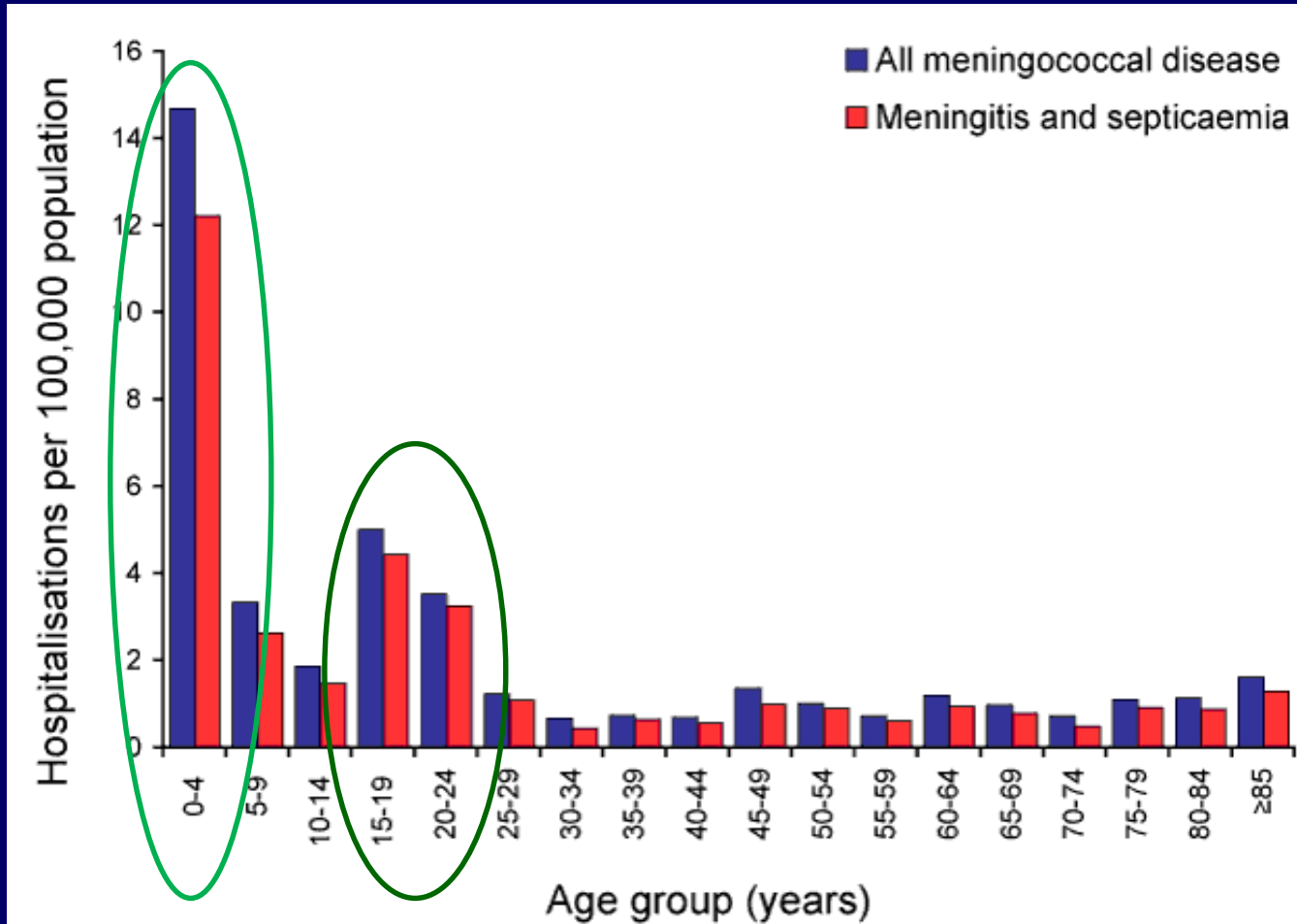
- If all cases have serogroup B disease and available information supports use of MenB vaccine, consult CDC regarding the use of MenB vaccine using a CDC-sponsored expanded access IND

An outbreak is defined as a chain of transmission including 2 or more cases linked in time and space.

IMH yaş dağılımı

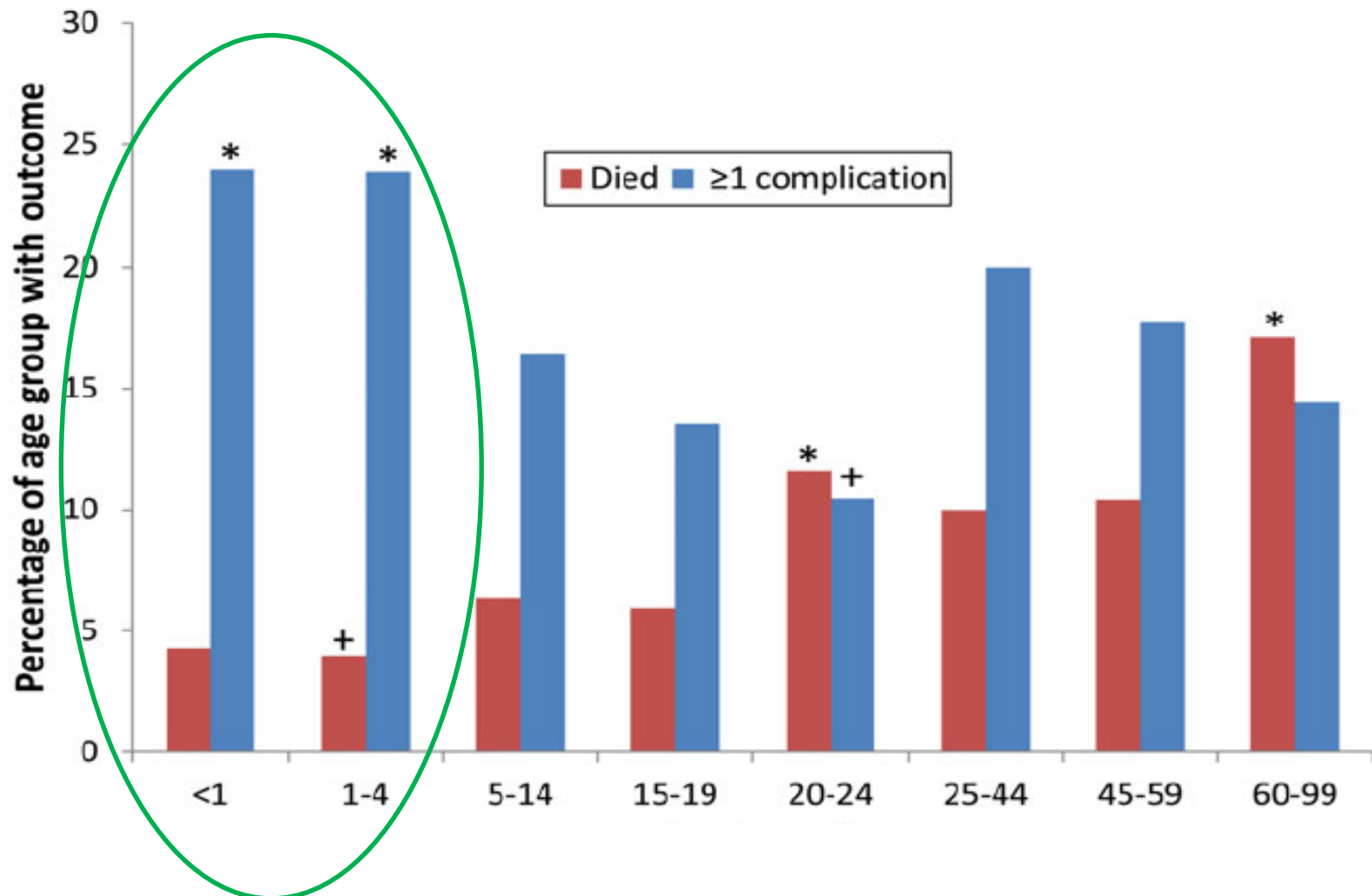


IMH yaş dağılımı, ABD



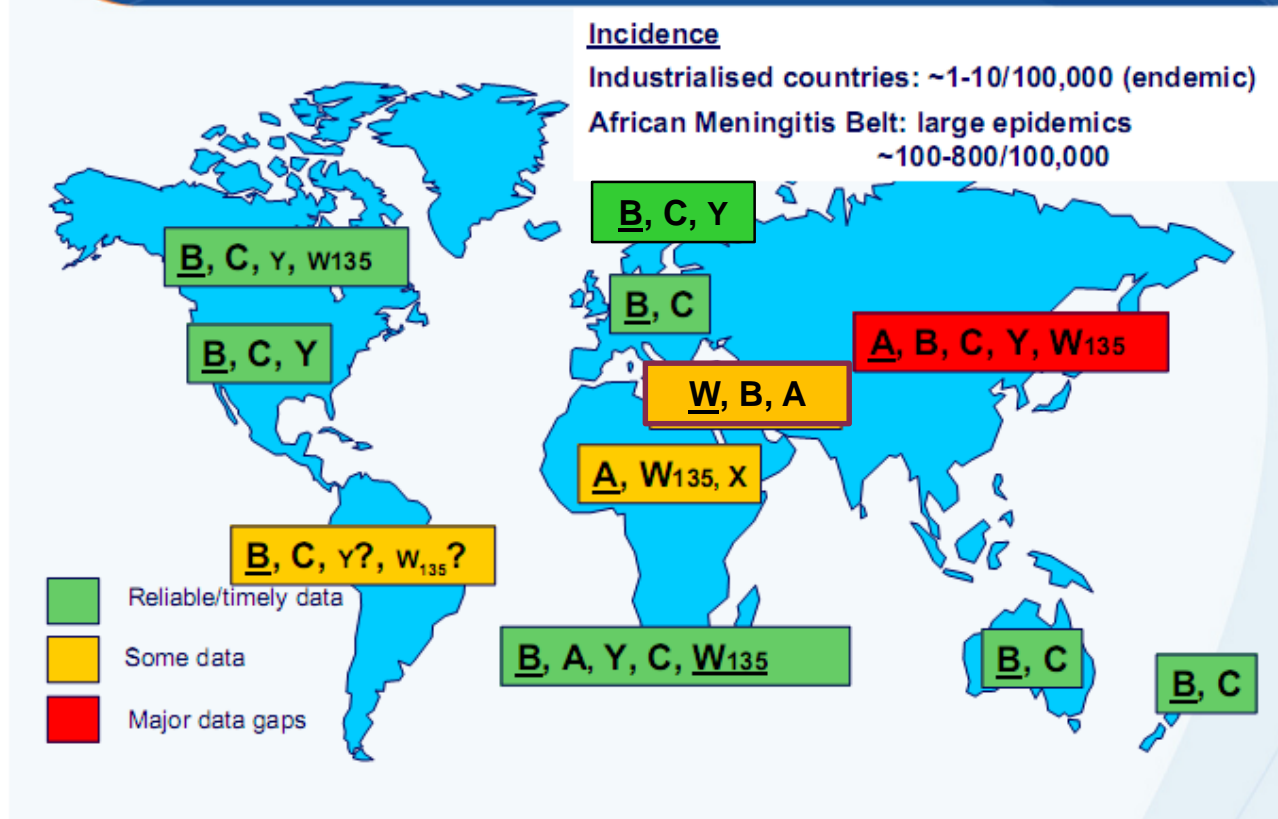
Source: Unpublished data, Active Bacterial Core surveillance (ABCs) system.

IMH Ölüm, Komplikasyon



IMH serogrup dağılımı

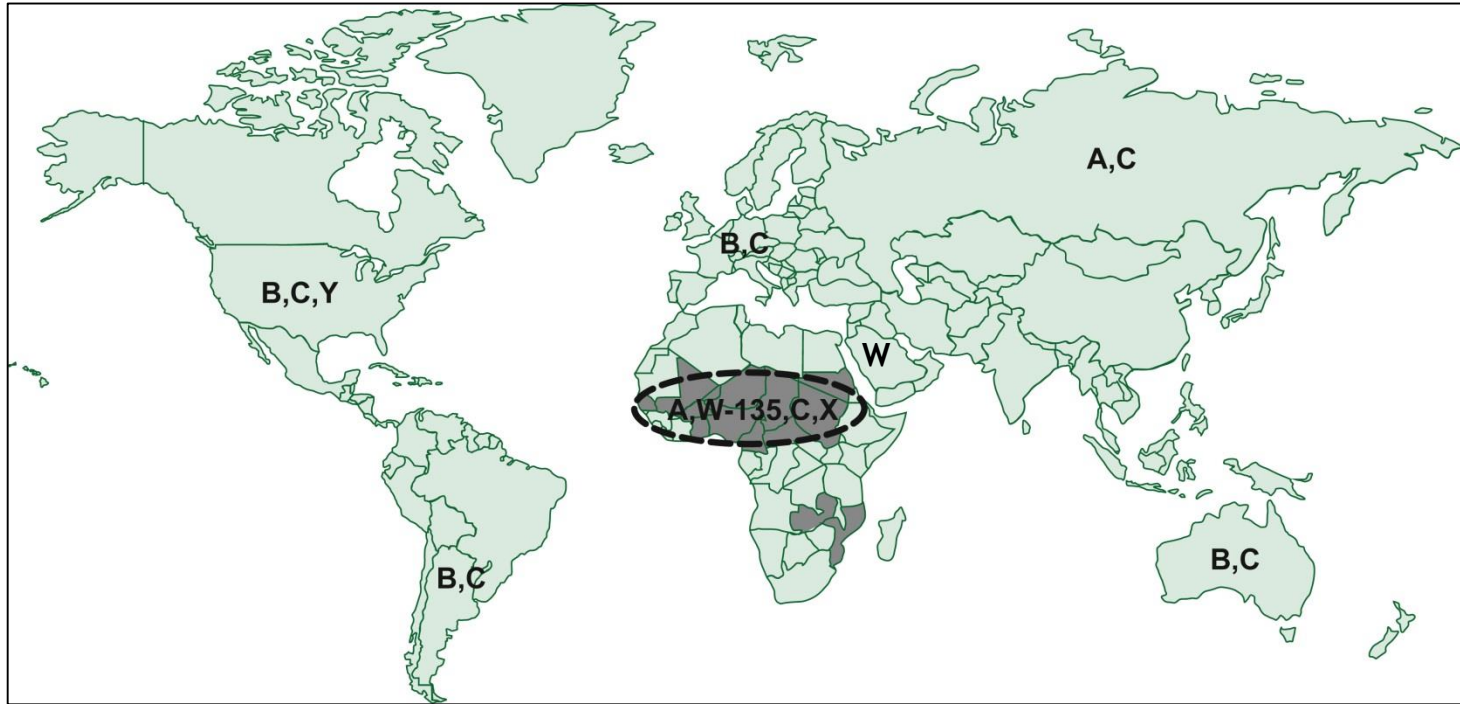
İnvazif meningokok hastalığı serogrup dağılımı



IMH serogrup dağılımı

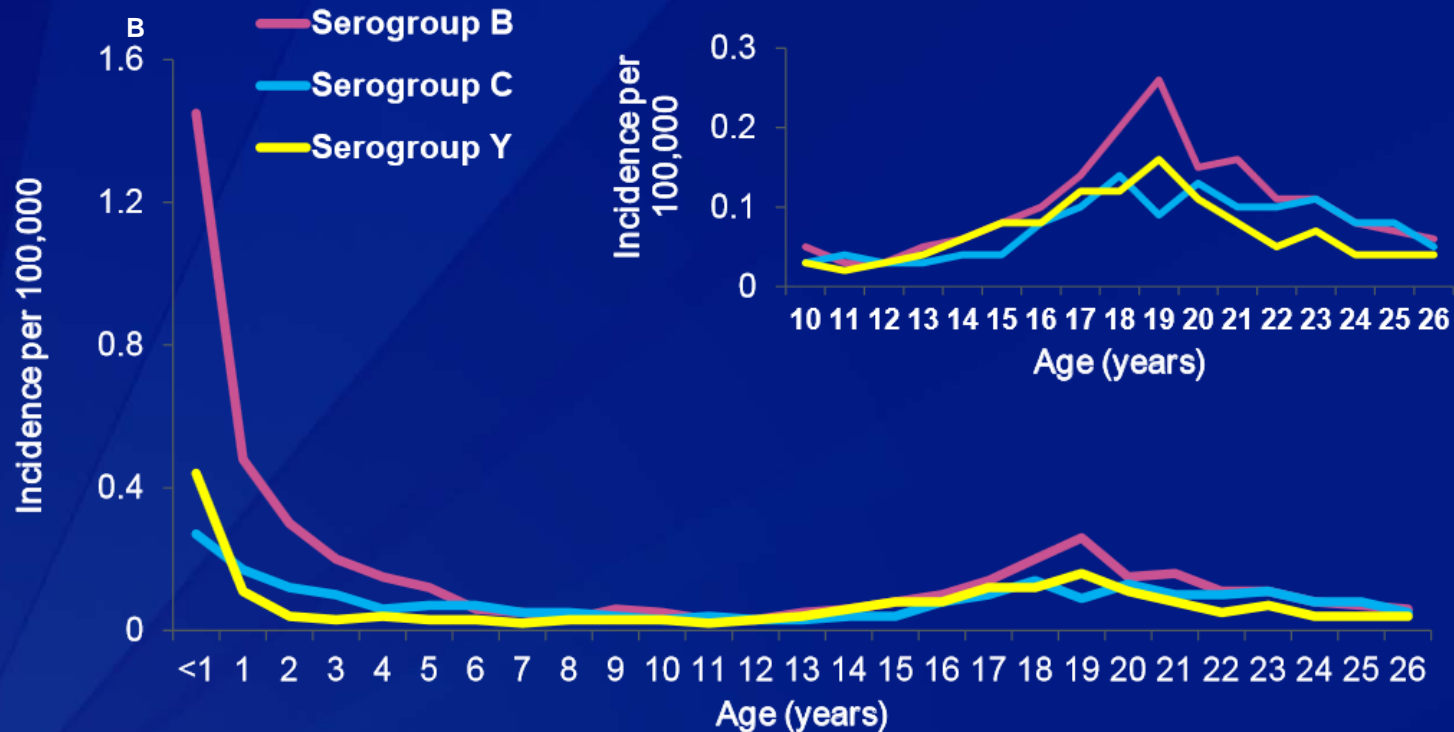


İnvazif meningokok hastalığı serogrup dağılımı



Serogrup dağılımı (ABD)

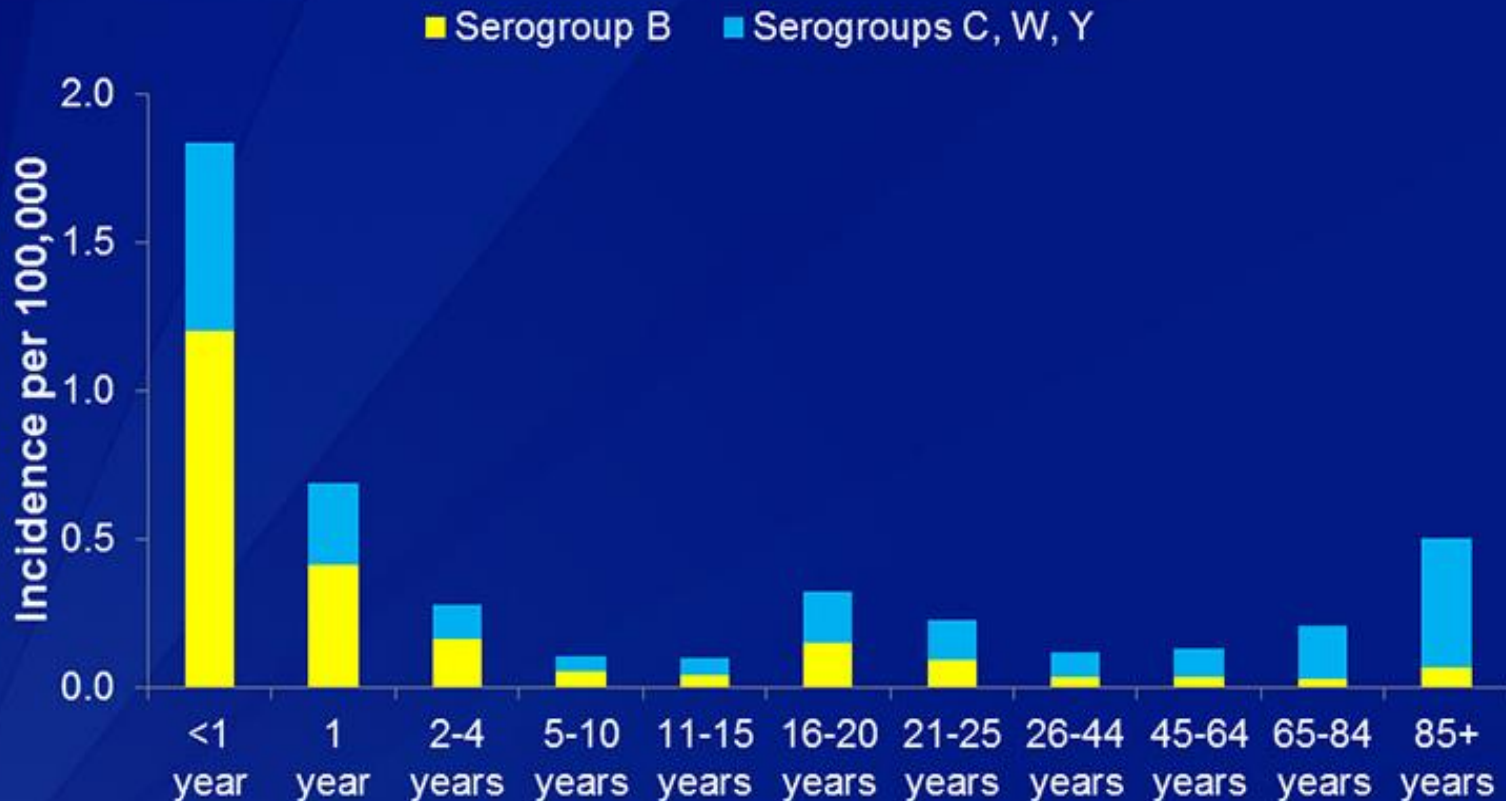
Incidence of Meningococcal Disease by Age and Serogroup, United States, 2005-2012*



*Source: National Notifiable Diseases Surveillance System (NNDSS) with additional serogroup data provided by state and local health departments

Serogrup dağılımı (ABD)

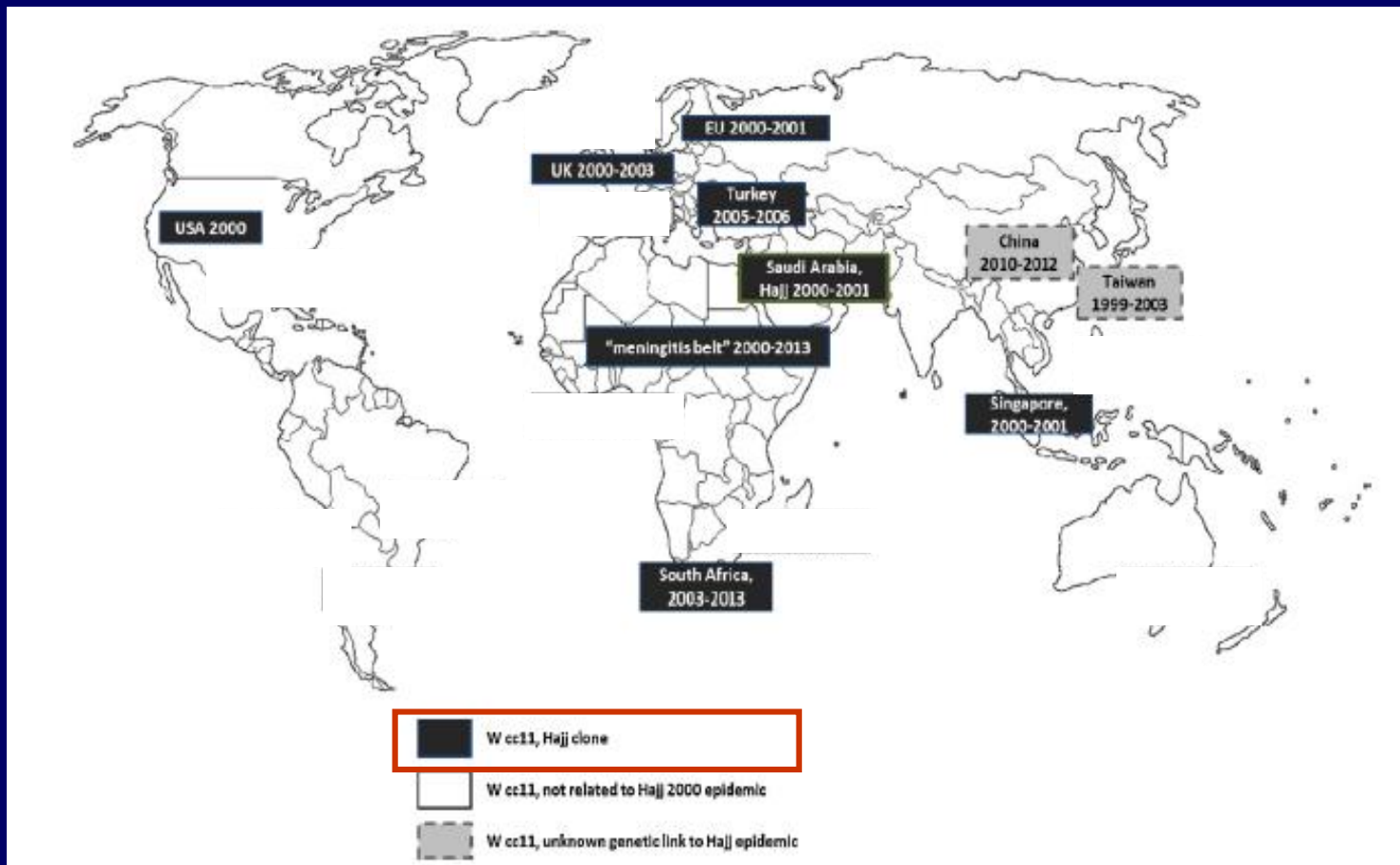
Meningococcal Incidence by Serogroup and Age-Group, 2006-2015



SOURCE: CDC; National Notifiable Diseases Surveillance System with additional serogroup data from Active Bacterial Core surveillance and state health departments.

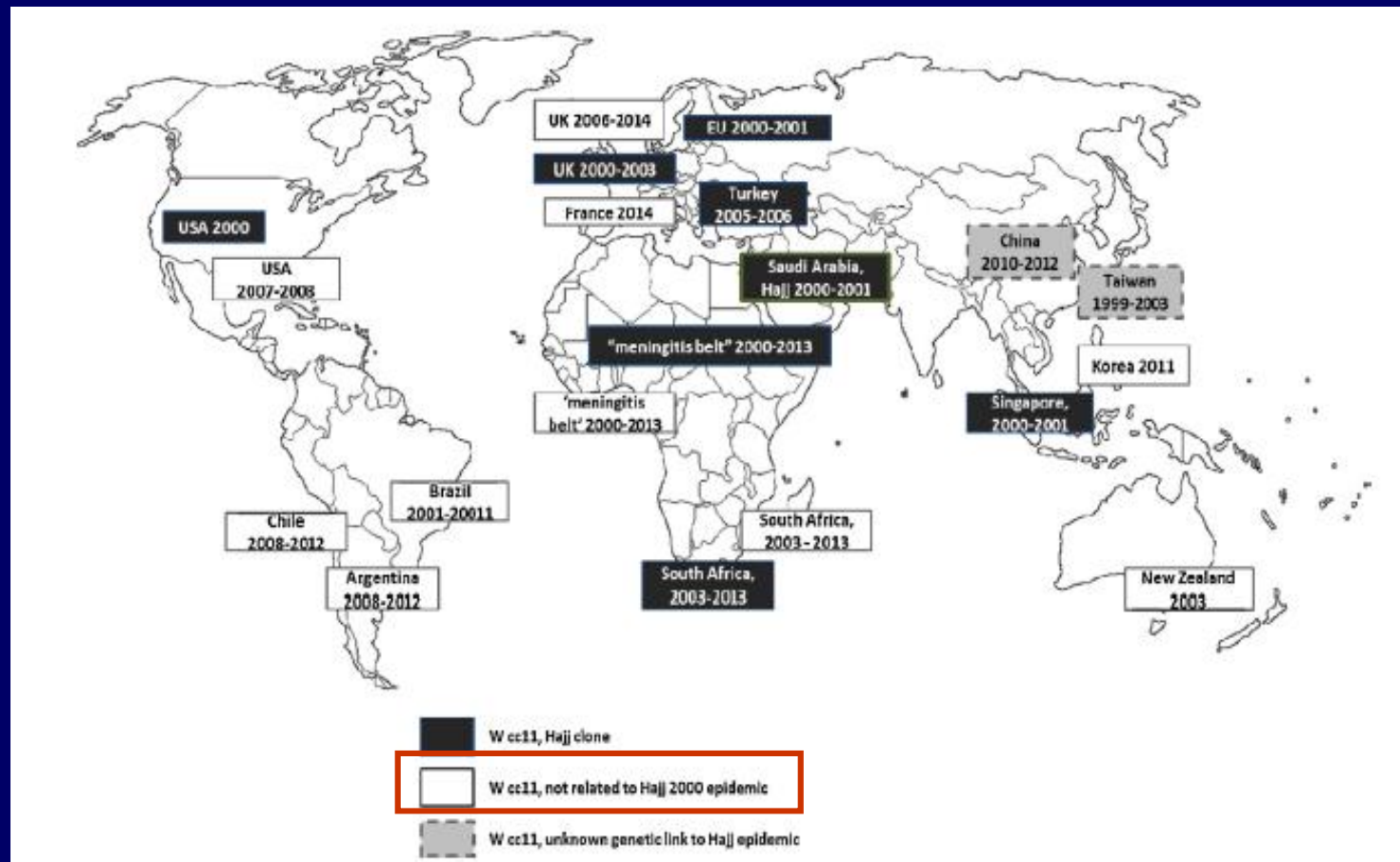
W salgınları





Global epidemiology of capsular group W meningococcal disease (1970–2015): Multifocal emergence and persistence of hypervirulent sequence type (ST)-11 clonal complex

Mustapha M. Mustapha, Jane W. Marsh, Lee H. Harrison*



FIGURE

Phylogenetic network of group W/clonal complex (cc)11 isolates, France, 2015–2016 (n=47)

RAPID COMMUNI

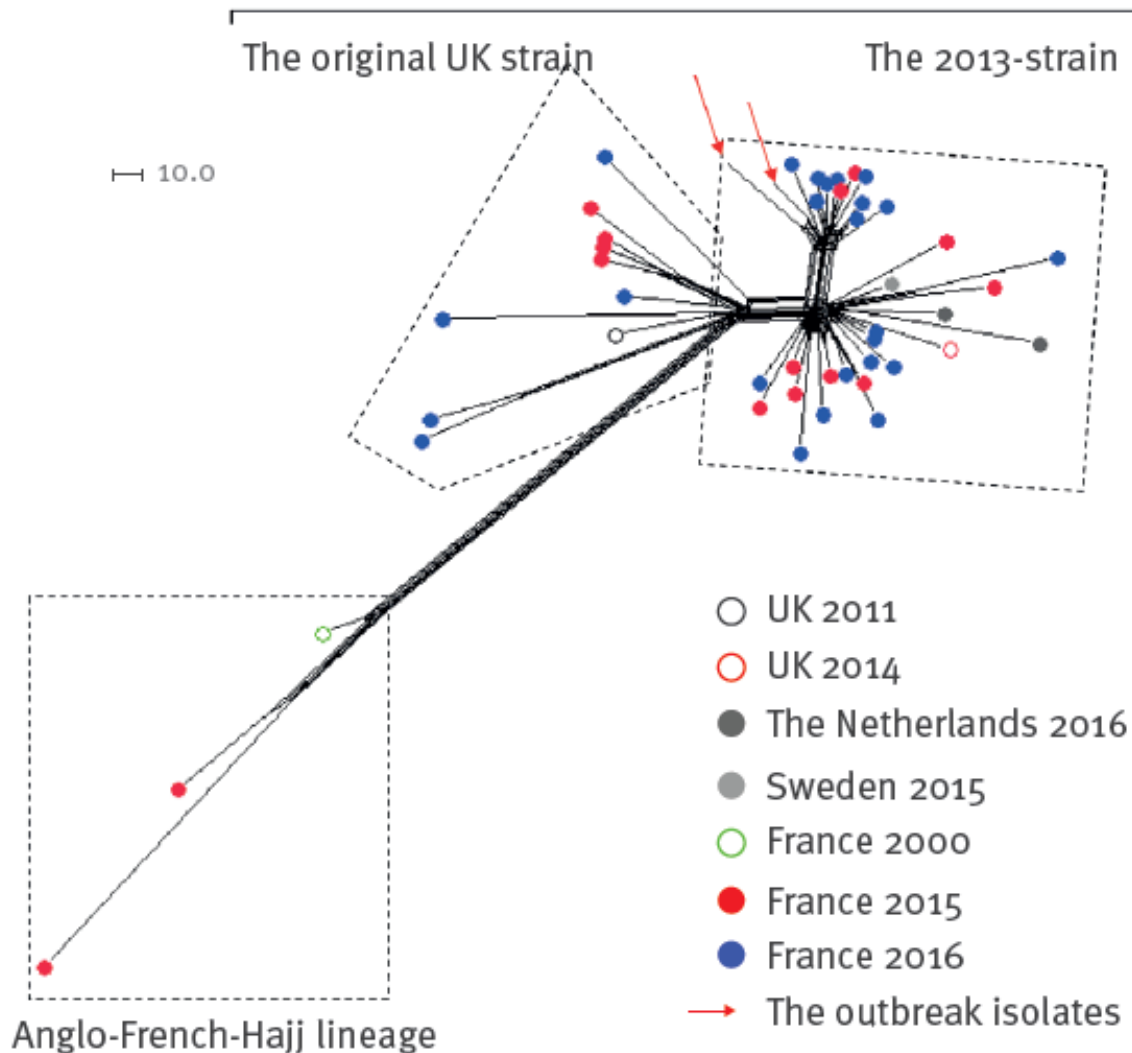
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January

H Campbell¹, SR P

1. Immunisation D
2. Meningococcal I
3. St. George's Uni

Correspondence: S

Citation style for this ar
Campbell H, Parikh SR, I
W meningococcal diseas
ES.2016.21.12.30175



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ccal
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associated with group
g/10.2807/1560-7917.

hed on 24 March 2016

RAPID COMMUNICATIONS

A cluster of invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* serogroup W among university students, France, February to May 2017

C Bassi¹, M Taha², C Merle³, E Hong², D Lévy-Bruhl⁴, A Barret^{4,5}, I Mouchetrou Njoya^{1,5}

1. Santé publique France, French National Public Health Agency, Regional Unit (Cire) Ile-de-France, Paris, France
2. National Reference Centre for Meningococci and Haemophilus influenzae, Institut Pasteur, Paris, France
3. Regional Health Agency in the Ile-de-France region (Agence régionale de santé d'Ile-de-France), Paris, France
4. Santé publique France, French National Public Health Agency, Saint-Maurice, France
5. These authors contributed equally to this work.

Correspondence: Clément Bassi (clement.bassi@ars.sante.fr)

Citation style for this article:

Bassi C, Taha M, Merle C, Hong E, Lévy-Bruhl D, Barret A, Mouchetrou Njoya I. A cluster of invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* serogroup W among university students, France, February to May 2017. *Euro Surveill.* 2017;22(28):pii=30574. DOI: <http://dx.doi.org/10.2807/1560-7917.ES.2017.22.28.30574>

HOLLANDA

- 2015 yılına kadar yılda 4-5 olgu
2016 ve 2017 yıllarında 50 olgu
- %93 olgu yeni Serogrup W- cc11
(UK-2013 strain)
- Septisemi ve pnömoni en sık
başvuru şekli
- 1 yaş altı olgu az, daha çok genç
erişkin ve yaşlılarda

İSPANYA

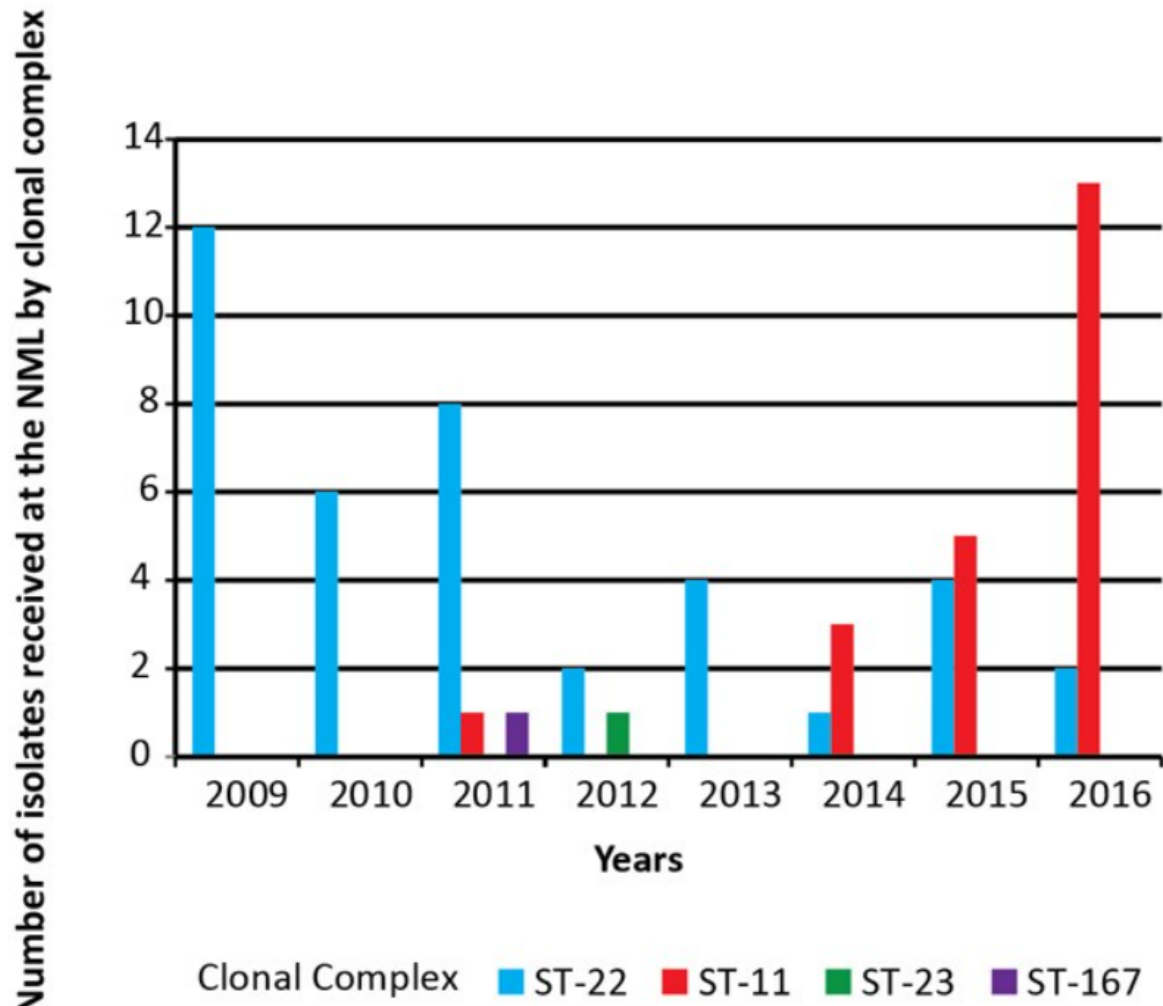
- 2016-2017'de tüm yaş
gruplarında
- W sıklığı 2 kat artmış
- Yeni olguların tamamı cc11
(UK-2013 strain)

14th Congress of the EMGM, European Meningococcal
and Haemophilus Disease Society

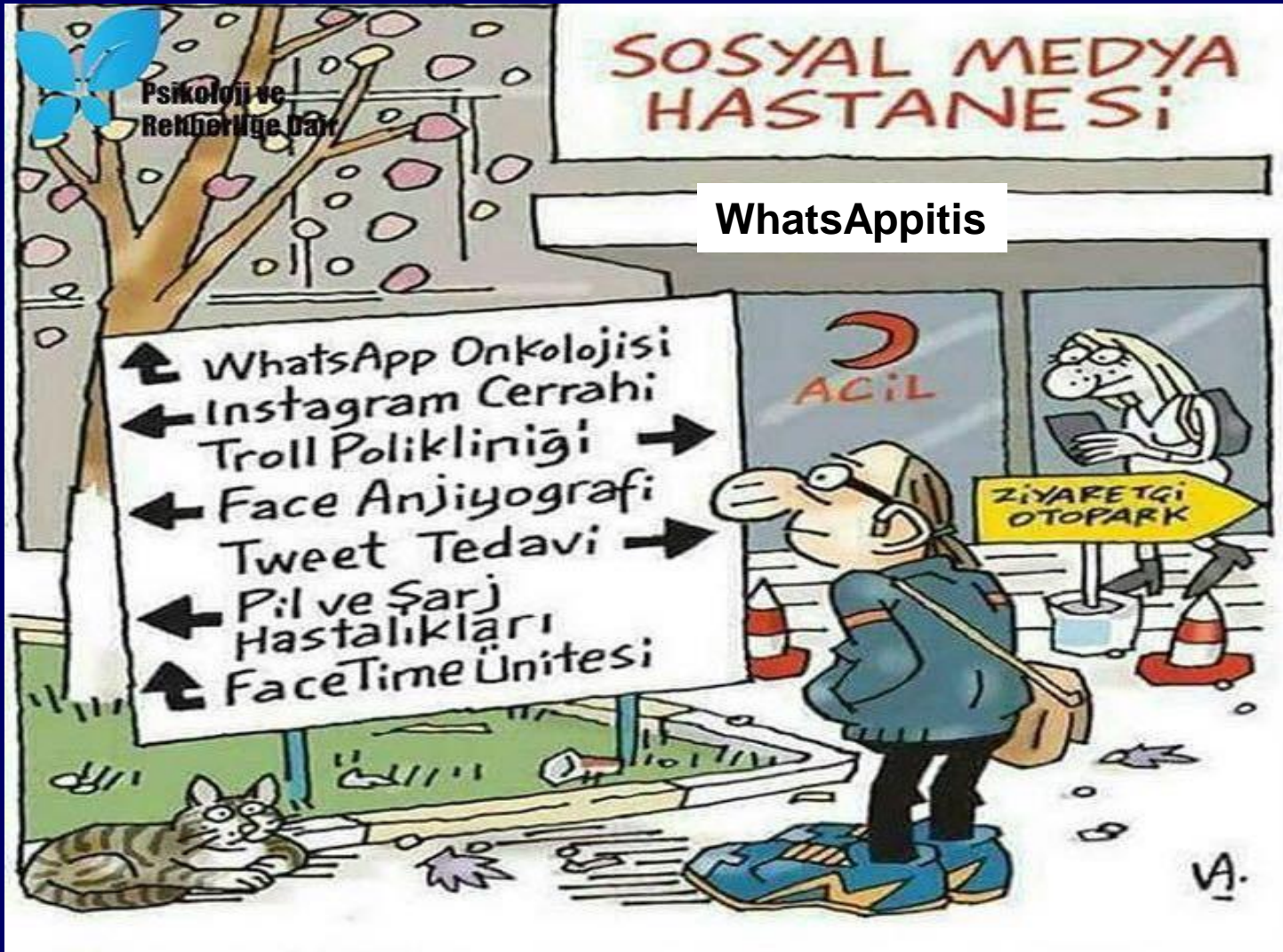
September 18-21, 2017 | Prague, Czech Republic
www.emgm2017.cz



Figure 1: Clonal analysis of invasive *Neisseria meningitidis* serogroup W (MenW) in Canada, 2009-2016



Türkiye'de İMH epidemiyolojisi



Türkiye'de IMH epidemiyolojisi



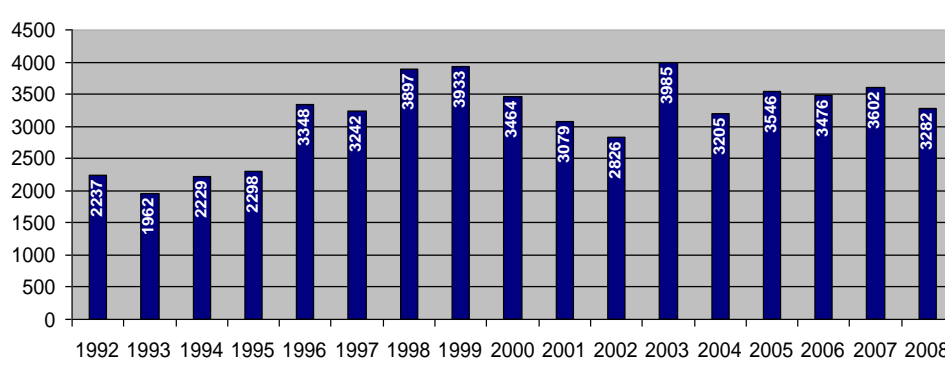
hacamat

**Her derde deva
HACAMAT**

Steril bir ortamda ameliyathane hemşiresi eşliğinde **hacamat ile hastalıklarınızdan kurtulun !**

⦿ Hacamat bağışıklık sistemini kuvvetlendirir, vücuda direnç kazandırır.

Türkiye'de IMH epidemiyolojisi



TÜİK verilerine göre yıllık meningokokal enfeksiyon kaynaklı ölümler, 1992-2008

Tablo 8.5 Bildirilen Bebek Ölüm Nedenleri, Türkiye, Sağlık Bakanlığı

Neden	2007	2008	Toplam	%'si
Prematüre Doğum	4964	3988	8952	%31
Doğum Anomalisi	2752	2164	4916	%17
Sepsis	1282	1568	2850	%10
Kalp Hastalığı	1461	917	2378	%8
Perinatal Asfiksi	929	903	1832	%6
Akut Solunum Yolu Enfeksiyonu	651	316	967	%3
Doğum Travması	251	97	348	%1
İshal	126	83	209	%1
Kaza	80	94	174	%1
Intravasküler Hemoraj	30	78	108	<%1
Meningjit	50	48	98	<%1
Malignansi	72	18	90	<%1
Yenidoğan tetanosu	0	7	7	<%1
Özel Durumlar	1102	672	1774	%6
Diğer	1425	2753	4178	%15
Toplam	15175	13706	28881	%100.0

Kaynak: Sağlık Bakanlığı, Bebek Ölümleri – 2009

Meningokok hastalığı kaynaklı ölümler (1992-2009)

- TC Sağlık Bakanlığı → 49-151
- Türkiye İstatistik Kurumu (TÜİK) → 1982-3985

Türkiye'de IMH epidemiyolojisi



Countries with moderate endemic rates (2 - 10 cases/100,000 population year)

Country	Year	Incidence/ 100,000 population	Predominant serogroup	Source	Comments
Switzerland	1999-2004	1.16-2.36	C	[24]	A conjugate vaccine for group C introduced in 2005
Turkey	1997-2005	0.3-2.2	*	[28]	

DSÖ'ne göre Türkiye ORTA endemisine kategorisinde bir ülkedir.

Türkiye menenjit sürveyansı

A Prospective Study of Etiology of Childhood Acute Bacterial Meningitis, Turkey

Mehmet Ceyhan,* Inci Yildirim,* Paul Balmer,† Ray Borrow,† Bunyamin Dikici,‡ Mehmet Turgut,§
Nese Kurt,§ Aysel Aydogan,¶ Cigdem Ecevit,¶ Yasar Anlar,# Ozlem Gulumser,# Gonul Tanir,**
Nuran Salman,†† Nezahat Gurler,†† Nevin Hatipoglu,†† Mustafa Hacimustafaoglu,‡‡ Solmaz
Celebi,‡‡ Yavuz Coskun,§§ Emre Alhan,¶¶ Umit Celik,¶¶ Yildiz Camcioglu,†† Gulden Secmeer,*
Deniz Gur,## and Steve Gray†

Türkiye menenjit sürveyansı

RESEARCH PAPER

Human Vaccines & Immunotherapeutics 10:09, 1–7; October 1, 2014; © 2014 Taylor & Francis Group, LLC

Meningitis Caused By Neisseria Meningitidis, Hemophilus Influenzae Type B and Streptococcus Pneumoniae During 2005–2012 in Turkey

A Multicenter Prospective Surveillance Study

Mehmet Ceyhan^{1,†}, Nezahat Gürler^{2,†}, Yasemin Ozsurekci^{1,†,*}, Melike Keser^{3,†}, Ahmet Emre Aycan^{1,†}, Venhar Gurbuz^{1,†}, Nuran Salman^{4,†}, Yildiz Camcioglu^{5,†}, Ener Cagri Dinleyici^{6,†}, Sengul Ozkan^{7,†}, Gulnar Sensoy⁸, Nursen Belet^{8,†}, Emre Alhan⁹, Mustafa Hacimustafaoglu^{10,†}, Solmaz Celebi^{10,†}, Hakan Uzun^{11,†}, Ahmet Faik Oner^{12,†}, Zafer Kurugol^{13,†}, Mehmet Ali Tas^{14,†}, Denizmen Aygun^{15,†}, Eda Karadag Oncel^{1,†}, Melda Celik^{1,†}, Olcay Yasa^{16,†}, Fatih Akin^{17,†}, and Yavuz Coşkun^{18,†}

Türkiye menenjit sürveyansı

HUMAN VACCINES & IMMUNOTHERAPEUTICS

2016, VOL. 0, NO. 0, 1–6

<http://dx.doi.org/10.1080/21645515.2016.1209278>



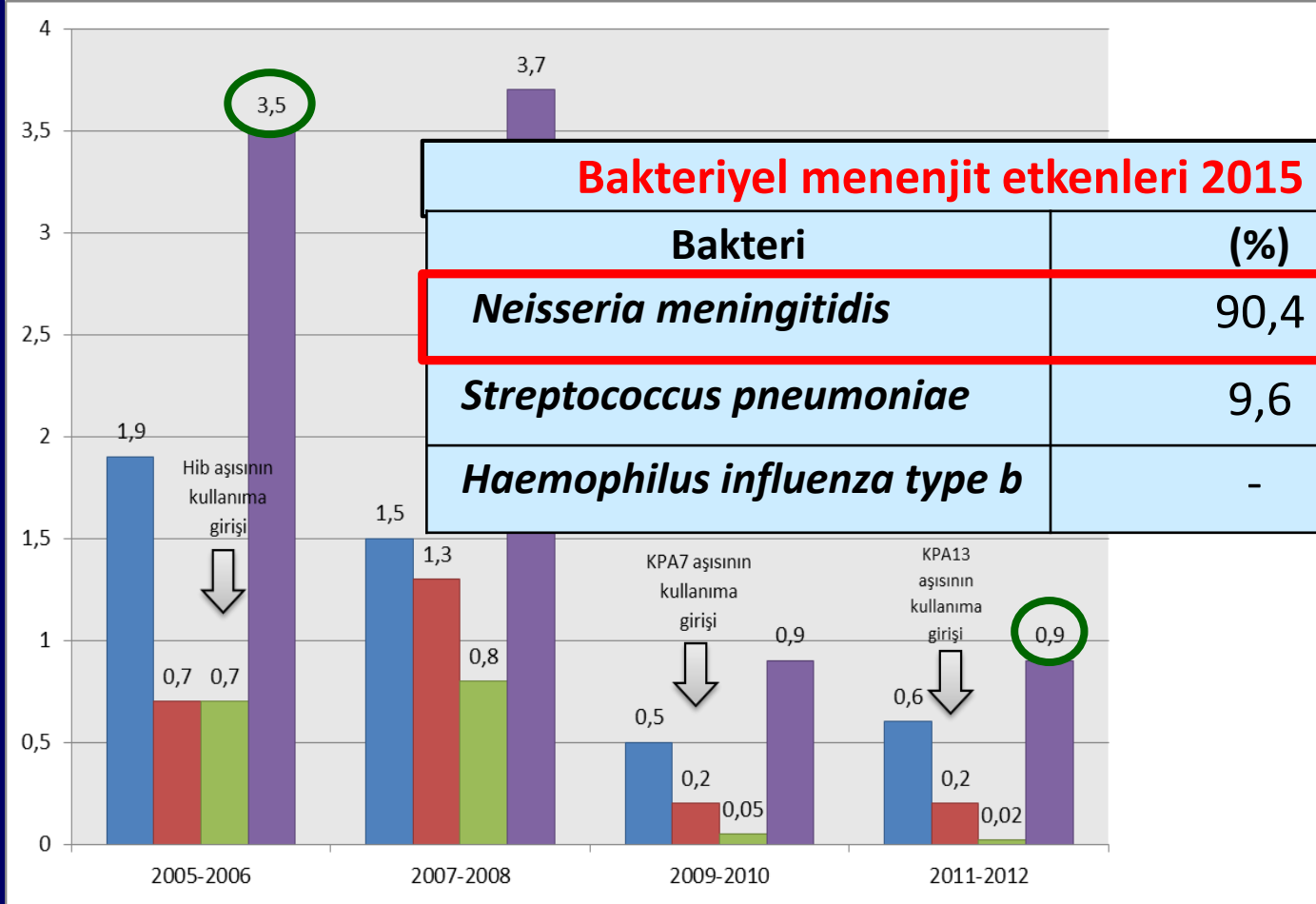
Taylor & Francis
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RESEARCH PAPER

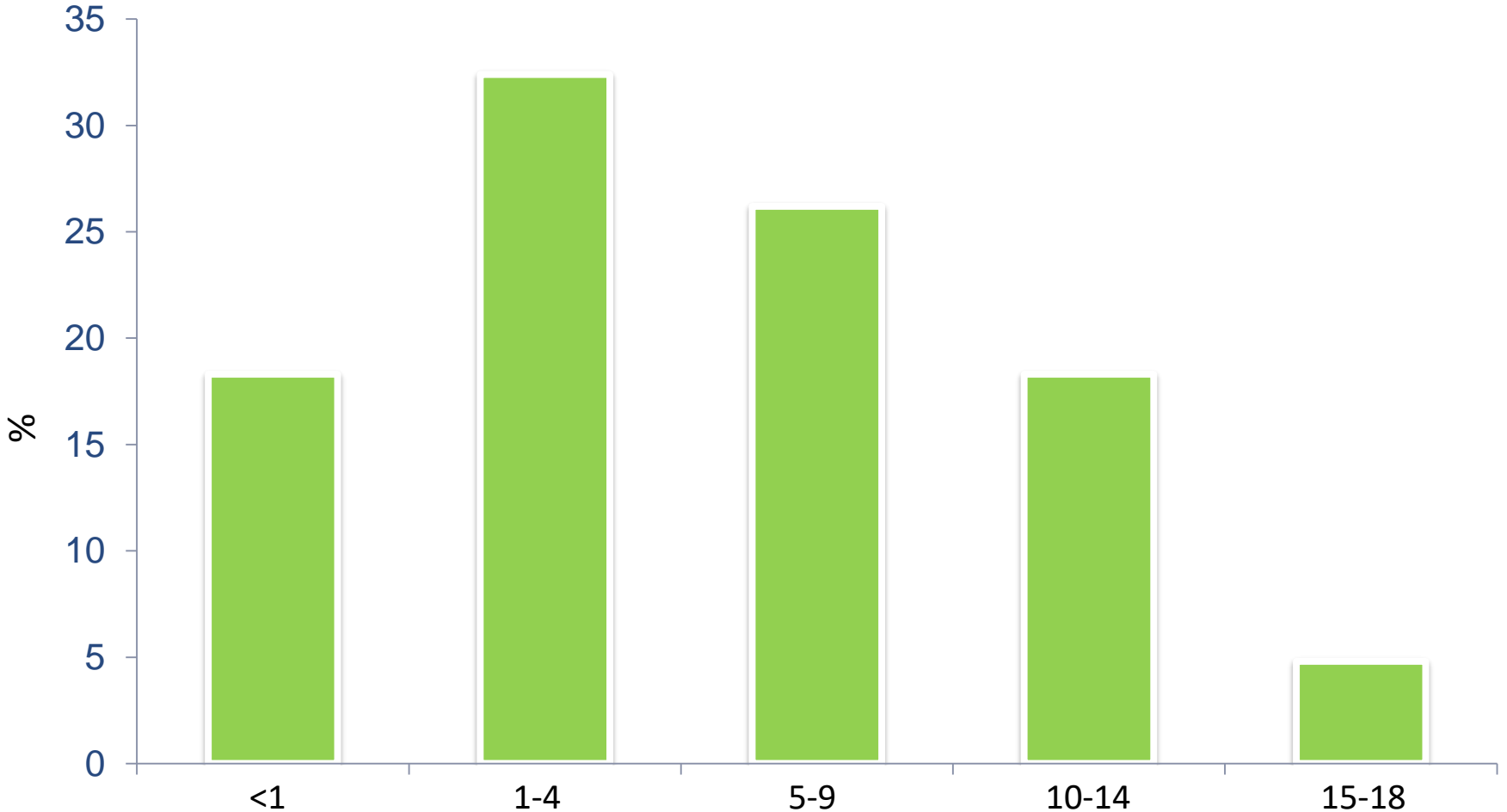
Bacterial agents causing meningitis during 2013–2014 in Turkey: A multi-center hospital-based prospective surveillance study

Mehmet Ceyhan^{a,#}, Yasemin Ozsurekci^{a,#}, Nezahat Gürler^{b,#}, Eda Karadag Oncel^{a,#}, Yıldız Camcioglu^{c,#}, Nuran Salman^{d,#}, Melda Celik^{e,#}, Melike Keser Emiroglu^{f,#}, Fatih Akin^{g,#}, Hasan Tezer^{h,#}, Aslinur Ozkaya Parlakay^{i,#}, Nilden Tuygun^{j,#}, Diyar Tamburaci^{k,#}, Ener Cagri Dinleyici^{l,#}, Adem Karbuz^{m,#}, Ünal Uluca^{n,#}, Emre Alhan^{o,#}, Ümmühan Çay^{o,#}, Zafer Kurugol^{p,#}, Nevin Hatipoğlu^{q,#}, Rengin Şiraneci^{q,#}, Tolga İnce^{r,#}, Gülnar Sensoy^{s,#}, Nursen Belet^{s,#}, Enes Coskun^{t,#}, Fatih Yılmaz^{t,#}, Mustafa Hacimustafaoglu^{u,#}, Solmaz Celebi^{u,#}, Ümit Celik^{v,#}, Metehan Ozen^{w,#}, Aybüke Akaslan^{w,#}, İlker Devrim^{x,#}, Necdet Kuyucu^{y,#}, Fatmanur Öz^{z,#}, Sefika Elmas Bozdemir^{aa,#}, and Ahu Kara^{x,#}

Türkiye menenjit sürveyansı



İMİH vakalarının yaşa göre dağılımı Türkiye (2005-2012)



İMİH vakalarının yaş dağılımı - Türkiye

Ref. No.	N	Olgu klinik dağılımı		Olgu yaş dağılımı		Mortalite	Bölgesi
		Meningokok oksemi (%)	Menenjit (%)	0-5 yaş	6-17 yaş		
Akyıldız	65	% 46,1	%30,7	% 81	% 19	%18,44	Istanbul
	83	%73,49	%26,51	% 66	% 44	%15,60	Erzurum
Elmastaş	41	%21,9	%48,8	% 66	% 44	Bilinmiyor	İzmir
Ersoy	85	%30,59	%20	Bilinmiyor	Bilinmiyor	%18,82	İzmir
Özdal	143	-	-	%71		%17	Diyarbakır
Kepenekli	7	%42	% 57	% 90	% 10	Bilinmiyor	Ankara
Kulcu	16	%87,50	%12,5	% 93	% 7	%43,75	Istanbul
Tüysüz	140	%78	%22	% 60	% 40	%8,62	Istanbul

Meningokok olgularının ortalama %74'ü 0-5 yaş arasındadır.

Adölesan piki görülmez.

Meningokok Serogrup Dağılımı (Türkiye, 1974-2014)

Yazar	Yıllar	Bölge	Serogrup Dağılımı, N (%)							Toplam
			A	B	C	W	Y	X	NG	
Berkman	1974-1979	Ankara	33 (%29)	53 (%46)	29 (%25)	0 (%0)	0 (%0)	0 (%0)	0 (%0)	115
Berkman	1980-1984	Ankara	8 (%32)	13 (%52)	4 (%16)	0 (%0)	0 (%0)	0 (%0)	0 (%0)	25
Tuncer	1987	Ankara	-	4 (%5)	36 (%95)	0 (%0)	0 (%0)	0 (%0)	0 (%0)	
Elmastaş	1990-1994	İzmir	1 (%2)	4 (%10)	36 (%88)	0 (%0)	0 (%0)	0 (%0)	0 (%0)	41
Ceyhan	2005-2006	Türkiye	%0.7	%31.1	0	%42.7	%2.2	0	%23.2	243
Toprak	2006-2009	Türkiye	1 (%2)	29 (%62)	2 (%4)	1 (%2)	0	1 (%2)	13 (%19)	47
Ceyhan	2005-2014	Türkiye	28 (%8.4)	87 (%26.1)	0	127 (%38.1)	3 (%0.9)	0	88 (%26.4)	333

Berkman E, Ozben G. Mikrobiyoloji Bülteni 1982;16:101-106.

Elmastaş H, ark. T Klin Pediatri 1992;1:58-61;

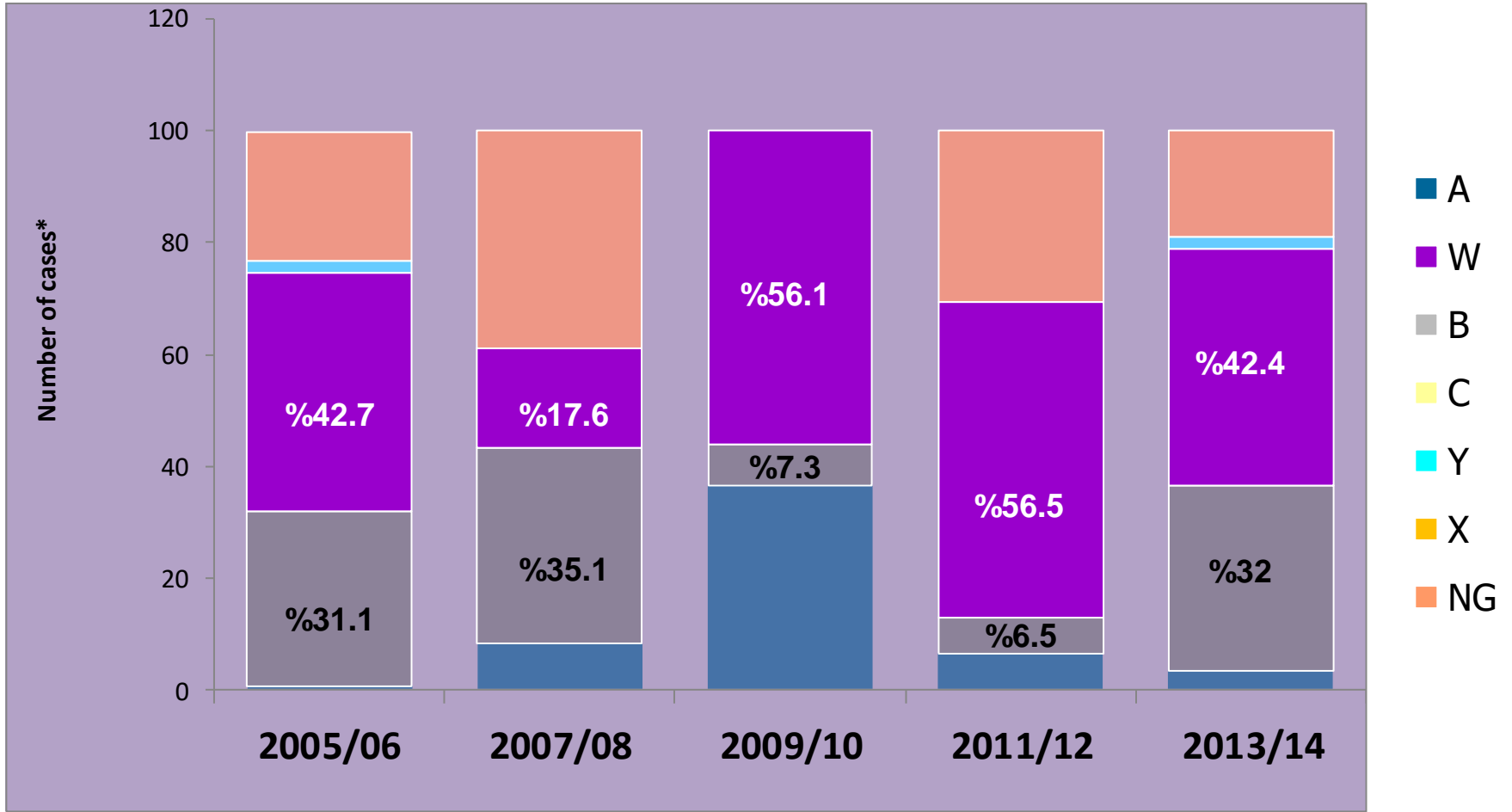
Ceyhan M, et al. Emerging Infectious Diseases 2008; 14: 1089-1096.

Toprak D, et al. PIDJ 2014; 33:1087-9.

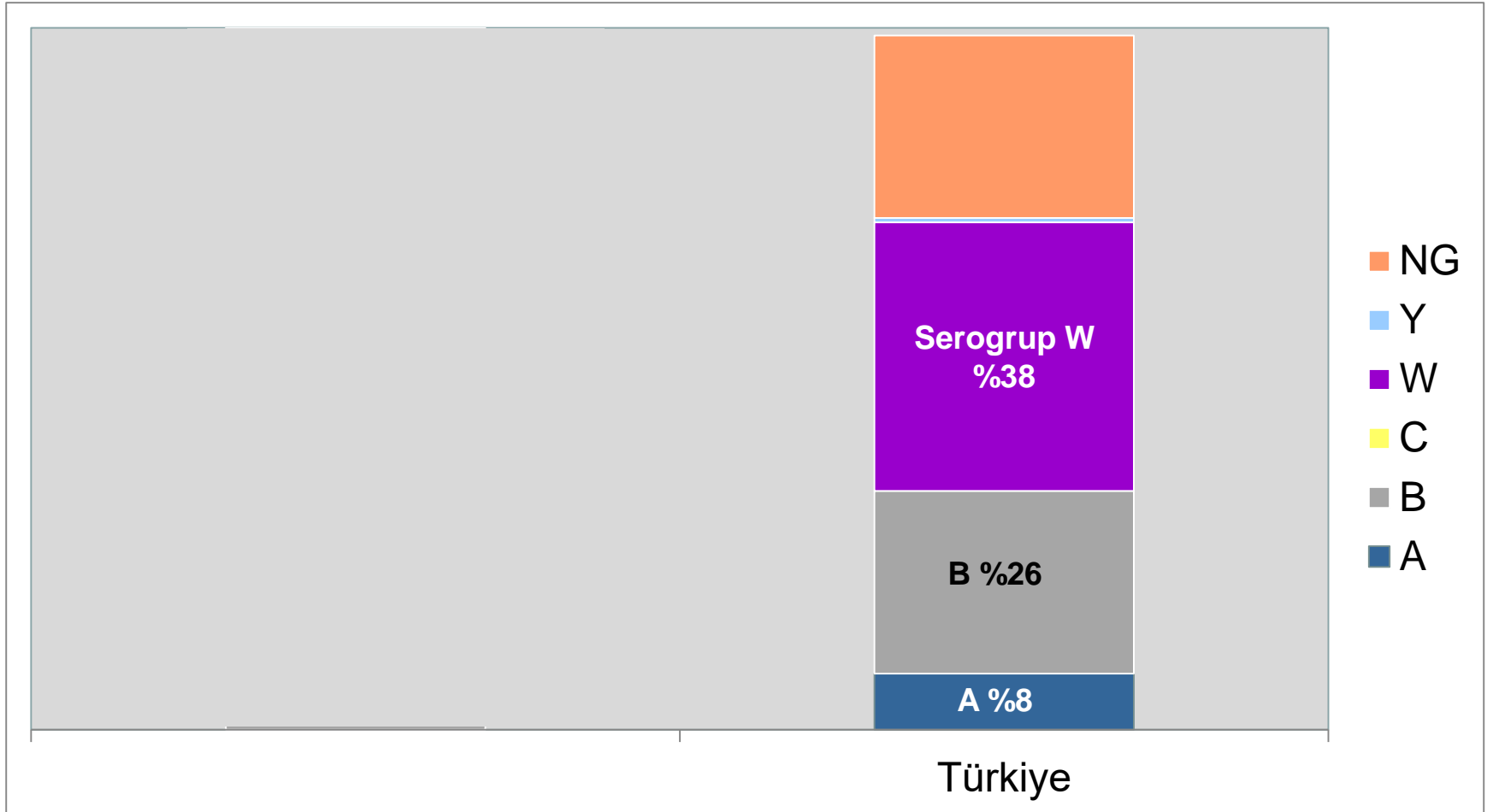
Ceyhan M, et al. Hum Vaccin Immunother 2014; 10:9, 2706-12.

Bakır M, Altınel S. Expert Rev Vaccines. 2015 Aug;14(8):1089-97.

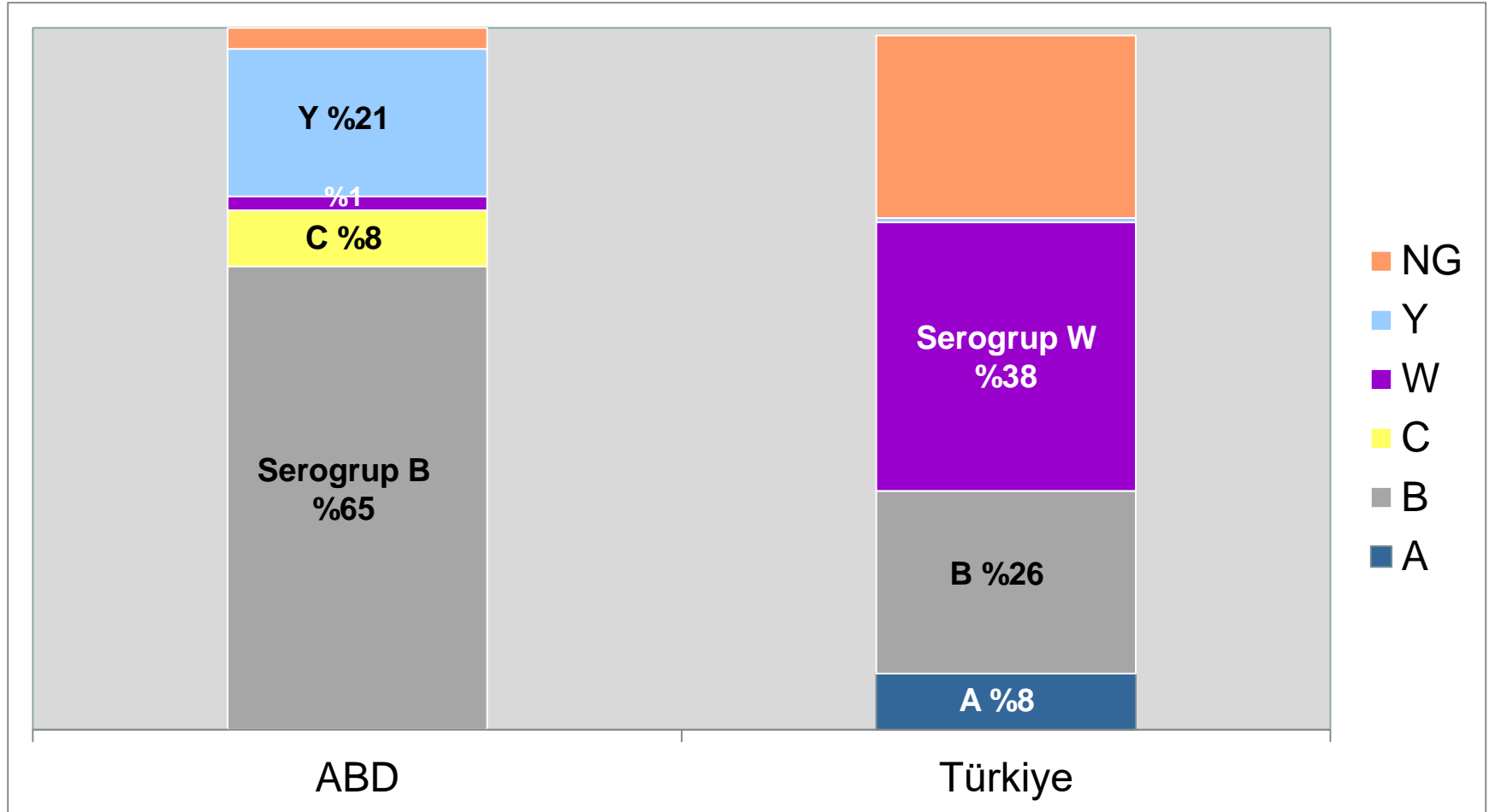
Meningokok Serogrup Dağılımı (Türkiye, 2005-2014)



Meningokok Serogrupları (Türkiye, 2005-2014)

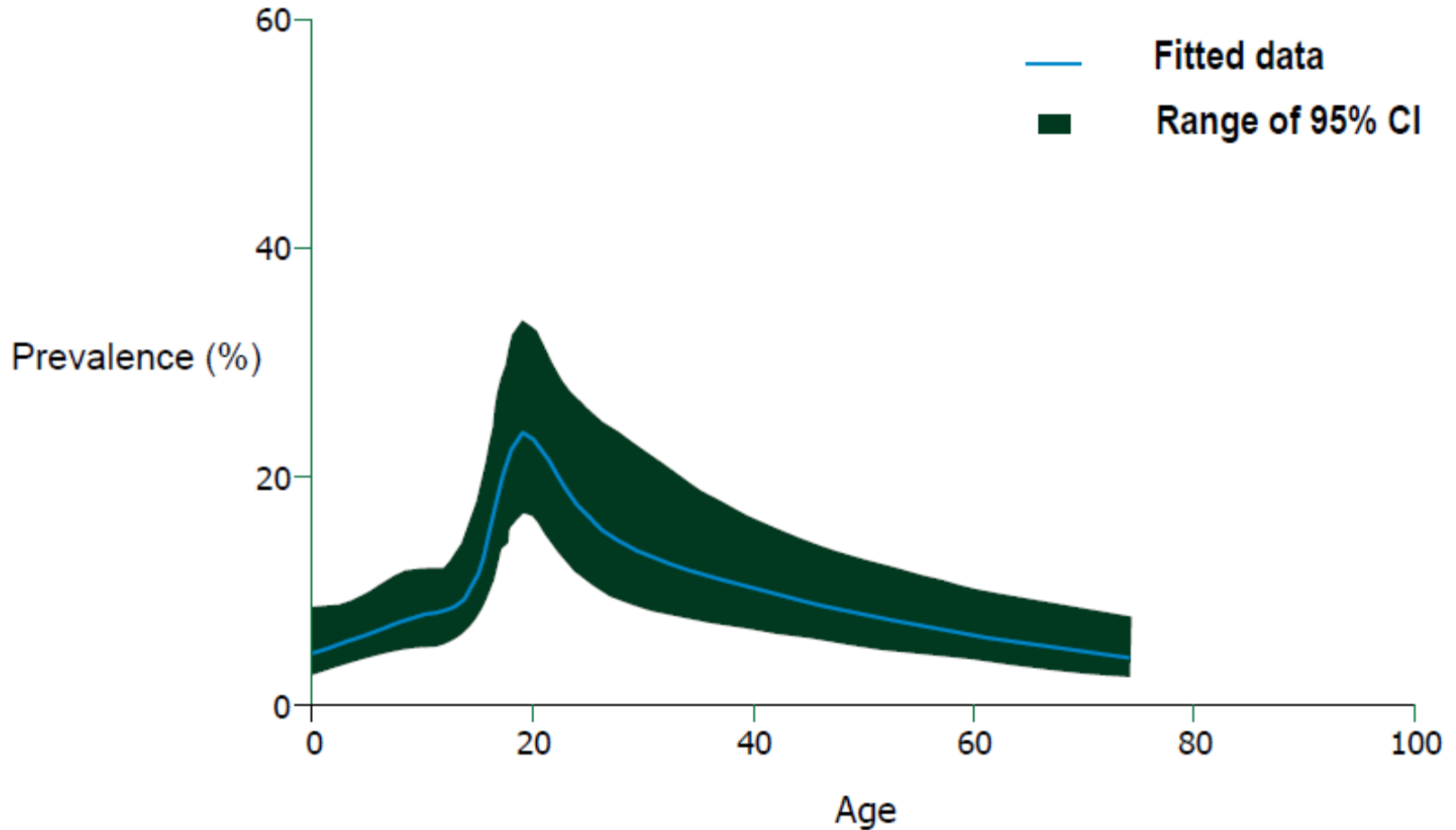


Meningokok Serogrupları (Türkiye, 2005-2014)

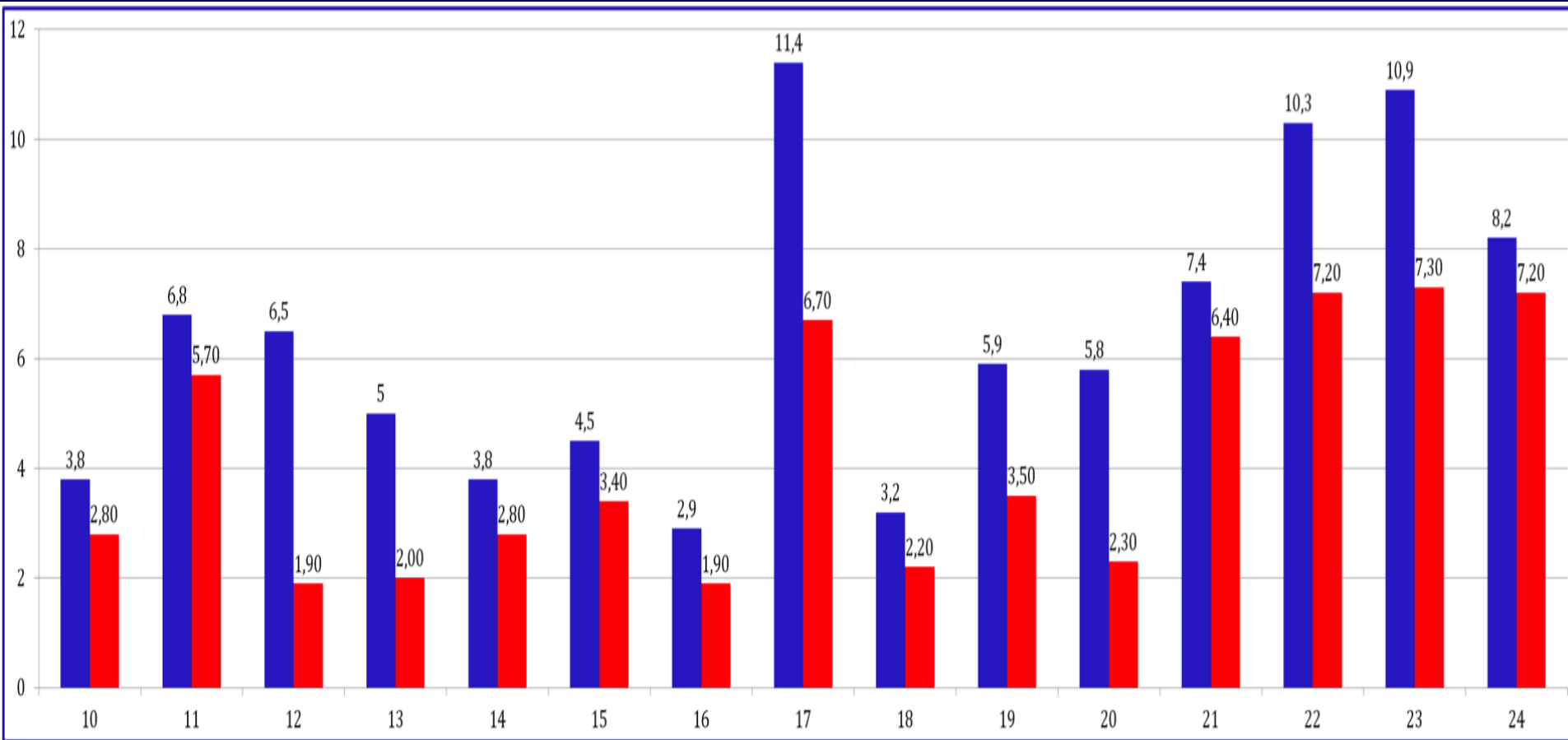


MENİNGOKOK TAŞIYICILIK

28 ÜLKEDEN 89 ÇALIŞMA



MENİNGOKOK TAŞIYICILIK TÜRKİYE



SEROGRUP W (%65.6)

IMH Hastalığı Korunma

IMH Hastalığı Korunma

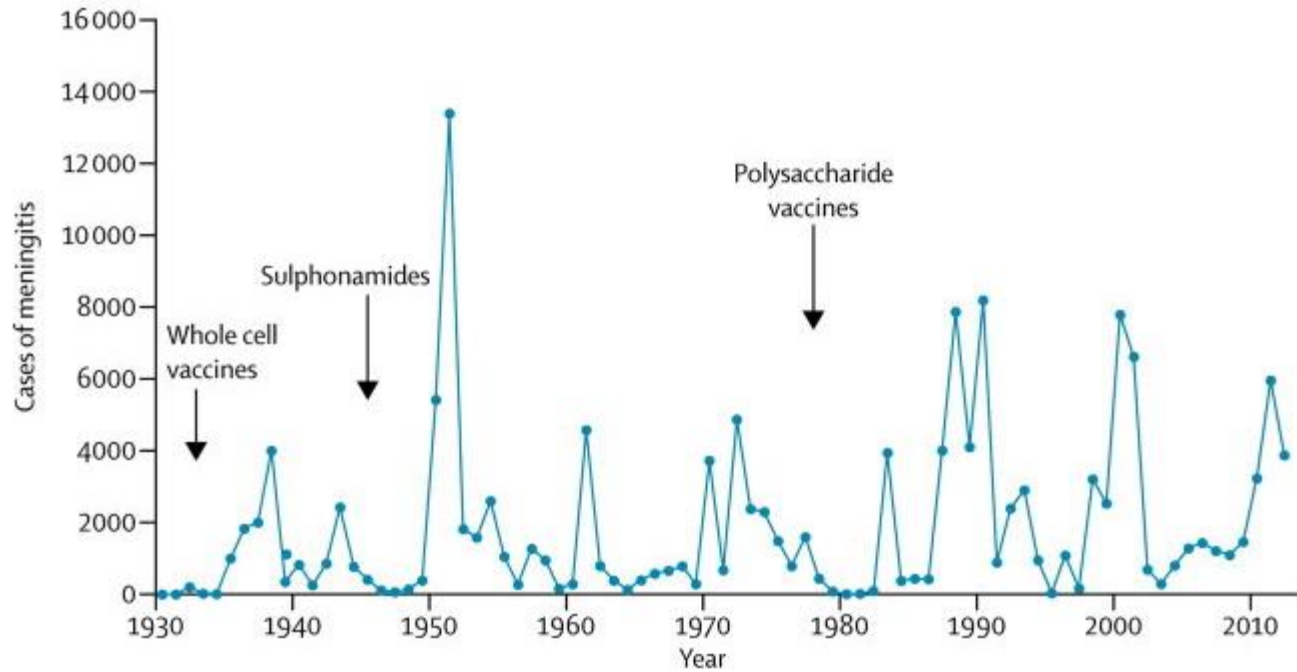


Table 2: Summary of WHO Position Papers – Recommended Routine Immunizations for Children

Antigen	Doses in	Interval Between Doses	Considerations (see footnotes for details)
16 Meningococcal			
Recommendations for all children			
BCG ¹			is HIV
Hepatitis B ²	Option 1		and low birth weight administration and combination
	Option 2		groups
Polio ³	OPV + IPV		1 dose sion and importation risk
	IPV / OPV Sequential		ter needed for early schedule dose given <8 weeks)
	IPV		interrupted schedule tion vaccine
DTP ⁴			se if >12 months of age mmended for children > 5 yrs interrupted schedule istration and combination
Haemophilus influenzae type b ⁵	Option 1		
	Option 2		
Pneumococcal (Conjugate) ⁶	Option 1		ptions efore 6 months of age istration 1 preterm neonates booster
	Option 2		ptions mmended if > 24 months old
Rotavirus ⁷	Rotarix		
	Rota Teq		
Measles ⁸			tion vaccine; HIV early on; Pregnancy
Rubella ⁹			and sustain 80% coverage ion vaccine and Co- ation; Pregnancy
HPV ¹⁰			13 year old girls y ≥ 15 years 3 doses immunocompromised

16 Meningococcal






- Position paper reference: [Weekly Epid. Record \(2011, 86: 521-540\)](#) [pdf 1.1Mb] and Update for MenA conjugate [Weekly Epid Record \(2015, 90: 57-68\)](#) [pdf 852KB]
- Conjugate vaccines are preferred over polysaccharide vaccines due to their potential for herd protection and their increased immunogenicity, particularly in children <2 years of age.
- Both conjugate and polysaccharide vaccines are efficacious and safe when used in pregnant women.
- MenA conjugate vaccine (5µg) a 1-dose schedule is recommended at 9-18 months of age based on local programmatic and epidemiologic considerations. The vaccine should be administered by deep intramuscular injection, preferably in the anterolateral aspect of the thigh. There is no reason to expect interference when co-administered with other vaccines. The need for a booster dose has not been established.
- If in a specific context there is a compelling reason to vaccinate infants younger than 9 months, a 2-dose schedule should be used starting at 3 months of age, with an interval of at least 8 weeks between doses.
- For monovalent MenC conjugate vaccine one single intramuscular dose is recommended for children aged >12 months, teenagers and adults. Children 2-11 months require 2 doses administered at an interval of a least 2 months and a booster about 1 year after. If the primary series is interrupted, vaccination should be resumed without repeating the previous dose.
- Quadrivalent conjugate vaccines (A,C,W135,Y-D and A,C,W135,Y-CRM) should be administered as one single intramuscular dose to individuals > 2 years. A,C,W135,Y-D is also licensed for children 9-23 months of age, and given as a 2-dose series, 3 months apart beginning at age 9 months. If the primary series is interrupted, vaccination should be resumed without repeating the previous dose.
- Meningococcal polysaccharide vaccines are less, or not, immunogenic in children under 2 years of age.
- Meningococcal polysaccharide vaccines can be used for those > 2 years of age to control outbreaks in countries where limited economic resources or insufficient supply restrict the use of meningococcal conjugate vaccines. Polysaccharide vaccines should be administered to individuals > 2 years old as one single dose. One booster 3-5 years after the primary dose may be given to persons considered to be a continued high risk of exposure, including some health workers. See position paper for details.

Refer to <http://www.who.int/immunization>

This table summarizes the WHO vaccination

National schedules should be based on local








Meningokok Aşıları

AŞI	TAŞIYICI PRÖTEİN	SEROGROUPS	DIĞER ANTİJENLER	
Nimenrix™	TT	A, C, W-135, Y	-	
Menveo™	CRM ₁₉₇	A, C, W-135, Y	-	
Menactra™	DT	A, C, W-135, Y	-	SANOPI PASTEUR 
Neisvac-C™	TT	C	-	Baxter
Meningitec™	CRM ₁₉₇	C	-	Nuron
Menjugate™	CRM ₁₉₇	C	-	Novartis
Menitorix™	TT	C	<i>Haemophilus type b</i>	
Menhibrix™	TT	C, Y	<i>Haemophilus type b</i>	
MenAfriVac™	TT	A	-	Meningitis Vaccine Project

Meningokok Aşıları

Hangi aşı

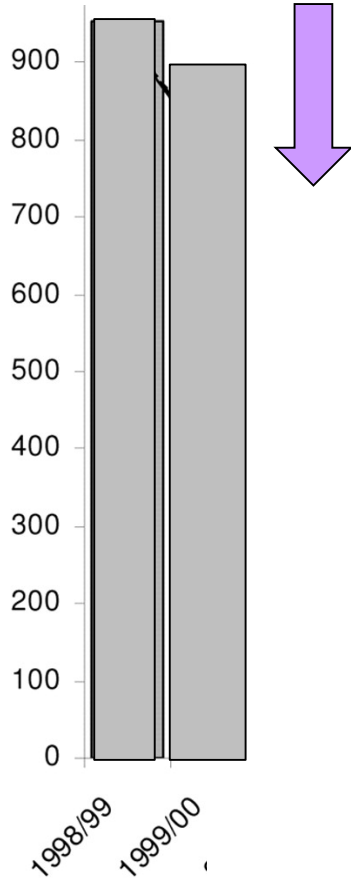


AŞI	TAŞIYICI PROTEİN	SEROGROUPS	DIĞER ANTİJENLER	
Nimenrix™	TT	A, C, W-135, Y	-	
Menveo™	CRM ₁₉₇	A, C, W-135, Y	-	
Menactra™	DT	A, C, W-135, Y	-	
Neisvac-C™	TT	C	-	Baxter
Meningitec™	CRM ₁₉₇	C	-	Nuron
Menjugate™	CRM ₁₉₇	C	-	Novartis
Menitorix™	TT	C	<i>Haemophilus type b</i>	
Menhibrix™	TT	C, Y	<i>Haemophilus type b</i>	
MenAfriVac™	TT	A	-	Meningitis Vaccine Project
Bexsero™	-	B	-	
Trumenba®	-	B	-	

**Bu sorusunun cevabı o ülkede
güncel olarak hangi serogrup (serogruplar)
hakimse onu (onları) içeren aşı**

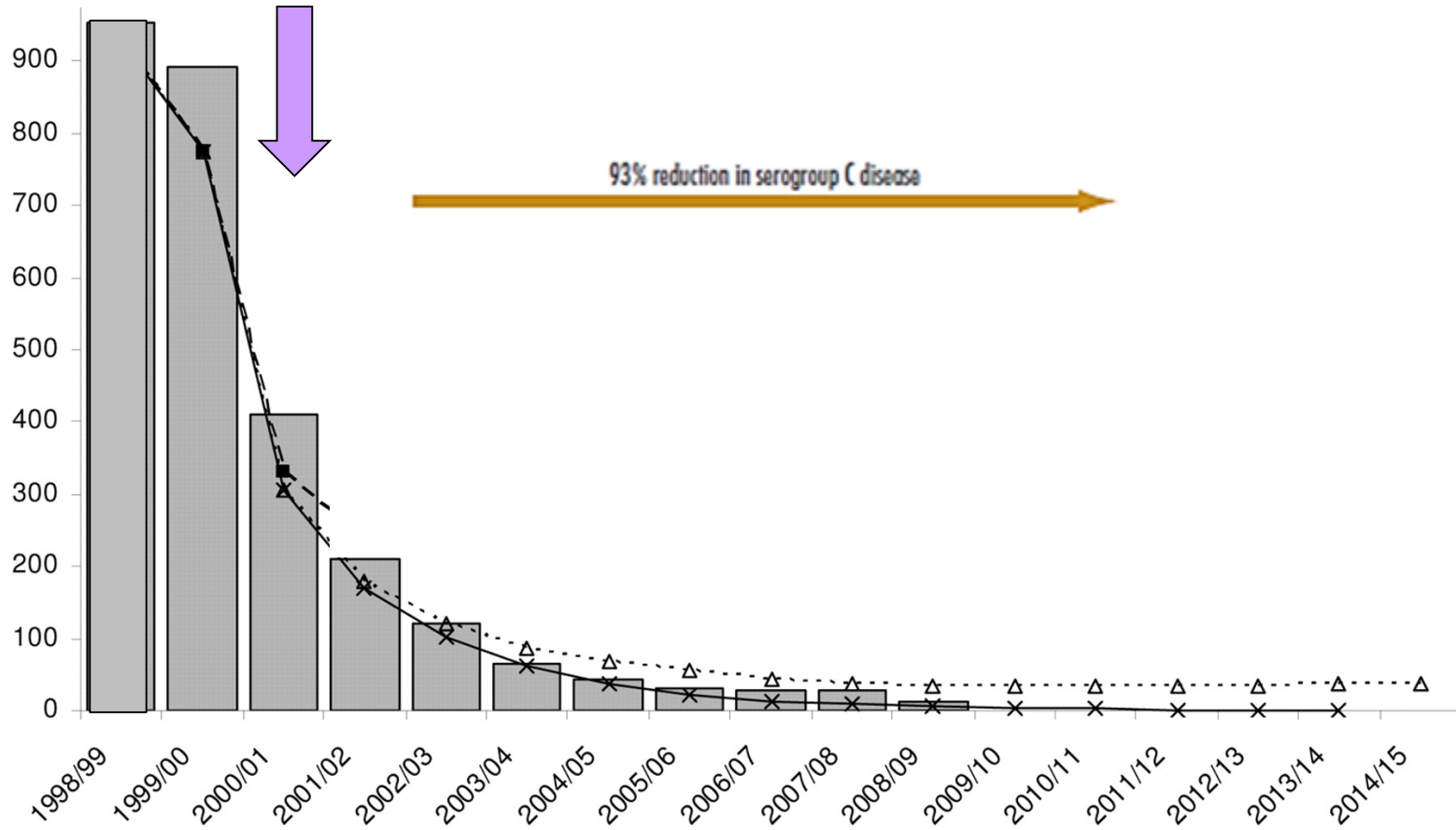
MenC aşısı- İNGİLTERE

Men C aşısı



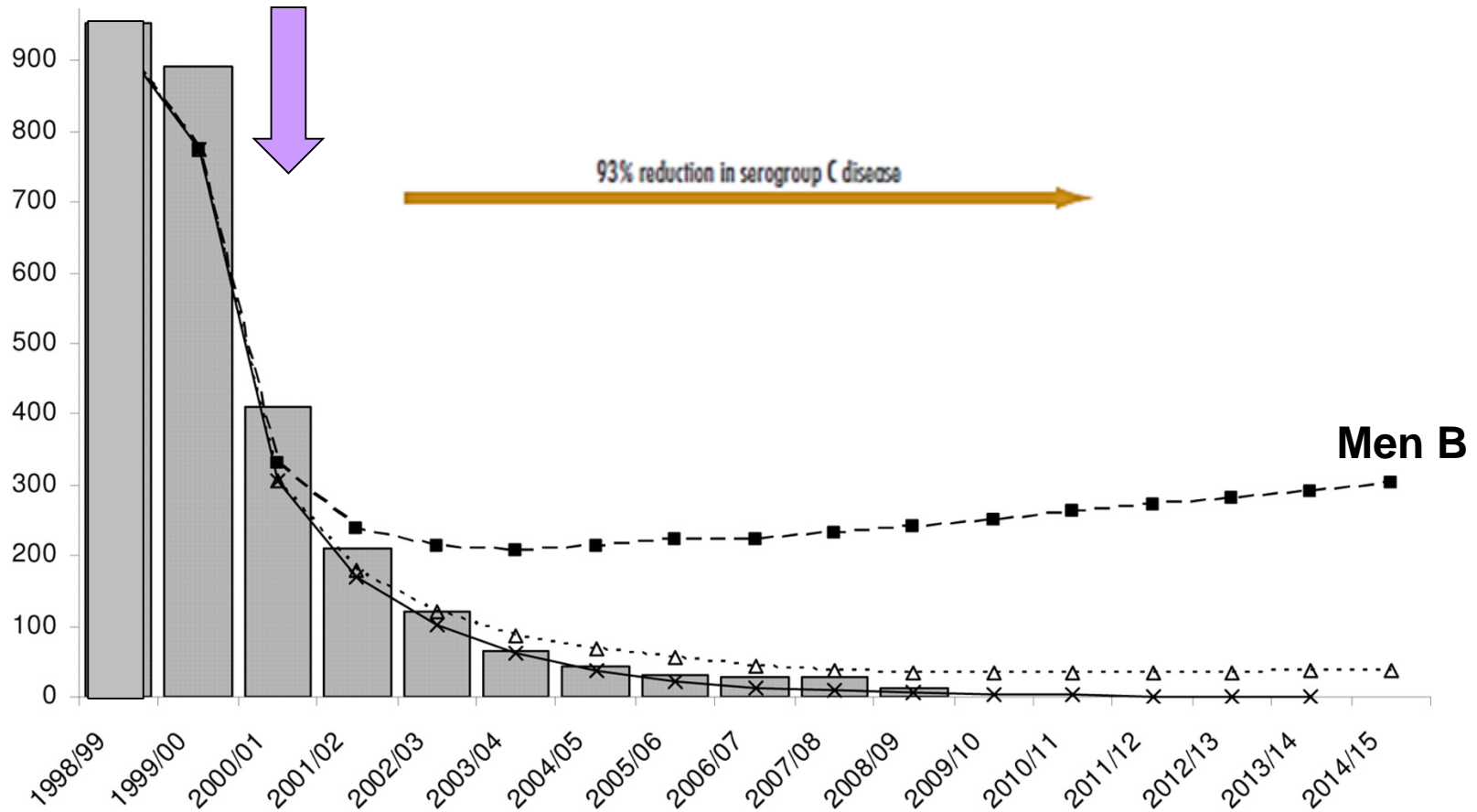
MenC aşısı- İNGİLTERE

Men C aşısı



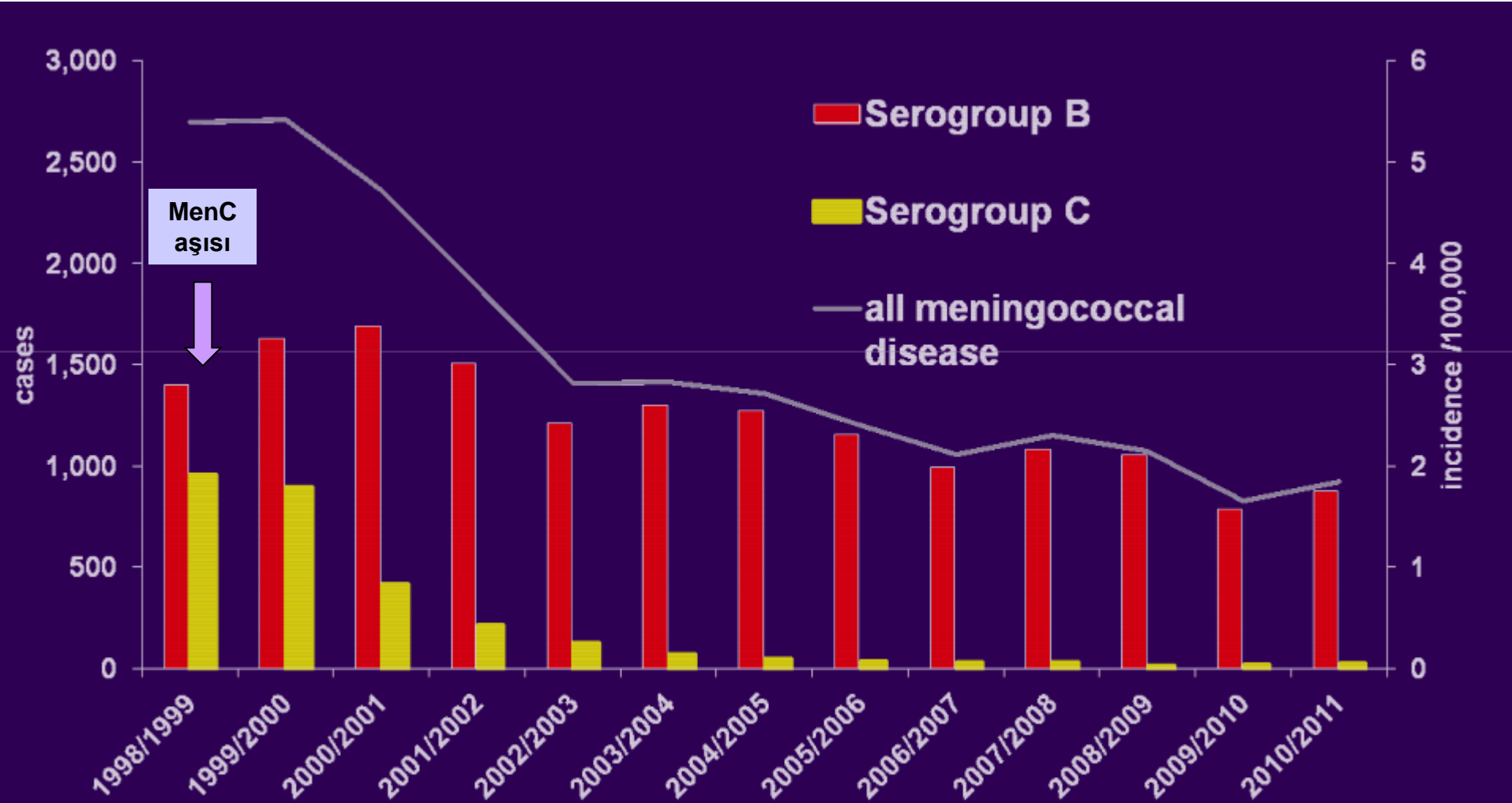
MenC aşısı- İNGİLTERE

Men C aşısı



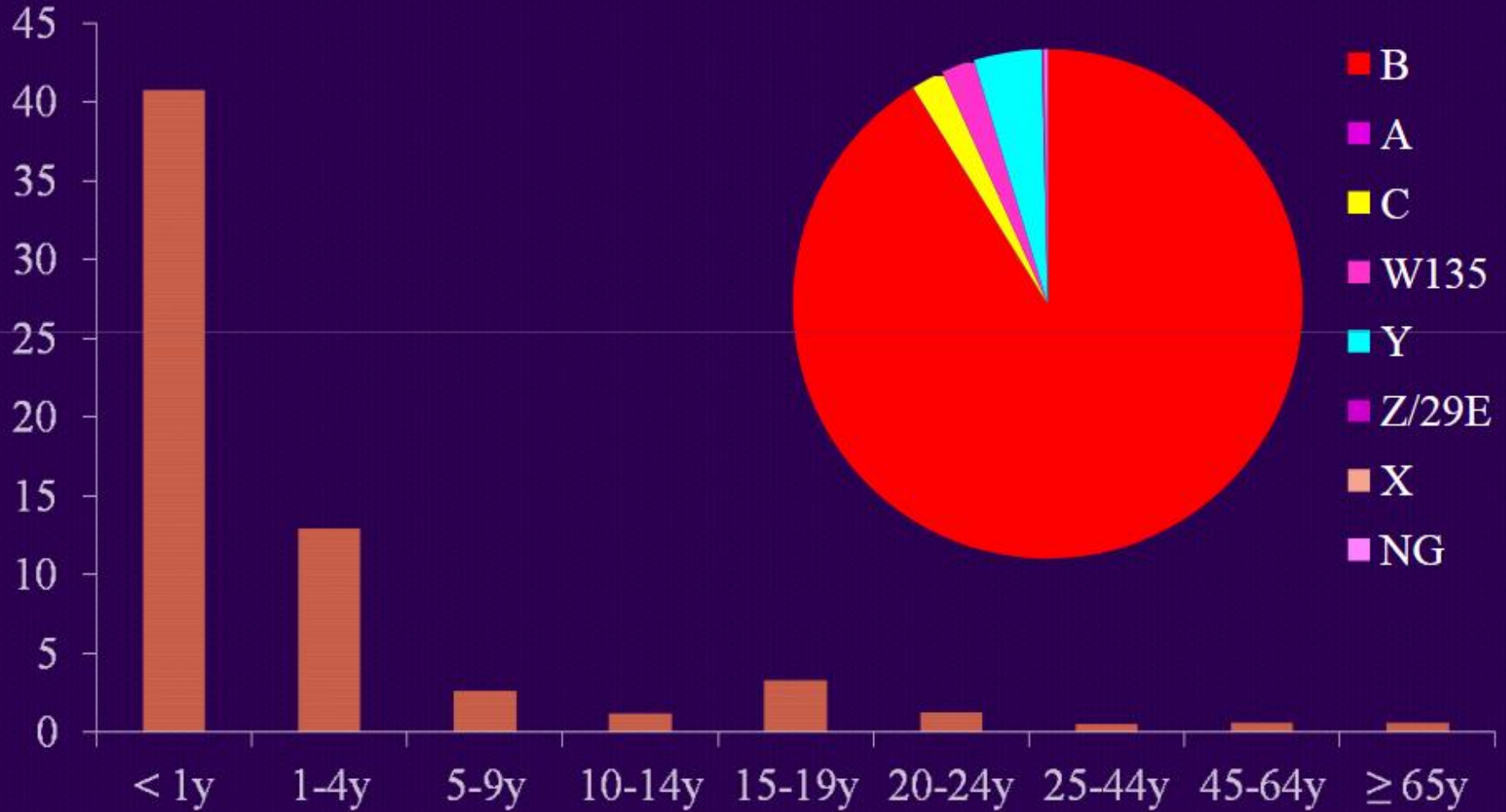
İNGİLTERE

IMH serogrup dağılımı



İNGİLTERE

IMH serogrup dağılımı



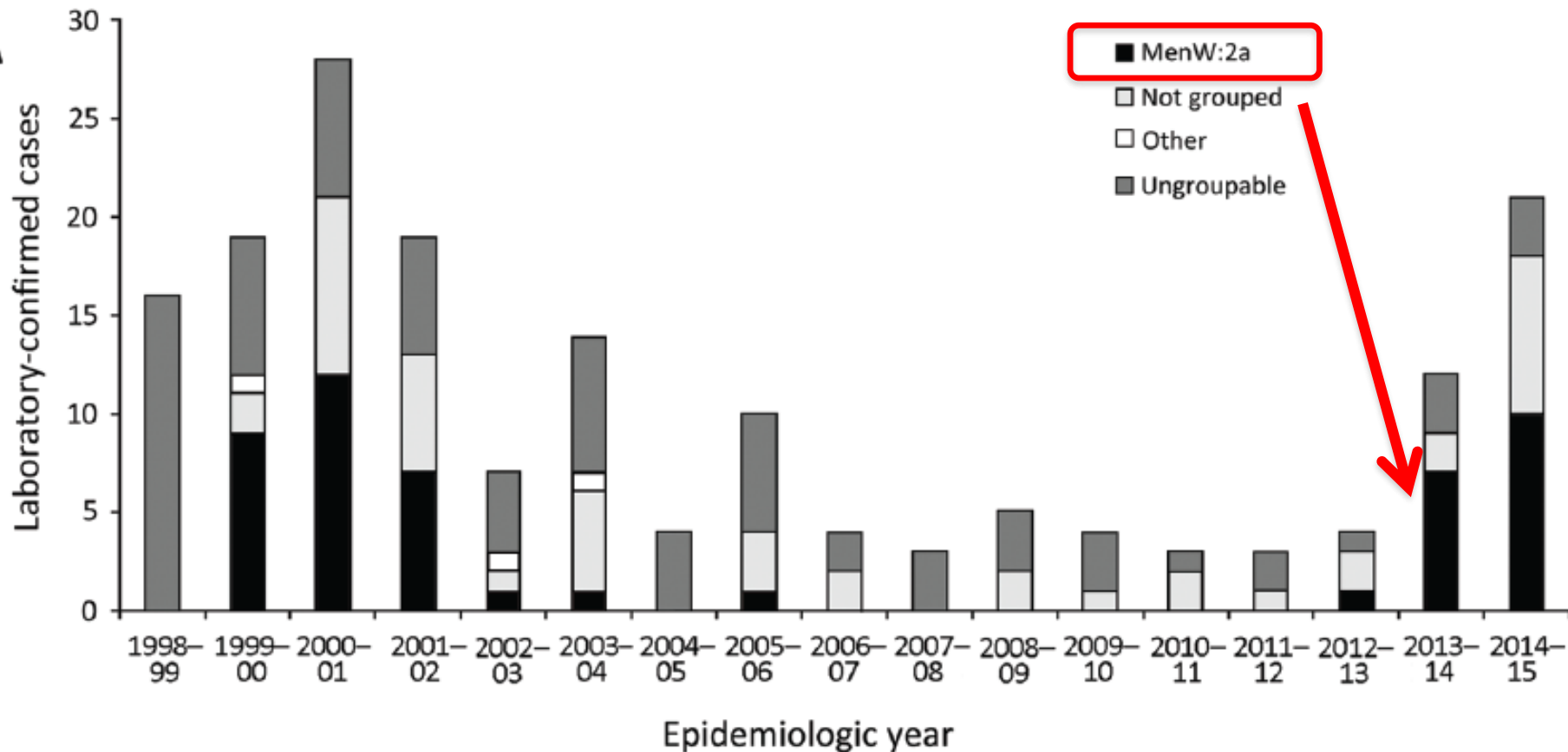
UK 2015 Immunisation Schedule



AGE	Immunisation (Vaccine Given)
2 months	<ul style="list-style-type: none">• DTaP/IPV(polio)/Hib (diphtheria, tetanus, pertussis (whooping cough), polio, and <i>Haemophilus influenzae</i> type b) - 5-in-one injection (Pediace® or Infanrix IPV Hib®); plus:• PCV (pneumococcal conjugate vaccine) - in a separate injection (Prevenar 13®).• Rotavirus (Rotarix®) - oral route (drops).• Meningitis B (Bexsero®).
3 months	<ul style="list-style-type: none">• DTaP/IPV(polio)/Hib 5-in-one injection, 2nd dose (Pediace® or Infanrix IPV Hib®); plus:• Rotavirus (Rotarix®) - oral route (drops).
4 months	<ul style="list-style-type: none">• DTaP/IPV(polio)/Hib 5-in-one injection, 3rd dose (Pediace® or Infanrix IPV Hib®); plus:• PCV 2nd dose (Prevenar 13®) - in a separate injection.• Meningitis B 2nd dose (Bexsero®).
Between 12 and 13 months	<ul style="list-style-type: none">• Hib/MenC (combined as one injection) - 4th dose of Hib and 1st dose of MenC (Menitorix®); plus:• MMR (measles, mumps and rubella) - combined as one injection (Priorix® or M-M-RVAXPRO®); plus:• PCV 3rd dose (Prevenar 13®) - in a separate injection.• Meningitis B 3rd dose (Bexsero®).

Meningococcal Group W Disease in Infants and Potential Prevention by Vaccination

A



RAPID COMMUNICATIONS

Presentation with gastrointestinal symptoms and high case fatality associated with group W meningococcal disease (MenW) in teenagers, England, July 2015 to January 2016

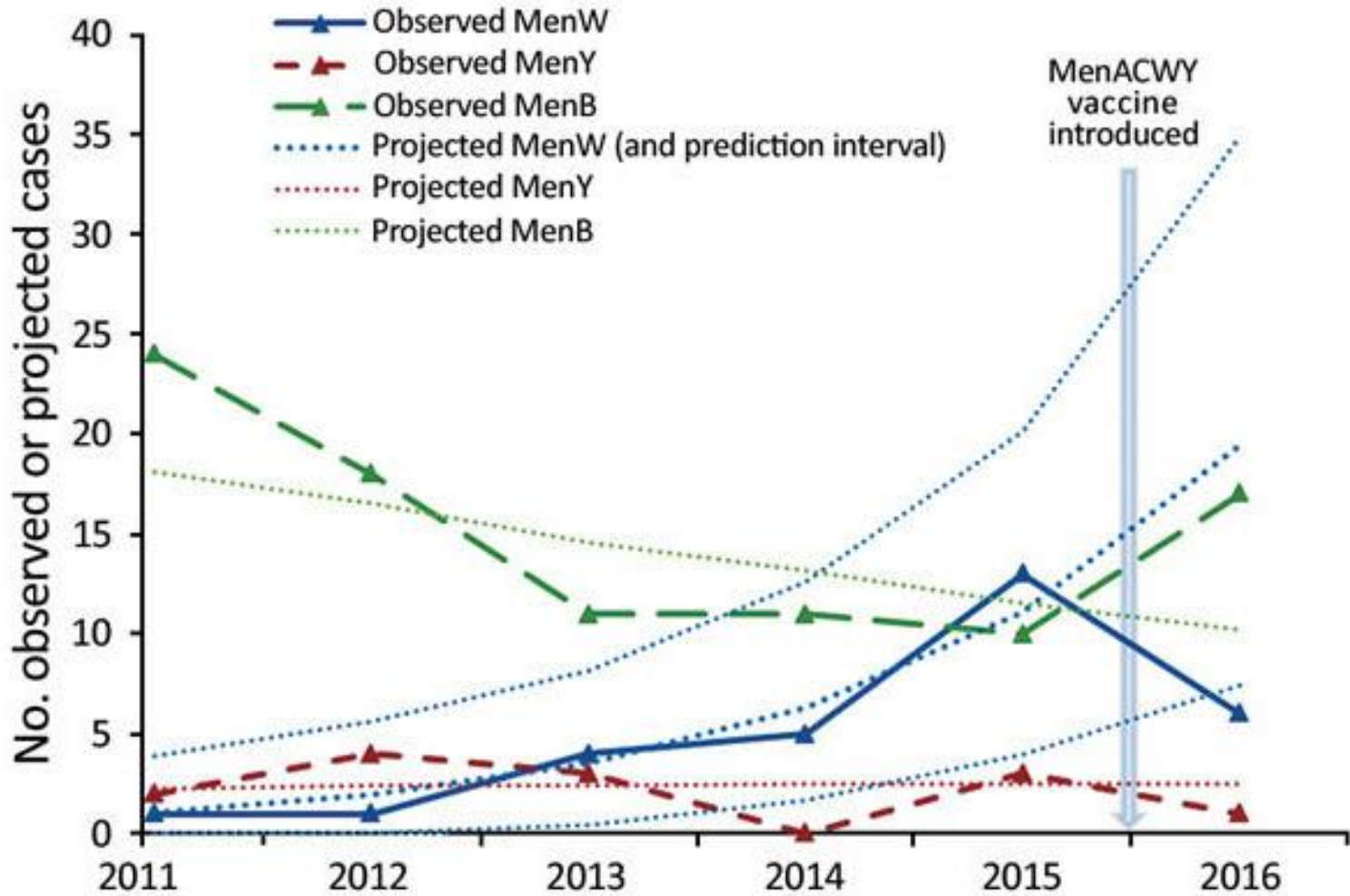
- 2015 Temmuz-2016 Ocak
- 15-19 yaş grubunda serogrup W salgını
- Hipervirulan ST-11 suşu
- 103 vaka
- GIS bulguları ile başvuru
- İlk 24 saat içinde ölümler
- Yüksek fatalite oranları

UK 2016 Immunisation Schedule

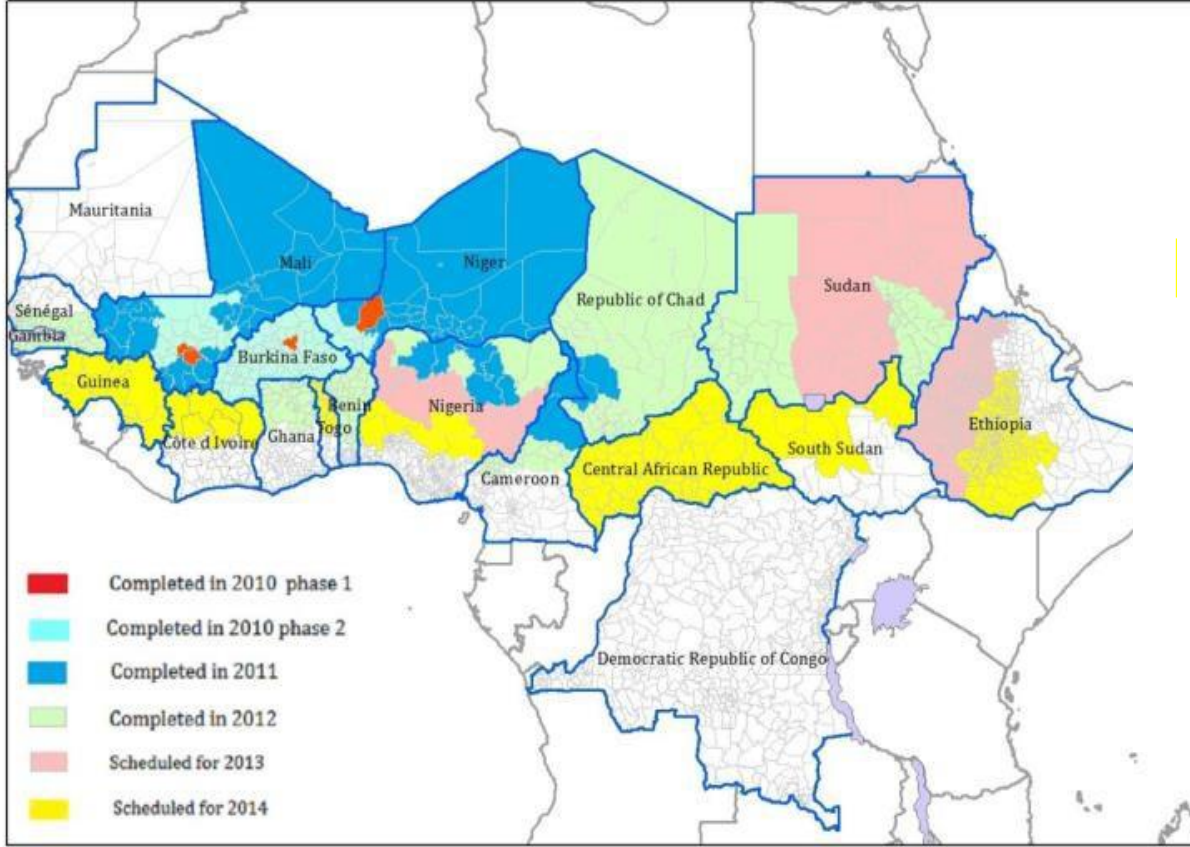


AGE

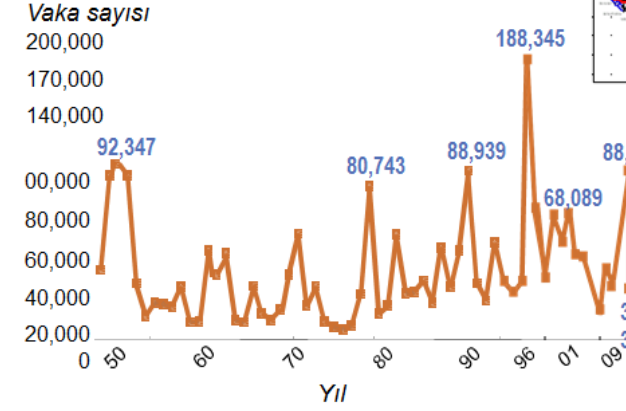
Immunisation (Vaccine Given)



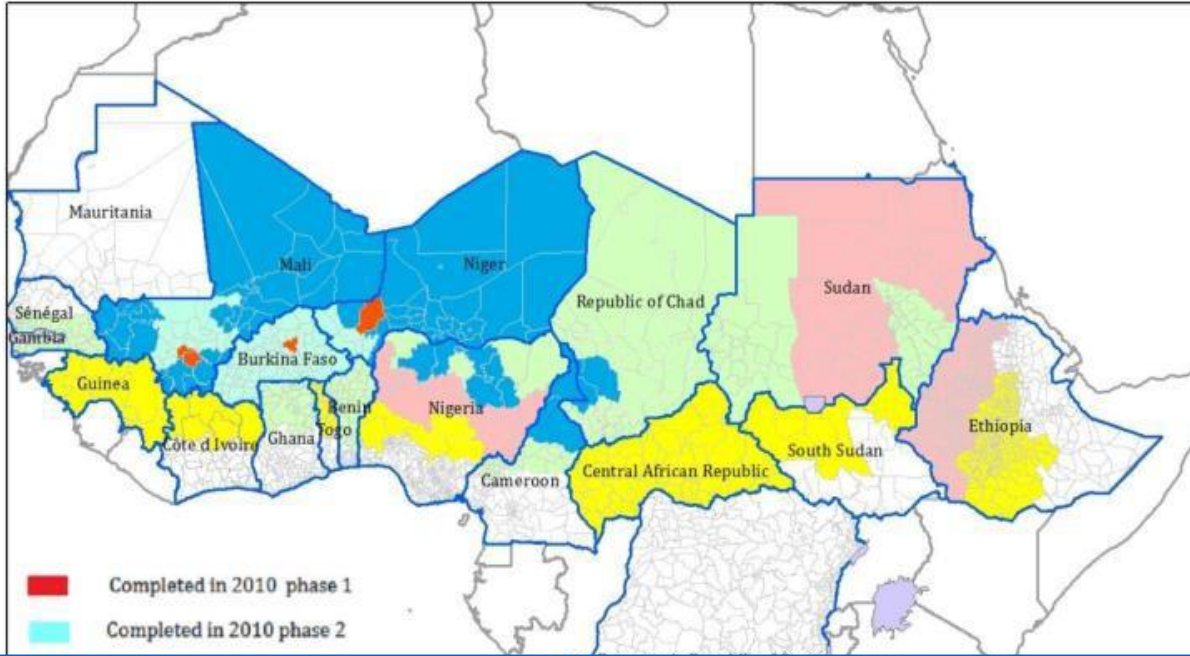
Afrika menenjit kuşağı



Yıllara göre vaka sayıları

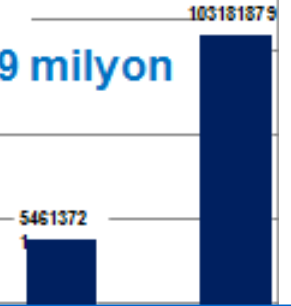


Men A Konjuge aşısı (MenAfriVac) (Kitlemel aşılama, 1-29 yaş)



2010-2012
103 milyon aşılama

2013 -+ 49 milyon
aşılama

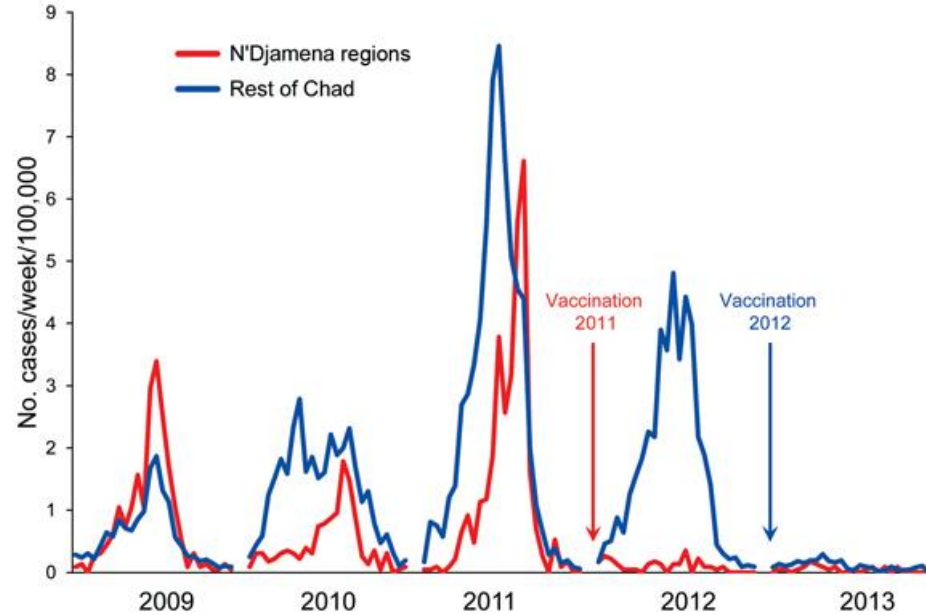


As of June 2016, over 235 million persons aged 1 to 29 years have received meningococcal A conjugate vaccine in 15 countries of the African belt.

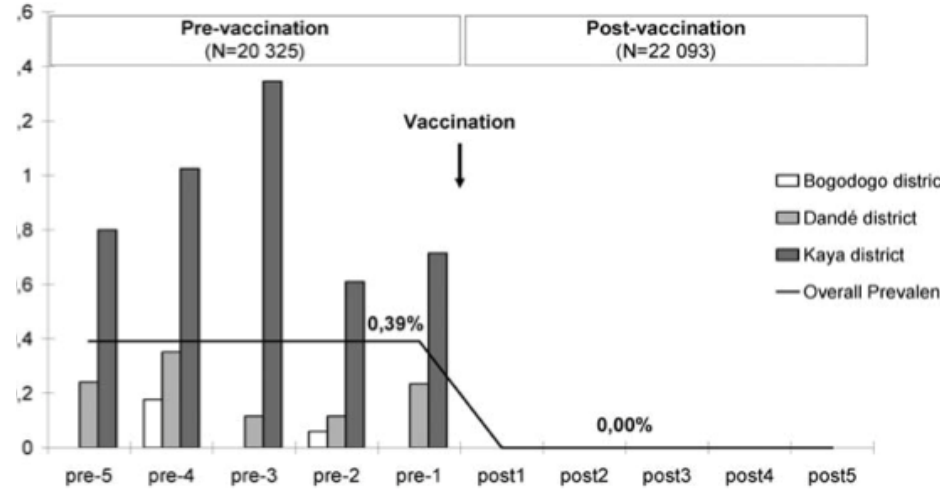
WHO - Serum Institute of India işbirliği ile PsA-TT aşısı

MenAfriVac etkinliđi

Effect of MenAfriVac[®] vaccination on number of meningitis cases

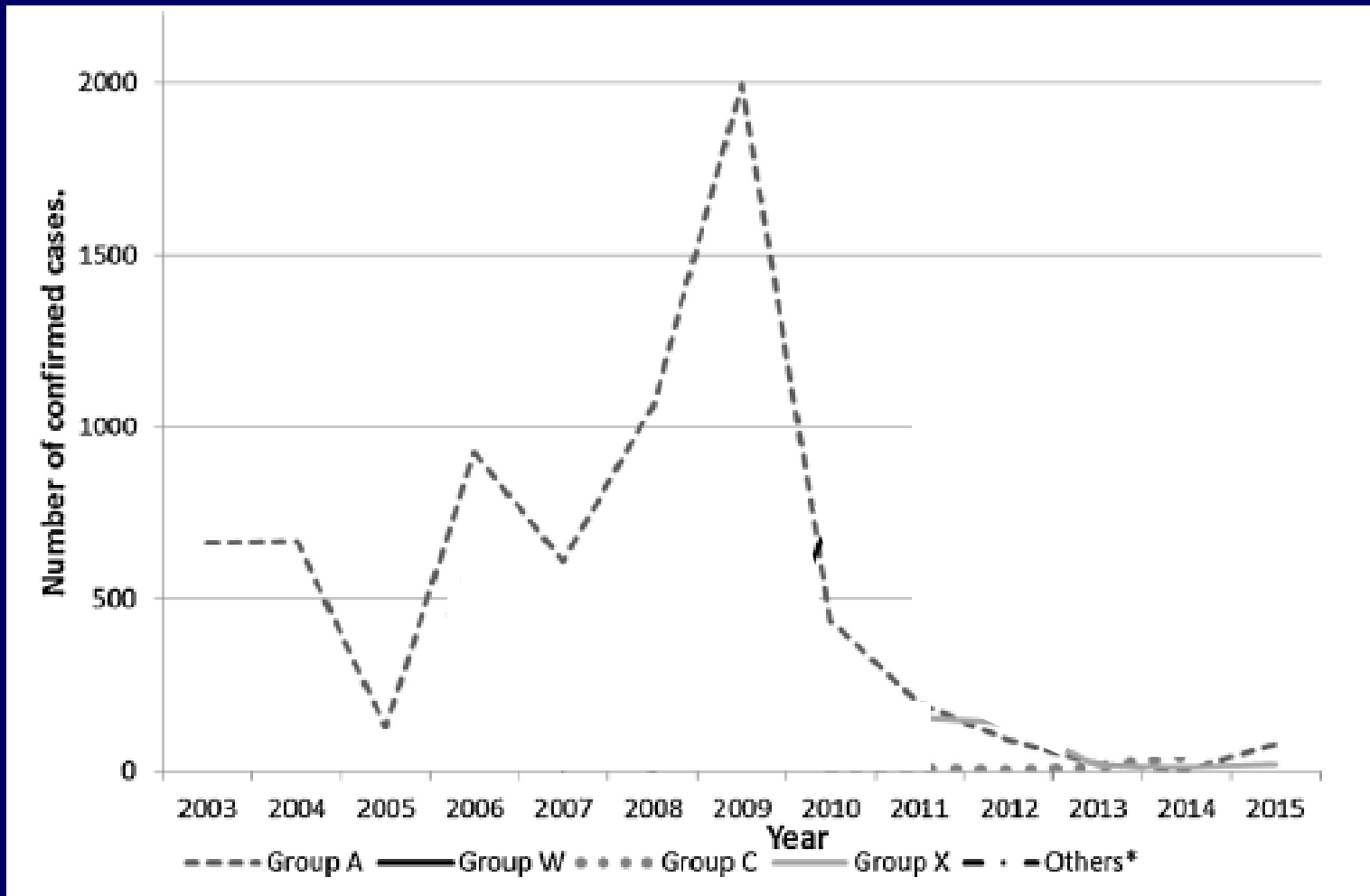


Carriage of serogroup A *Neisseria meningitidis* at 5 timepoints before (pre-5 to pre-1) and 5 timepoints after (post1 to post5) MenAfriVac vaccination.



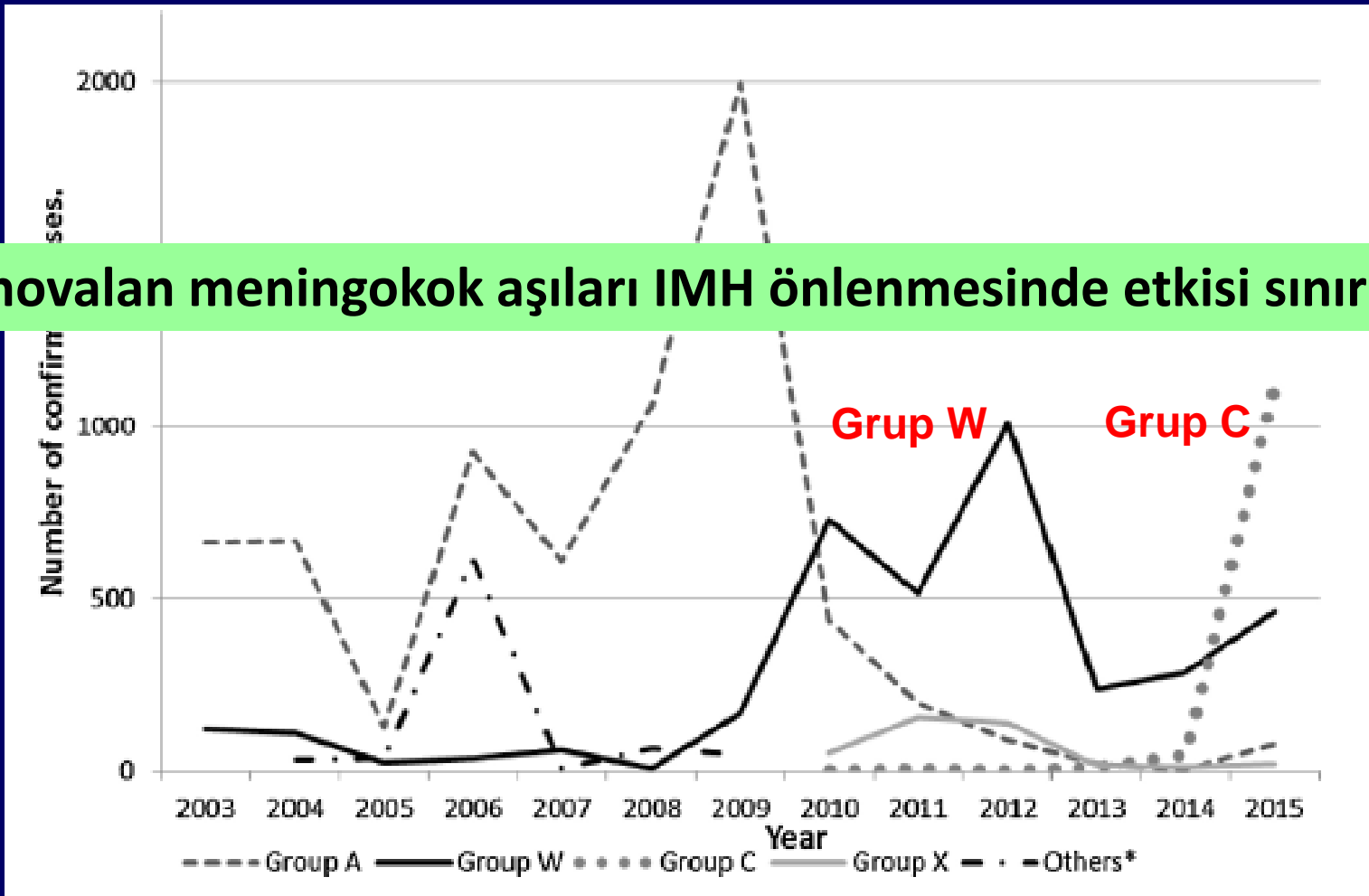
MenAfrivac, serogroup A'ya bađlı invaziv meningokok hastalıđının ve taşıyıcılıđın önlenmesinde çok etkili bulunmuştur.

Afrika menenjit kuşağı IMH vakalarının dağılımı (2003-2015)



Afrika menenjit kuşığı IMH vakalarının dağılımı (2003-2015)

Monovalan meningokok aşıları IMH önlenmesinde etkisi sınırlıdır.



Distribution of capsular groups among confirmed invasive meningococcal disease cases, African meningitis belt, 2003–2015.

Konjuge MenACWY aşıları

	MenACWY-TT	MenACWY-CRM	MenACWY-DT
Türkiye	<ul style="list-style-type: none">12 aylıktan itibaren her yaşta tek doz	<ul style="list-style-type: none">2 ay-55 yaş2-9 ay: risk grubuna9 aydan itibaren sağlıklı bireylere	<ul style="list-style-type: none">9 ay-55 yaş9-23 ay: iki doz (3 ay ara ile)2-55 yaş: tek doz
EMA	<ul style="list-style-type: none">6.haftadan itibaren uygulanır.6 ila 12 haftalık bebeklere üç (2+1) doz12 ay ve üzeri tek doz	<ul style="list-style-type: none">2 yaş ve üzeri tek doz	<ul style="list-style-type: none">EMA onayı yok
FDA		<ul style="list-style-type: none">2 ay-55 yaş	<ul style="list-style-type: none">9 ay-55 yaş

Konjuge MenACWY-TT aşısı (Nimenrix)

- Serogrup A,C,W,Y içeren dört bileşenli konjuge meningokok aşısı
- Taşıyıcı protein: Tetanoz toksoidi (TT)
- Adjuvan ve thimerosal içermez
- İntramuskuler olarak uygulanır.

<i>Neisseria meningitidis</i> serogrup A polisakkariti ¹	5 µg
<i>Neisseria meningitidis</i> serogrup C polisakkariti ¹	5 µg
<i>Neisseria meningitidis</i> serogrup W ₁₃₅ polisakkariti ¹	5 µg
<i>Neisseria meningitidis</i> serogrup Y polisakkariti ¹	5 µg
¹ tetanoz toksoid taşıyıcı proteine konjuge	44 µg

MenACWY-TT aşısı (Nimenrix)

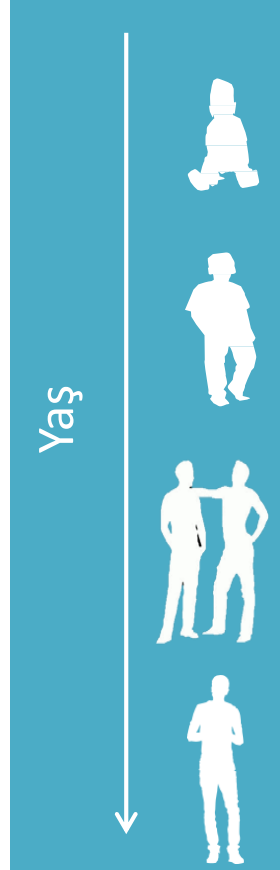
- EMEA tarafından Nisan 2012' de onaylanmıştır.
- 12 aydan büyük çocuk ve erişkinlerde tek doz intramuskuler olarak uygulanması önerilmektedir.
- 2016 yılında EMEA 6. haftadan itibaren (2+1 şeması ile) uygulama onayı vermiştir (Avrupa'da)
- Türkiye'de halen 12.ay sonrası kullanım onaylıdır.

MenACWY-TT aşıısı

- İmmünojenite ve güvenirlilik alıřmaları
- Birlikte uygulama alıřmaları
- Antikor persistansı alıřmaları

MenACWY-TT aşısı immunojenite çalışmaları

Nimenrix ile ilgili **>8000** kişide Faz II ve Faz III çalışma yürütülmüştür.



1052 bebek (6-12 hafta ilk doz için)

3079 toddlers (12-23 ay)

909 çocuk (2-5 yaş arası)

990 büyük çocuk (6-10 yaş arası)

2317 adölesan (11-17 yaş arası)

2326 erişkin (18-55 yaş arası)

374 deneyimli erişkin (56 yaş üstü)

(ABD, Meksika, Panama, Lübnan, Suudi Arabistan, Avusturya, Çek Cumhuriyeti, Danimarka, Finlandiya, Yunanistan, Almanya, İsveç, Fransa, Hindistan, Tayvan, Tayland, Filipinler)

İmmünojenite çalışmaları

hSBA (İnsan komplemanı serum bakterisidal antikor) analizleri

≥1:4 değerindeki hSBA titreleri, koruma eşik değeri olarak kabul edilir

rSBA (Tavşan komplemanı serum bakterisidal antikor) analizleri

≥1:8 değerindeki rSBA titreleri, koruma eşik değeri olarak kabul edilir.

İnsan veya yavru tavşan komplemanı kullanılan SBA analizleri, DSÖ³ ve ruhsatlandırma kurumları tarafından kabul edilmektedir⁴

MenACWY-TT Klinik Çalışmaları

**12 AY BEBEKLERDE
TEK DOZ MENACWY-TT İMMUNOJENİK VE GÜVENİLİR**

Vaccine 34 (2016) 3363–3370

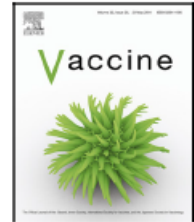


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Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Safety and immunogenicity of a CRM or TT conjugated meningococcal vaccine in healthy toddlers



Gianni Bona^a, Paolo Castiglia^b, Giorgio Zoppi^c, Maurizio de Martino^d,
Annaelisa Tasciotti^e, Diego D'Agostino^f, Linda Han^g, Igor Smolenov^{f,*}

MenACWY-TT Klinik Çalışmaları

**12-23 AY VE 3-5 YAŞ ARASI ÇOCUKLARDA TEK DOZ MENACWY-TT
İMMUNOJENİK VE GÜVENİLİR**

Vaccine 28 (2010) 744–753



Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



A dose-range study assessing immunogenicity and safety of one dose of a new candidate meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate (MenACWY-TT) vaccine administered in the second year of life and in young children

M. Knuf^a, D. Kieninger-Baum^a, P. Habermehl^a, P. Muttonen^b, H. Maurer^c, P. Vink^d,
J. Poolman^d, D. Boutriau^{d,*}

MenACWY-TT Klinik Çalışmaları

2-10 YAŞ ARASI ÇOCUKLARDA TEK DOZ MENACWY-TT İMMUNOJENİK VE GÜVENİLİR

Eur J Pediatr (2013) 172:601–612
DOI 10.1007/s00431-012-1924-0

ORIGINAL ARTICLE

Immunogenicity and safety of the quadrivalent meningococcal serogroups A, C, W-135 and Y tetanus toxoid conjugate vaccine (MenACWY-TT) in 2–10-year-old children: results of an open, randomised, controlled study

Markus Knuf • Olivier Romain • Klaus Kindler •
Uta Walther • Phu-My Tran • Heidemarie Pankow-Culot •
Thomas Fischbach • Dorothee Kieninger-Baum •
Véronique Bianco • Yaela Baine • Jacqueline Miller

MenACWY-TT Klinik Çalışmaları

**10-25 YAŞ ARASI ADÖLESAN VE GENÇ ERİŞKİNLERDE TEK DOZ MENACWY-TT
İMMUNOJENİK VE GÜVENİLİR**

ORIGINAL STUDIES

Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal ACWY Tetanus Toxoid Conjugate Vaccine in Healthy Adolescents and Young Adults 10 to 25 Years of Age

Roger Baxter, MD, Yaela Baine, PhD,† Kathleen Ensor, BA, RN,* Veronique Bianco, MS,‡
Leonard R. Friedland, MD,† and Jacqueline M. Miller, MD†*

MenACWY-TT Klinik Çalışmaları

11-55 YAŞ ARASI ADÖLESAN VE ERİŞKİNLERDE TEK DOZ MENACWY-TT İMMUNOJENİK VE GÜVENİLİR

Borja-Tabora *et al. BMC Infectious Diseases* 2013, **13**:116
<http://www.biomedcentral.com/1471-2334/13/116>



RESEARCH ARTICLE

Open Access

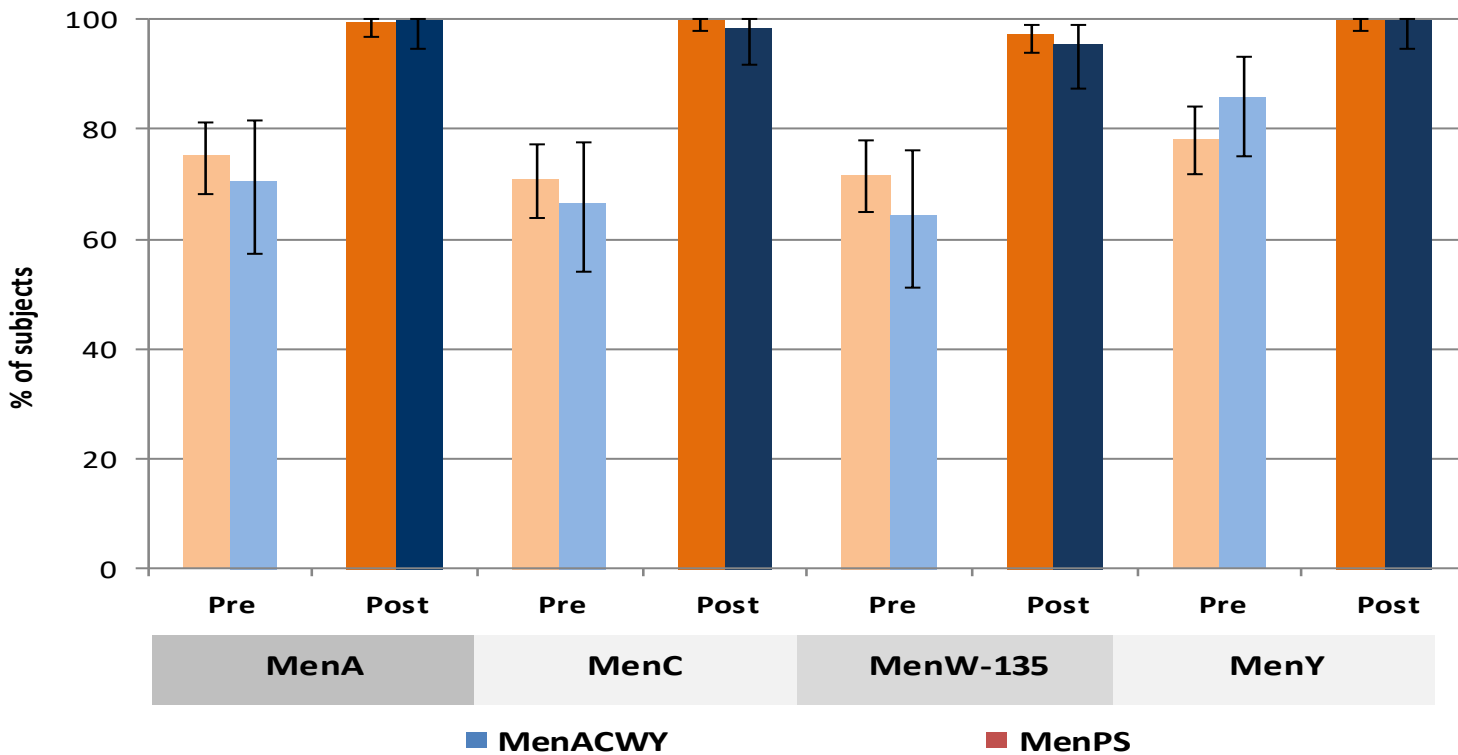
Immune response, antibody persistence, and safety of a single dose of the quadrivalent meningococcal serogroups A, C, W-135, and Y tetanus toxoid conjugate vaccine in adolescents and adults: results of an open, randomised, controlled study

Charissa Borja-Tabora¹, Cecilia Montalban², Ziad A Memish^{3*}, Marie Van der Wielen⁴, Veronique Bianco⁴, Dominique Boutriau⁴ and Jacqueline Miller⁵

MenACWY-TT Klinik Çalışmaları

**56-103 YAŞ DENEYİMLİ ERİŞKİNLERDE
TEK DOZ MENACWY-TT İMMUNOJENİK VE GÜVENİLİR**

rSBA: % of subjects with antibody titers $\geq 1:8$



MenACWY-TT Klinik Çalışmaları

2 AYLIK BEBEKLERDE 2+1 ŞEMASI İLE UYGULANAN MENACWY-TT AŞISI İMMUNOJENİK VE GÜVENİLİR

Abstract

Background:

This was the first study evaluating the immunogenicity and safety of the quadrivalent meningococcal tetanus toxoid conjugate vaccine (MenACWY-TT) coadministered with routine childhood vaccines in young infants.

Methods:

In this open, randomized, controlled, phase III study (NCT01144663), 2095 infants (ages 6–12 weeks) were randomized (1:1:1) into 4 groups to receive MenACWY-TT at 2, 3, 4 and 12 months of age, or MenACWY-TT, MenC-cross-reactive material (CRM197) or MenC-TT at 2, 4 and 12 months of age. All participants received PHiD-CV and DTPa-HBV-IPV/Hib at 2, 3, 4 and 12 months of age. Immune responses were measured by serum bactericidal activity assays using rabbit (rSBA) and human (hSBA) complement. Solicited and unsolicited symptoms were recorded during 8 and 31 days post-vaccination, respectively, and serious adverse events throughout the study.

Results:

Noninferiority of immune responses to MenC induced by 2 or 3 doses of MenACWY-TT versus 2 doses of MenC-TT or MenC-CRM197 was demonstrated. Predefined criteria for the immunogenicity of MenACWY-TT to MenA, MenW and MenY were met. One month after 2 or 3 primary MenACWY-TT doses, ≥93.1% and ≥88.5% of infants had rSBA and hSBA titers ≥1:8 for all serogroups. The robust increases in rSBA and hSBA titers observed for all vaccine serogroups postbooster vaccination suggested that MenACWY-TT induced immune memory. MenACWY-TT coadministered with childhood vaccines had a clinically acceptable safety profile.

Conclusions:

This study supports the coadministration of MenACWY-TT with routine childhood vaccines as 2 or 3 primary doses during infancy followed by a booster dose in the second year of life.

Child
hood

MD, II

PhD, III
PhD, §§§§

(...)

MenACWY-TT İstenmeyen Etkiler

SİSTEMİK İSTENMEYEN ETKİLER

- 12-23 ay: irritabilite, halsizlik, ateş, iştahsızlık
- 2-5 yaş yaş: halsizlik, irritabilite, ateş, iştahsızlık
- 6-10 yaş: halsizlik, baş ağrısı, GIS bulguları, ateş
- 11-17 yaş: halsizlik, baş ağrısı, GIS bulguları, ateş
- 18-55 yaş: baş ağrısı, halsizlik, GIS bulguları, ateş
- >55 yaş: çok nadiren baş ağrısı

ORIGINAL REPORT

Risk of GBS		Vaccinations before GBS onset date		gate	
1354	MCV4	9 (12.5)	67,471)*	administration MCV4, n (%)†	
	MPSV4	2 (2.0)			
	Tdap	10 (10.1)			
	Tetanus	0 (0.0)			
	Td	3 (3.0)			
	Influenza	9 (9.1)			
	HepB	3 (3.0)			
	HPV§	5 (10.9)			
	Vaccinations within 42 days of GBS onset date				
	MCV4	0 (0.0)			85 (0.2)§
MPSV4	1 (1.0)	,991 (22.8)			
Tdap	0 (0.0)	1,535 (3.9)			
Tetanus	0 (0.0)	93 (0.2)			
Influenza	2 (2.0)	1,817 (4.6)			
HepB	1 (1.0)	2,708 (6.9)			
HPV§	2 (4.3)	,430 (11.3)			

MCV4
MPSV4
Tdap
Td
Tetanus
Influenza
HepB
HPV

⁶Department
⁷Optum Insig
⁸Highmark In
⁹Duke Clinica
¹⁰Aetna, Blue
¹¹Kaiser Peri
¹²World Hea

ORIGINAL REPORT

	Vaccinations before GBS onset date		
Risk of vaccination	MCV4	9 (12.5)	L. Syat ¹ , M. Crane ³ , D. F. Crane ³ , J. M. Crane ³ , P. M. Crane ³
	MPSV4	2 (2.0)	
	Tdap	10 (10.1)	
	Tetanus	0 (0.0)	
	Td	3 (3.0)	
	Influenza	9 (9.1)	
Priscilla M. Crane ³	HepB	3 (3.0)	L. Syat ¹ , M. Crane ³ , D. F. Crane ³ , J. M. Crane ³ , P. M. Crane ³
Donnie F. Crane ³	HPV [§]	5 (10.9)	
Judith M. Crane ³	Vaccinations within 42 days of GBS onset date		
Peter M. Crane ³	MCV4	0 (0.0)	
	MPSV4	1 (1.0)	
	Tdap	1 (1.0)	
	Tetanus	0 (0.0)	A, USA
	Td	0 (0.0)	
	Influenza	2 (2.0)	
	HepB	1 (1.0)	
	HPV [§]	2 (4.3)	
	MCV4 vaccination was not associated with increased GBS risk.		

¹ Department of

² Outcome Research

³ Department of

⁴ Harvard Medical School

⁵ HealthCare

⁶ Department of

⁷ Optum Inc.

⁸ Highmark

⁹ Duke Clinical Research Institute

¹⁰ Aetna, Inc.

¹¹ Kaiser Permanente

¹² World Health Organization

MenACWY-TT aşıısı

- İmmünojenite ve güvenirlilik alıřmaları
- **Birlikte uygulama alıřmaları**

MenACWY-TT Birlikte Uygulama Çalışmaları

Vaccine 29 (2011) 4274–4284



Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Tetravalent meningococcal serogroups A, C, W-135 and Y conjugate vaccine is well tolerated and immunogenic when co-administered with measles–mumps–rubella–varicella vaccine during the second year of life: An open, randomized controlled trial

Timo Vesikari^{a,*}, Aino Karvonen^a, Veronique Bianco^b, Marie Van der Wielen^b, Jacqueline Miller^c

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^b GlaxoSmithKline Biologicals, Belgium

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ABSTRACT

Co-administration of meningococcal ACWY-tetanus toxoid conjugate vaccine (ACWY-TT) with MMRV vaccine was investigated in 1000 12–23-month old children randomized (3:3:1:1) to receive co-administered ACWY-TT+MMRV, or a single dose of ACWY-TT, MMRV or MenC-CRM₁₉₇. Non-inferiority of ACWY-TT to MenC-CRM₁₉₇ and non-inferiority of ACWY-TT+MMRV to ACWY-TT and MMRV alone, and the immunogenicity of serogroups AWY were demonstrated according to pre-defined criteria. Fever reactions in ACWY+MMRV and MMRV groups were comparable. ACWY-TT can be co-administered with MMRV without affecting immunogenicity or safety profiles of either vaccine.

This study has been registered at www.clinicaltrials.gov NCT00474266.

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MenACWY-TT Birlikte Uygulama Çalışmaları

- **KKK - suçiçeği aşısı,**
- **Difteri-tetanoz-asellüler boğmaca-IPA-HBV-Hib,**
- **Hepatit A-B aşısı,**
- **10-bileşenli konjuge pnömokok aşısı,**
- **13-bileşenli konjuge pnömokok aşısı,**
- **HPV aşısı,**
- **Tdab,**
- **Mevsimsel grip aşısı ile birlikte uygulanabilir.**

MenACWY-TT aşıısı

- **Noninferiorite alıřmaları, menACWY-TT aşıısının diđer ocukluk dnemi ařılıyla veya mevsimsel grip aşıısı ile birlikte uygulandıđında immunojenesitesinin veya birlikte uygulandıđı ařının immunojenesitesinin deđiřmediđini gstermiřtir.**

MenACWY-TT aşısı

- **MenACWY-TT tek başına veya rutindeki diğer aşılarla birlikte uygulandığında, tüm yaş gruplarında iyi tolere edilir. Grade 3 lokal veya sistemik istenmeyen etkilerin insidansı (ilk 4 günde) ve ciddi yan etki insidansı (6 aylık izlem periyodunda) düşüktür (<%4.5).**

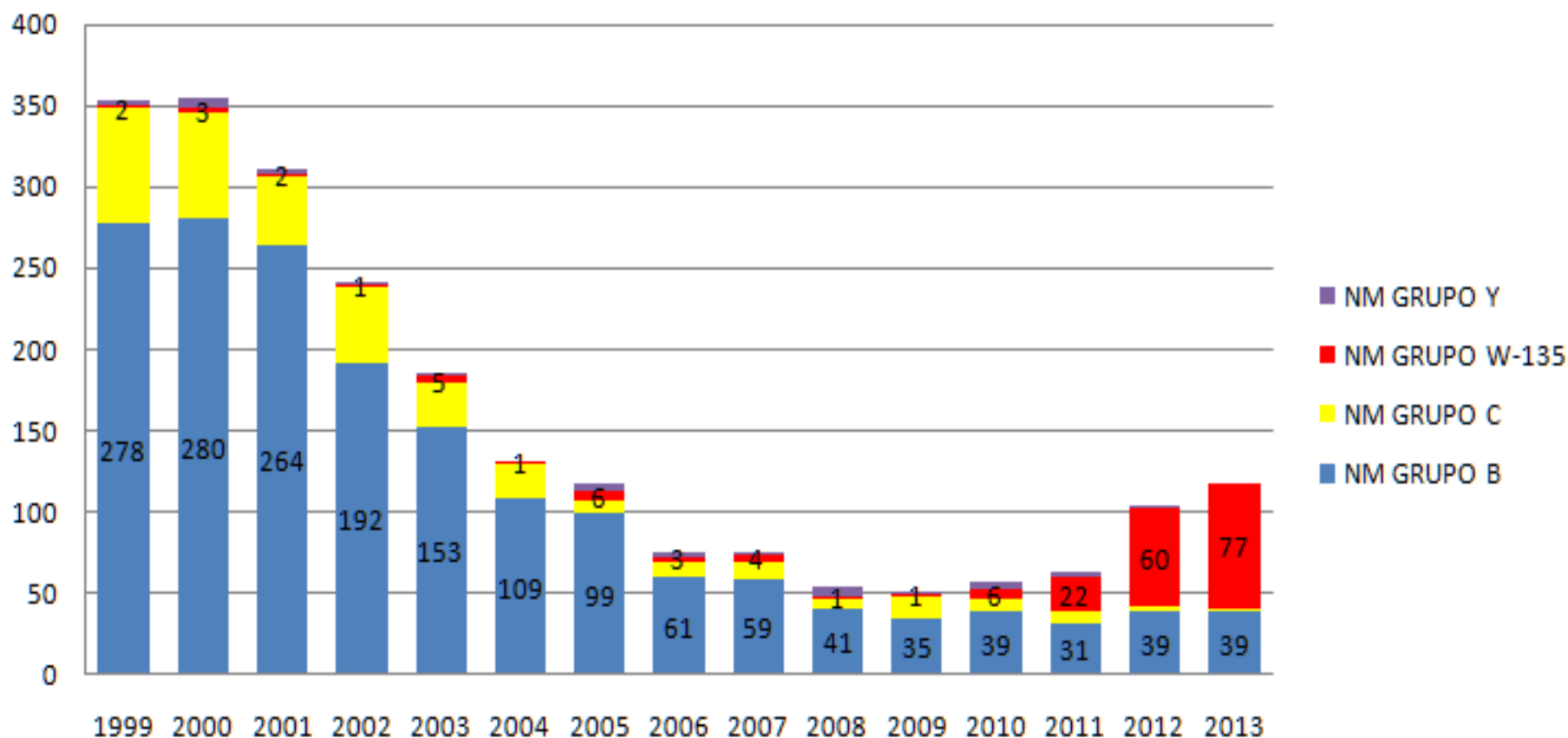
Nimenrix 71 ülkede ruhsatlıdır

Avrupa Birliği Ülkeleri		Diğer Ülkeler	
ALMANYA		SUUDİ ARABİSTAN	FİLİPİNLER
BELÇİKA			BRUNEİ
BULGARİSTAN		BRAZİLYA	KENYA
HİRVATİSTAN			KONGO
KIBRIS		İSRAİL	BAHREYN
ÇEK CUMHURİYETİ			FİLDİŞİ SAHİLİ
DANİMARKA		BİRLEŞİK KRALLIK	GANA
ESTONYA			ETİYOPYA
FİNLANDİYA		TÜRKİYE	HONG KONG
FRANSA			KOLOMBİYA
ALMANYA		BOSNA HERSEK	MALEZYA
YUNANİSTAN		BANGLADEŞ	KONGO
MACARİSTAN		KAMERUN	BİRLEŞİK ARAP EMİRLİKLERİ
İRLANDA		NİJER	SİNGAPUR
İTALYA		MALİ	YENİ ZELANDA
LETONYA		KUVEYT	TANZANYA
LİTVANYA		KANADA	UKRAYNA
LÜKSEMBURG		TAYLAND	KAZAKİSTAN
MALTA		LÜBNAN	
HOLLANDA		GİNE	
POLONYA		GABON	
PORTEKİZ		FAS	
ROMANYA		SENEGAL	
SLOVAKYA		TUNUS	
SLOVENYA		KATAR	
İSPANYA		PANAMA	
İSVEÇ		UGANDA	
		NİJERYA	
		AVUSTRALYA	
		ŞİLİ	
		FİLİPİNLER	
		BRUNEİ	

Şili'de meningokok hastalığı

Serogrup W salgını

Distribución de Serogrupos de N.meningitidis.
Chile, años 1999-2013* (SE 45)



The Global Meningococcal Initiative: global epidemiology, the impact of vaccines on meningococcal disease and the importance of herd protection

<http://dx.doi.org/10.1080/14760584.2017.1258308>

Ray Borrow, Pedro Alarcón, Josefina Carlos, Dominique A. Caugant, Hannah Christensen, Roberto Debbag, Philippe De Wals, Gabriela Echániz-Aviles, Jamie Findlow, Chris Head, Daphne Holt, Hajime Kamiya, Samir K Saha, Sergey Sidorenko, Muhamed-Kheir Taha, Caroline Trotter, Julio A. Vázquez Moreno, Anne von Gottberg & Marco A. P. Sáfadion behalf of the Global Meningococcal Initiative

3.3.2. MenW control

Vaccination strategies for controlling MenW and other *N. meningitidis* strains using multivalent conjugate vaccines are being rolled out in a number of countries. An immunization campaign began in 2012 in Chile with the quadrivalent conjugate vaccine (MenACWY; Menveo®; Table 1), initially targeting children aged from 9 months to <5 years. The incidence of MD in this age group before and after introduction of quadrivalent *N. meningitidis* (MenACWY) vaccination is shown in Figure 4. Since 2012, approximately 1 million children have been vaccinated, and vaccine uptake of 95% has been attained in these age groups (data from ISPCH Laboratorio de Agentes de Meningitis Bacteriana). In addition, since 2012, a temporary vaccination strategy was established in which children aged from 9 months to 5 years were vaccinated, and infants from 9 months old were given a second dose to increase protection. The vaccines Menactra® (Table 1) and Menveo® have been used as part of this temporary vaccination strategy. On 1 January 2014, vaccination became part of the national immunization schedule and was mandatory for all children aged ≥ 1 year, with a one-dose schedule of Nimenrix® (Table 1) implemented.

The Global Meningococcal Initiative: global epidemiology, the impact of vaccines on meningococcal disease and the importance of herd protection

<http://dx.doi.org/10.1080/14760584.2017.1258308>

Ray Borrow, Pedro Alarcón, Josefina Carlos, Dominique A. Caugant, Hannah Christensen, Roberto Debbag, Philippe De Wals, Gabriela Echániz-Aviles, Jamie Findlow, Chris Head, Daphne Holt, Hajime Kamiya, Samir K Saha, Sergey Sidorenko, Muhamed-Kheir Taha, Caroline Trotter, Julio A. Vázquez Moreno, Anne von Gottberg & Marco A. P. Sáfadion behalf of the Global Meningococcal Initiative

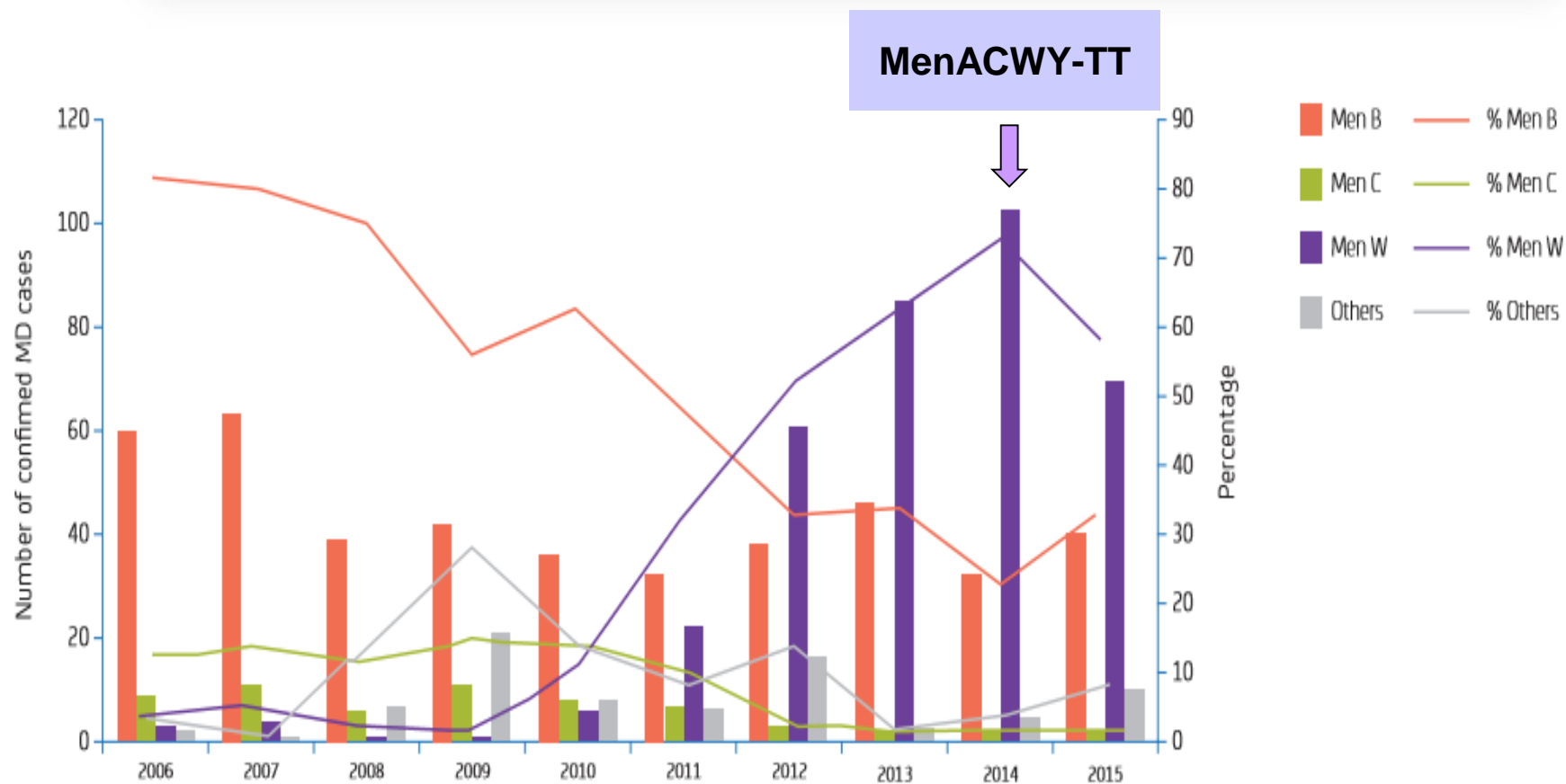


Figure 4. Incidence of MD in Chile in children between 9 months and <5 years of age before and after introduction of quadrivalent *Neisseria meningitidis* (MenACWY) vaccination in 2012 (unpublished data from Instituto de Salud Pública de Chile, Laboratorio de Agentes de Meningitis Bacteriana, Santiago, Chile).

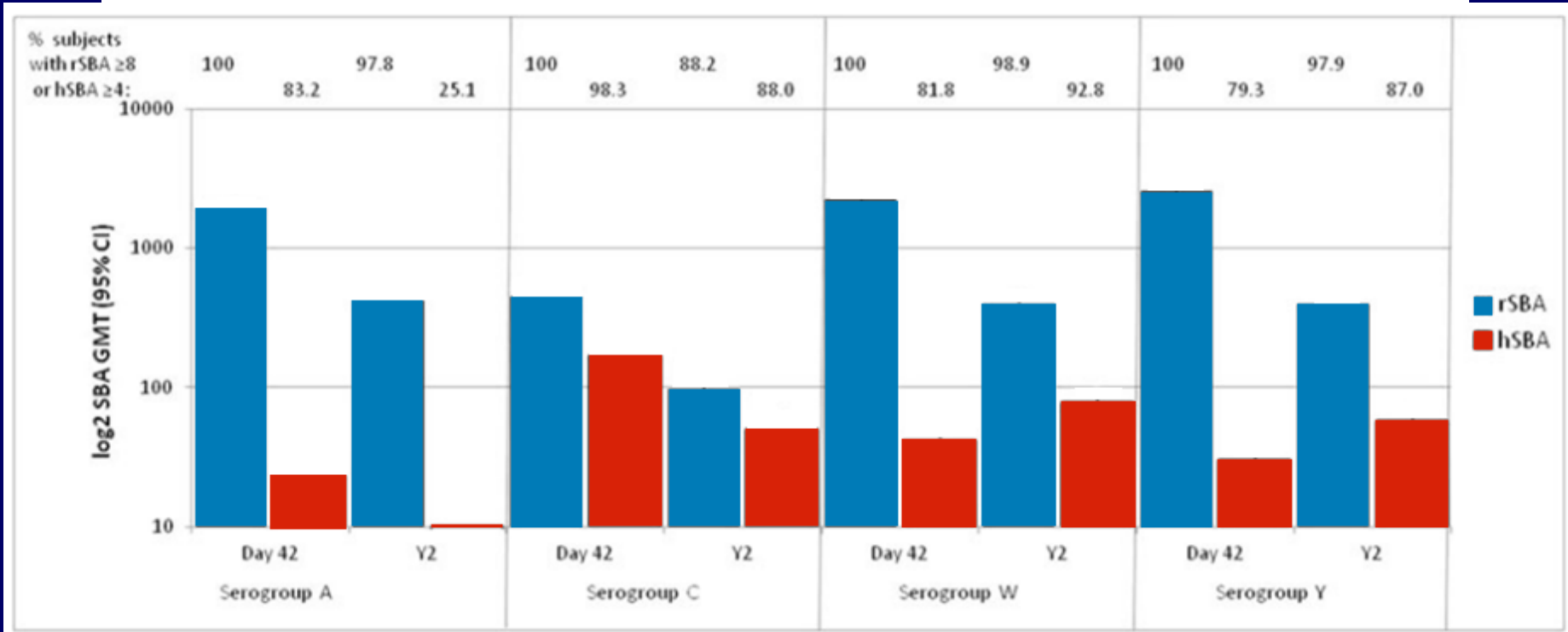
MD: meningococcal disease; Men: *Neisseria meningitidis* serogroup.

MenACWY-TT aşıısı

- İmmünojenite ve güvenirlilik alıřmaları
- Birlikte uygulama alıřmaları
- **Antikor persistansı**



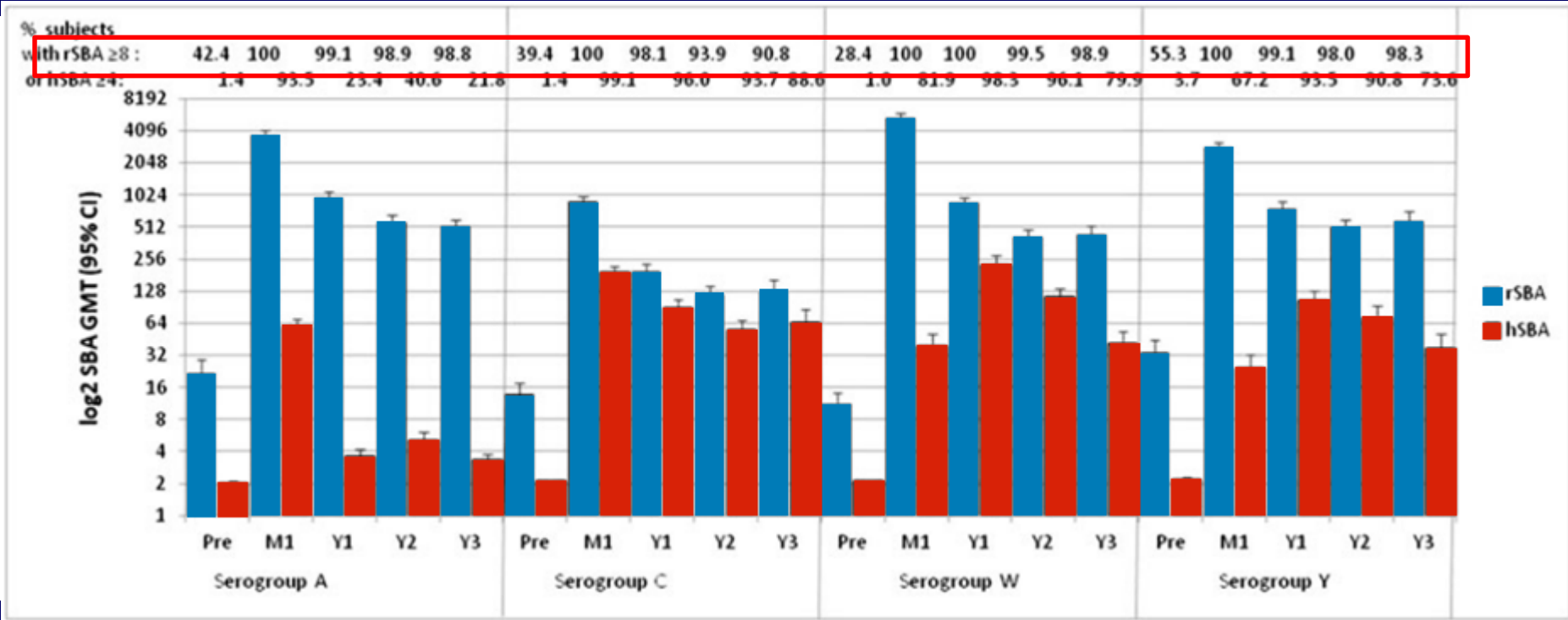
MenACWY-TT Antikor Persistansı (24. ay)



Percentage of toddlers with rSBA or hSBA titres ≥ 8 or ≥ 4 , respectively, and rSBA GMTs at pre-vaccination and 1 month, 1,2 and 3 y post-vaccination with ACWYTT

12. ayda tek doz MenACWY-TT uygulanan 2-10 yaş grubu çocuklarda aşılamadan 24 ay sonra yeterli aşı yanıtının devam ettiği gösterilmiştir.

MenACWY-TT Antikor Persistansı (36. ay)



Percentage of toddlers with rSBA or hSBA titres ≥8 or ≥4, respectively, and rSBA GMTs at pre-vaccination and 1 month, 1,2 and 3 y post-vaccination with ACWYTT

12. ayda tek doz MenACWY-TT uygulanan 1-10 yaş grubu çocuklarda aşılamadan 36 ay sonra yeterli aşı yanıtının devam ettiği gösterilmiştir.

MenACWY-TT Antikor Persistansı (60. ay)

We studied the persistence of serum bactericidal antibody using rabbit and human complement (rSBA/hSBA, cut-offs 1:8) 5 y after a single dose of meningococcal serogroups A, C, W, Y tetanus toxoid conjugate vaccine (MenACWY-TT) compared with age-appropriate control vaccines in toddlers and children (NCT00427908). Children were previously randomized (3:1) to receive either MenACWY-TT or control vaccine (MenC-CRM₁₉₇ in 1-<2 y olds; MenACWY-polysaccharide vaccine [Men-PS] in 2-<11 y olds). Subjects with rSBA-MenC titers <1:8 at any time point were revaccinated with MenC conjugate vaccine and discontinued from the study. A repeated measurement statistical model assessed potential selection effects due to drop-outs. At year 5 in MenACWY-TT-vaccinated-toddlers for serogroups A, C, W, and Y respectively, percentages with rSBA titers \geq 1:8 were 73.5%, 77.6%, 34.7%, and 42.9%, hSBA \geq 1:8 were 35.6%, 91.7%, 82.6% and 80.0%. For MenC-CRM₁₉₇ recipients, 63.6% had persisting rSBA-MenC titers \geq 1:8 and 90.9% had hSBA-MenC \geq 1:8 (not significantly different versus MenACWY-TT for either assay: exploratory analyses). In 2-<11 y olds rSBA titers \geq 1:8 in MenACWY-TT-vaccinees were 90.8%, 90.8%, 78.6%, and 78.6% and 15.4%, 100%, 0.0%, 7.7% in Men-PS-vaccinees (significantly different for serogroups A, W and Y, exploratory analyses). Serogroups A, W and Y rSBA GMTs were \geq 26-fold higher in MenACWY-TT-vaccinees. As expected, GMTs modeled at year 5 to assess the impact of subject drop out (mainly for revaccination), appeared lower for serogroup C. No vaccine-related SAEs were reported. **Antibody persistence was observed for all serogroups up to 5 y after MenACWY-TT vaccination.**

Tek doz MenACWY-TT uygulanan 12 ay - 10 yaş çocuklarda, aşılamadan 5 yıl sonra tüm aşı serogruplarına antikor yanıtının devam ettiği gösterilmiştir.

MenACWY-TT Antikor Persistansı (10-25 yaş)



The Pediatric Infectious Disease Journal

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VACCINE REPORTS

Five-year Antibody Persistence and Booster Response to a Single Dose of Meningococcal A, C, W and Y Tetanus Toxoid Conjugate Vaccine in Adolescents and Young Adults

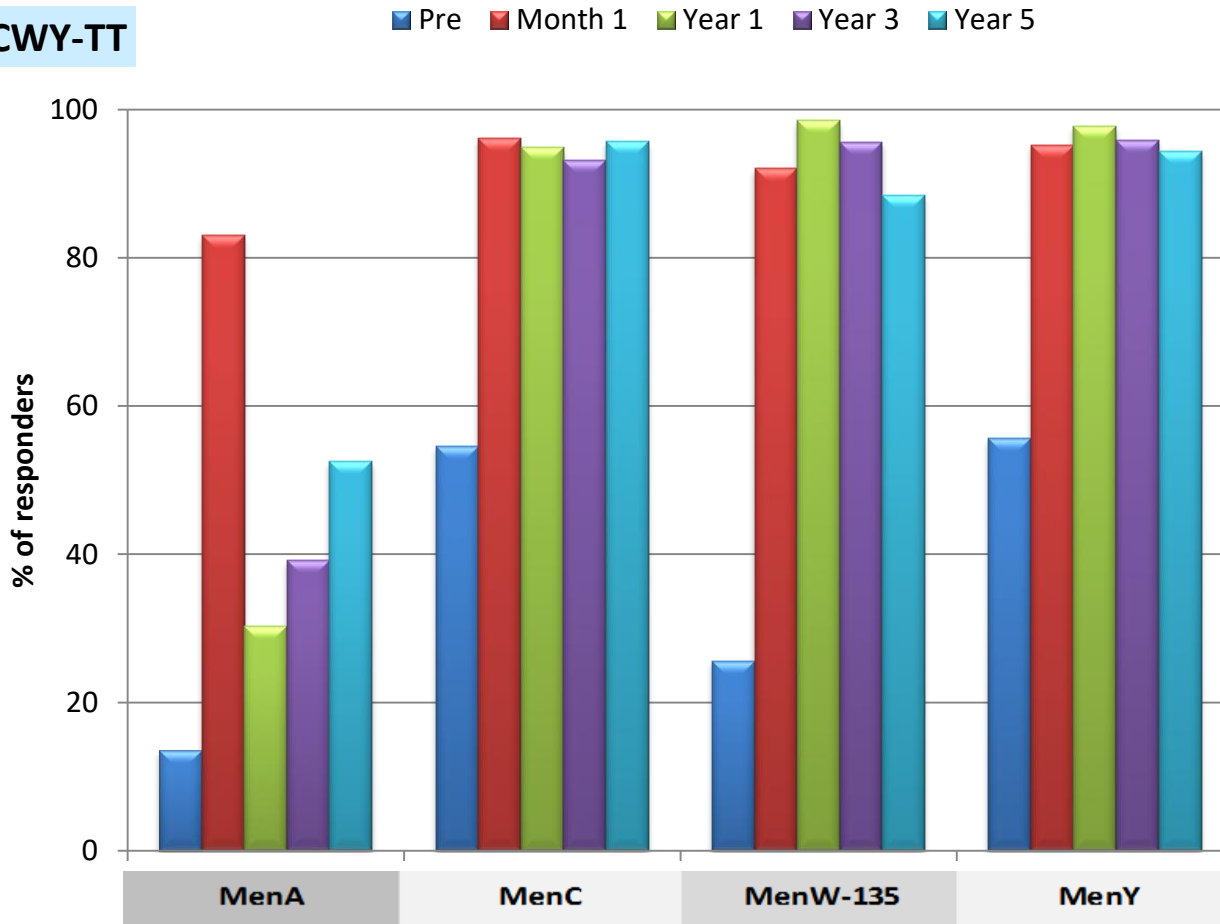
An Open, Randomized Trial

Roger Baxter, MD, Yaela Baine, PhD,† Devayani Kolhe, MSc,‡ Carmen I. Baccharini, MD,†
Jacqueline M. Miller, MD,† and Marie Van der Wielen, MD§*

MenACWY-TT Antikor Persistansi

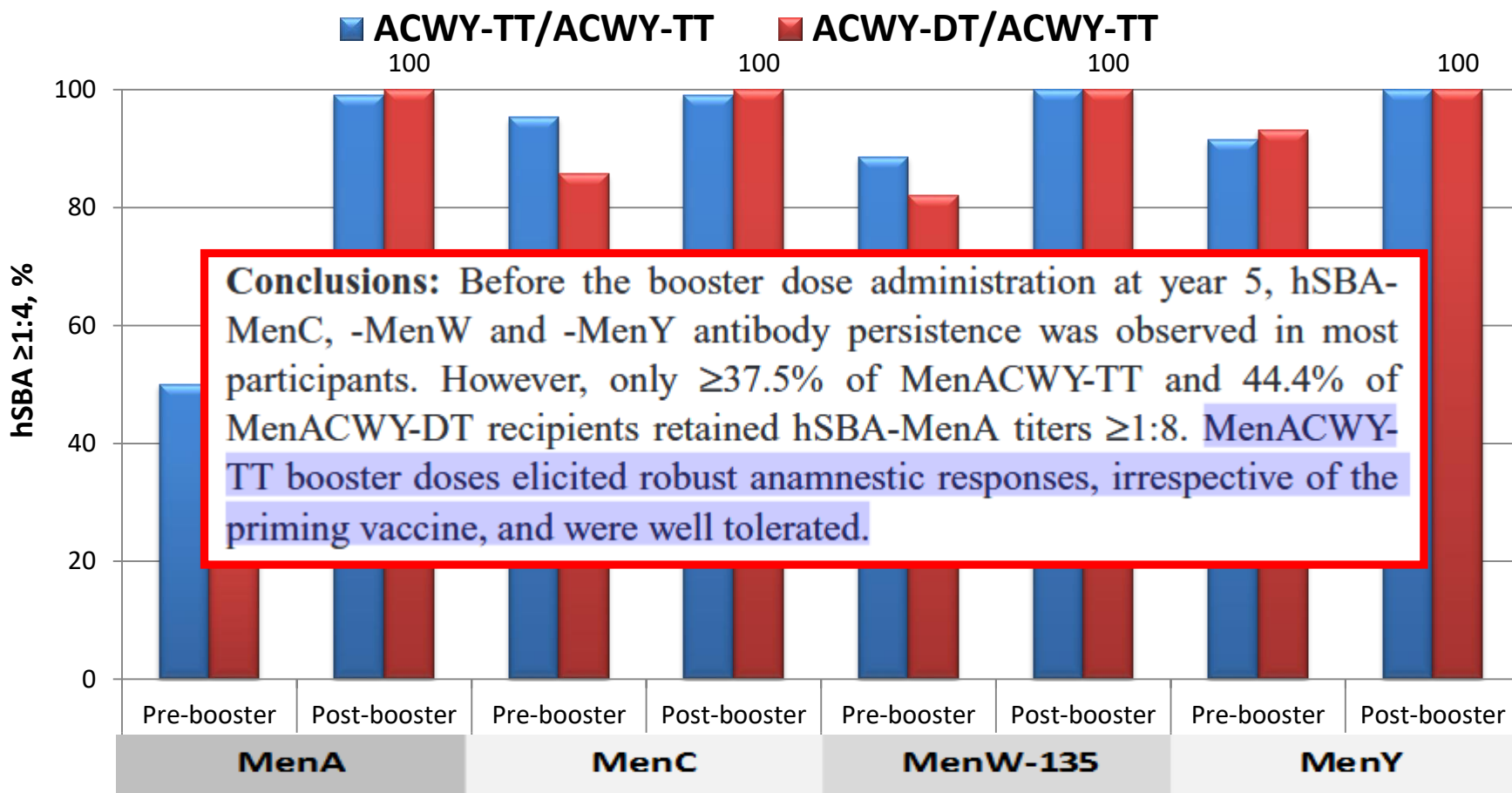
Percentage of participants with hSBA antibody titers $\geq 1:4$

ACWY-TT



Rapel yaniti

Percentage of participants with hSBA antibody titers $\geq 1:4$ before and one month after administration of a booster dose of MenACWY-TT



Conclusions: Before the booster dose administration at year 5, hSBA-MenC, -MenW and -MenY antibody persistence was observed in most participants. However, only $\geq 37.5\%$ of MenACWY-TT and 44.4% of MenACWY-DT recipients retained hSBA-MenA titers $\geq 1:8$. MenACWY-TT booster doses elicited robust anamnestic responses, irrespective of the priming vaccine, and were well tolerated.

Tek doz yeterli mi?

Küçük çocuklarda; tek doz MenACWY-TT uygulamasından 5 yıl sonra tüm serogruplara yüksek antikor titresi devam etmektedir

VACCINE REPORTS

This study found that antibody persistence 5 years after MenACWY-TT vaccination in infancy did not differ substantially between children who received 1 or 2 doses

We observed no other potentially significant differences with respect to antibody persistence of serogroups A, C and Y. Overall, 5 years after primary vaccination with MenACWY-TT, there was no clear evidence of benefit of receiving 2 versus 1 dose of vaccine in infancy.

Tek doz yeterli mi?

Küçük çocuklarda; tek doz ya da iki doz MenACWY-TT uygulamasından 5 yıl sonra rapel yapıldığında güçlü anemnestik yanıt

VACCINE REPORTS

Antibody	N	ACWY-1	N	ACWY-2
		% (95% CI)		% (95% CI)
MenA	31	100 [88.8–100]	35	100 [90.0–100]
MenC	30	93.3 [77.9–99.2]	34	91.2 [76.3–98.1]
MenW	31	100 [88.8–100]	35	100 [90.0–100]
MenY	26	100 [86.8–100]	31	100 [88.8–100]

MenACWY-TT elicited robust anamnestic responses

ÖZET

- **MenACWY-TT aşısı, 12. aydan itibaren tek doz uygulandığında, tüm yaş gruplarında, aşının içerdiği 4 meningokok serogrupa karşı güçlü, uzun süreli ve güvenli bir koruma sağlar.**

SABRINIZ İÇİN TEŞEKKÜR EDERİM



11. Ulusal Çocuk Enfeksiyon Hastalıkları Kongresi

4 - 8 Nisan 2018

Maxx Royal
Belek, Antalya



www.cocukenfeksiyon2018.org

Aşılama: Hasta Davranışı ve Sağlık Personeli Önerisinin Önemi

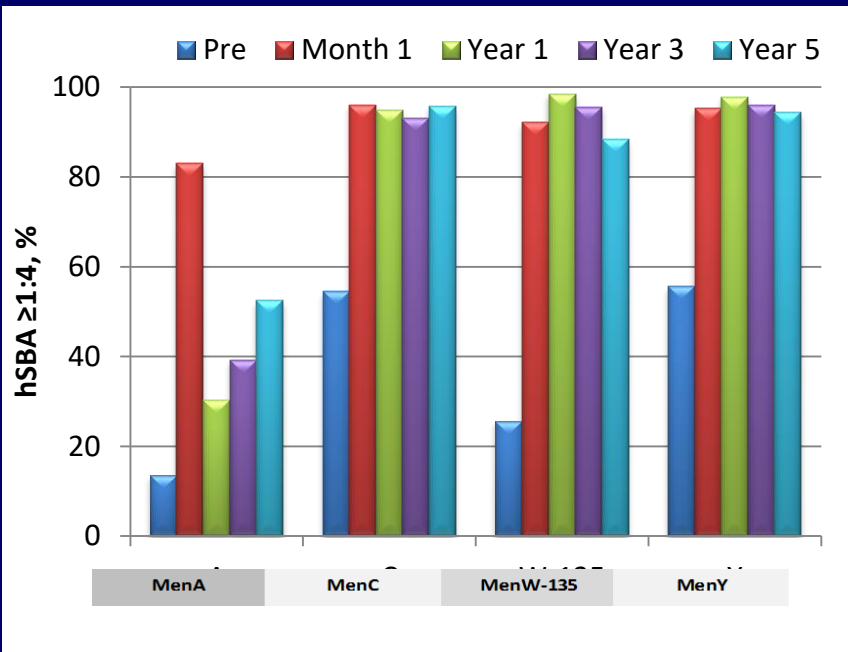
Hasta Davranışı	Doktor Önerisi	Aşılanan %
Pozitif	Evet	84
Negatif	Evet	63
Pozitif	Hayır	7

Adapted from *MMWR* 1988;37:657.

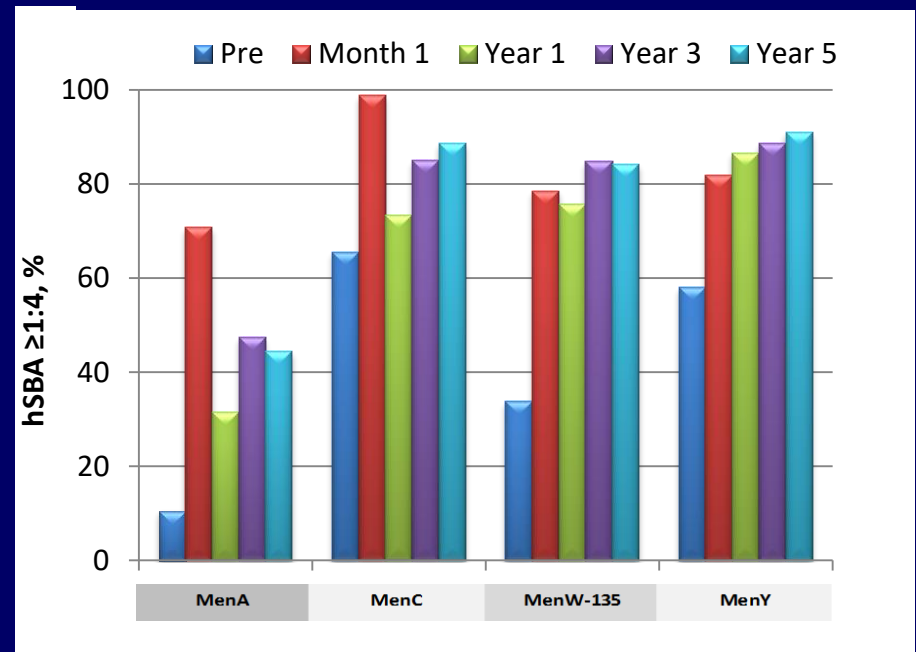
MenACWY-TT Antikor Persistansı

Percentage of participants with hSBA antibody titers $\geq 1:4$

ACWY-TT

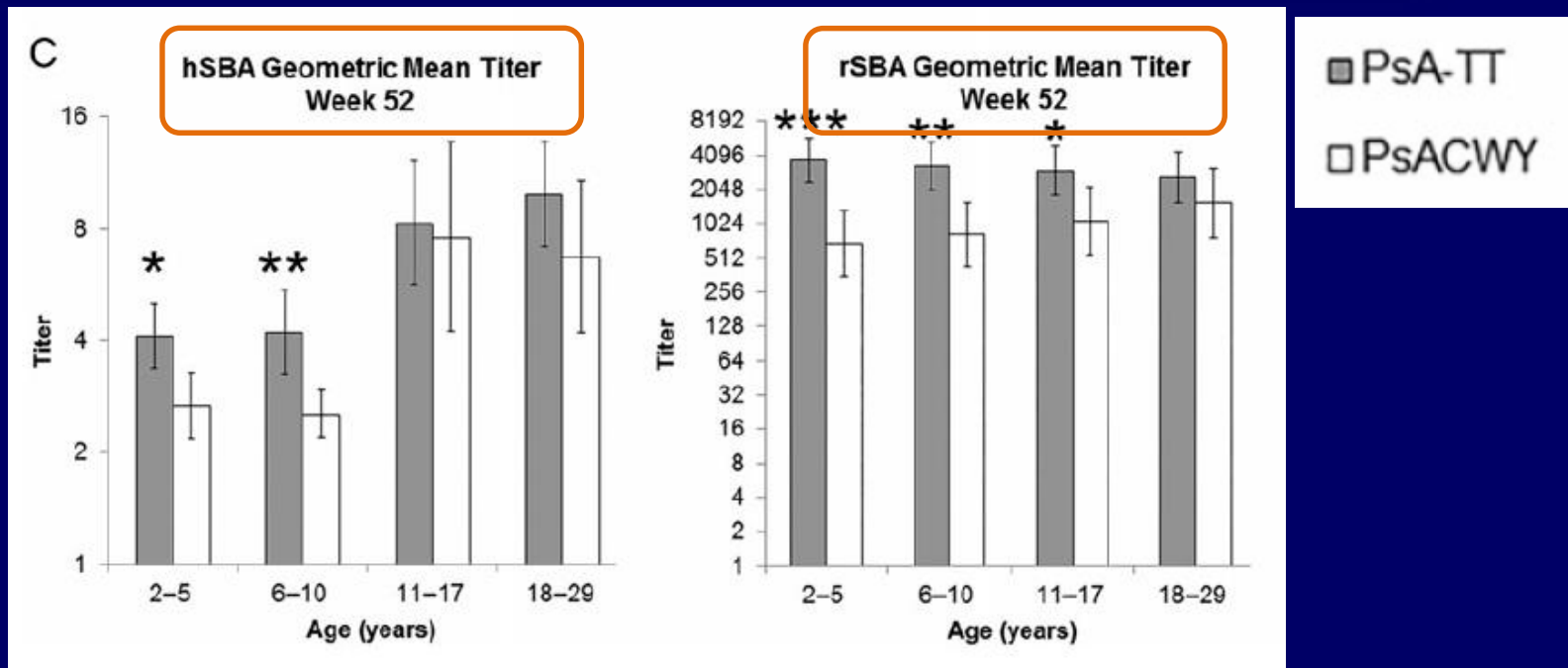


ACWY-DT



Human Complement Bactericidal Responses to a Group A Meningococcal Conjugate Vaccine in Africans and Comparison to Responses Measured by 2 Other Group A Immunoassays

Gregory A. Price,¹ Aimee M. Hollander,^{1,a} Brian D. Plikaytis,^{2,b} Brian T. Mocca,¹ George Carlone,^{2,b} Helen Findlow,³ Ray Borrow,³ Samba O. Sow,⁴ Aldiouma Diallo,⁵ Olubukola T. Idoko,⁶ Godwin C. Enwere,⁷ Cheryl Elie,² Marie-Pierre Preziosi,^{7,8} Prasad S. Kulkarni,⁹ and Margaret C. Bash¹



Regardless of the discrepancies between hSBA and rSBA titers and anti-PsA IgG as presented here, the PsA-TT vaccine has had a dramatic effect in the field. To date, no individuals immunized with PsA-TT have become ill due to MenA