



Meningococcal vaccines

ARVAC 2024 Alumni Refresher Vaccinology Course

International Collaboration on Advanced Vaccinology Training (ICAVT)

Marie-Pierre Preziosi, 4 and 11 June 2024

Content



- Global meningitis burden, Global road map to defeat meningitis, "meningitis vaccines"
- Meningococcal disease burden and serogroup distribution
- Meningococcal vaccines: (polysaccharide vaccines), conjugate vaccines, protein-based vaccines and their use
- Current and future perspectives

Global meningitis burden

- Meningitis affects everyone, everywhere
- Many pathogens can cause meningitis, with an estimated 2.5 million new cases, including 1.6 million cases and 240 000 deaths from bacterial meningitis worldwide, across all ages¹
- Acute bacterial meningitis is one of the deadliest and most disabling forms of this illness
 1 in 6 people affected die, death can occur in <24h
 1 in 5 people surviving live with a long-lasting disability
 It can cause epidemics
 - Highest burden in babies and young children; mortality rates vary, with the highest overall burden in Africa
 - Clusters, community outbreaks and epidemics can occur in all regions of the world, the meningitis belt of sub-Saharan Africa that crosses the continent is prone to major epidemics of meningococcal meningitis
 - Yet, while meningitis epidemics are devastating, over 80% of cases around the world are not associated with an outbreak





- High degree of disabling sequelae among people affected by bacterial meningitis
 - Highest proportions, yet likely underestimated, for meningitis caused by Group B streptococcus (32%), pneumococcus (25%) and around 15% for meningococcus
 - People living in low-income countries worst affected;
 enormous impact on families and communities, both
 emotionally and financially

A road map to defeat meningitis



November 2020: the 73rd World Health Assembly

- Endorsed the first resolution on meningitis prevention and control (WHA73.9)
- Approved the <u>global roadmap on defeating meningitis</u>
 <u>by 2030</u>

September 2021: Official launch of the Global Roadmap

The roadmap focuses on organisms responsible for the majority of acute bacterial meningitis, and all preventable or potentially (soon) preventable by vaccination



- Neisseria meningitidis
- Streptococcus pneumoniae
- Haemophilus influenzae
- Streptococcus agalactiae (Group B streptococcus, GBS)

A global strategy to achieve a vision Towards a world free of meningitis

Visionary goals to be achieved by 2030

- Eliminate bacterial meningitis epidemics
- Reduce cases by 50% and deaths by 70% from vaccine-preventable bacterial meningitis
- Reduce disability and improve quality of life after meningitis due to any cause

Prevention and epidemic and treatment

Advocacy Disease surveilance

Support and care for people affected by meningitis

5 interconnected pillars

- Prevention and Epidemic Control
- Diagnosis and Treatment
- Disease Surveillance
- > Support and Care for people affected by meningitis
- > Advocacy and Engagement

The first high-level meeting to defeat meningitis

Under the high patronage of the President of the French Republic

Paris – Institut Pasteur – 26 April 2024



Prevention and epidemic control pillar





Strategic Goals

SG1: achieve and maintain high coverage of licensed/WHO prequalified vaccines against Nm, Spn and Hib with equitable access in all countries, and introduce these vaccines in countries that have not yet introduced them in line with WHO recommendations

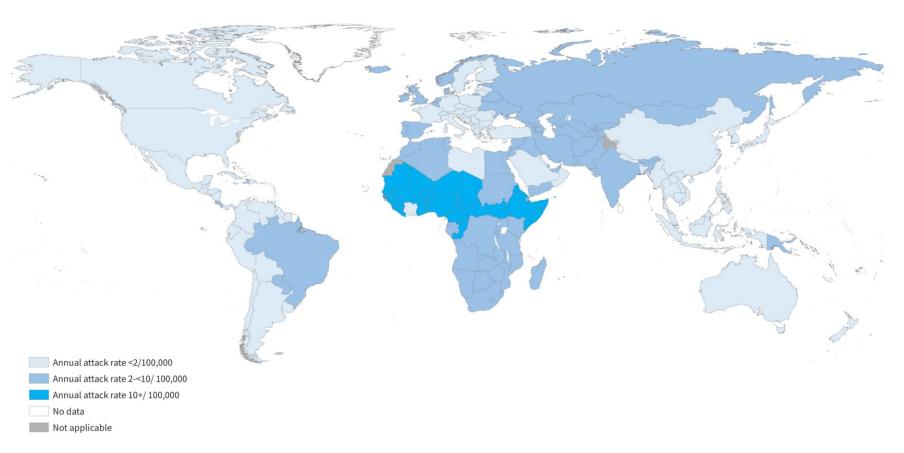
SG2: introduce effective and affordable new WHO prequalified vaccines targeting Nm, Spn, Hi and GBS

SG3: develop evidence-based policy on Nm, Spn, Hi and GBS vaccination strategies that result in optimal individual protection and, where possible, herd protection

Selected milestones

- By 2022, at least one affordable multivalent (ACWXY) meningococcal conjugate vaccine licensed and WHO prequalified
- By 2023, introduction of vaccination against Nm serogroups
 ACWY/ACWXY in routine immunization programmes started in at least five meningitis belt countries
- By 2024, locally relevant meningococcal disease vaccination strategies maintained or introduced in all countries as appropriate, in alignment with the epidemiological evidence and according to regional policies
- By 2026, locally relevant meningococcal disease vaccination programmes, including Nm multivalent conjugate vaccines and/or Nm serogroup B vaccines as relevant, introduced in alignment with epidemiological evidence and according to regional policy in >=10 countries

Global estimates of meningococcal meningitis incidence 2019



The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: Institute of Health Metrics and Evaluation (IHME) Global burden of disease study 2019 Map Production: WHO GIS Centre for Health, DNA/DDI

Map Creation Date: 18 May 2022

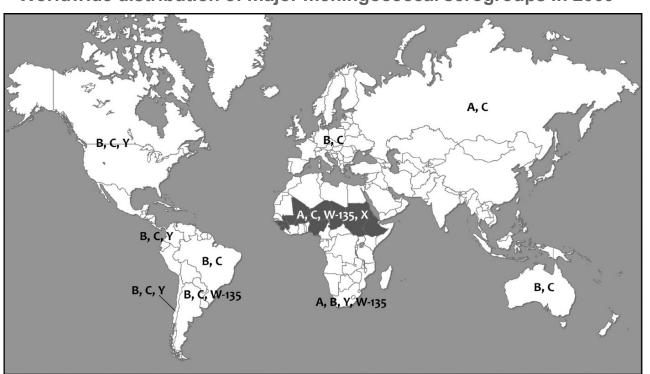


Global distribution of serogroup causing disease



Meningococci are classified into 12 serogroups based on their capsular polysaccharide. Serogroups A, B, C, W, X and Y cause most of the disease worldwide, with their distribution varying across regions

Worldwide distribution of major meningococcal serogroups in 2009¹



In the last decade^{2,3}

- A eliminated in the African meningitis belt
- B still predominant in Americas, Australia and Europe
- C,W,Y variable in their distribution over time and by country
- X further expanded in the African meningitis belt

^{1.} Harrison LH et al 2009. Global epidemiology of meningococcal disease; Vaccine 27S: B51–B63

^{2.} Acevedo R et al 2019, The Global Meningococcal Initiative meeting on prevention of meningococcal disease worldwide: Epidemiology, surveillance, hypervirulent strains, antibiotic resistance and high-risk populations; Expert Rev Vaccines 18: 15-30

^{3.} Purmohamad A et al 2019. Global estimate of *Neisseria meningitidis* serogroups proportion in invasive meningococcal disease: A systematic review and meta-analysis; Microb Pathog 134:103571

Multivalent meningococcal conjugate vaccines ACWY and X



- Meningococcal polysaccharide vaccines, which have been used for over 50 years, have important limitations:
 - o no or poor/short lived immunogenicity in infants and young children (poor antibody avidity / bactericidal activity), no induction of immune memory/poor response to booster, no effect on nasopharyngeal carriage and no induction of herd protection, and can induce immunologic hyporesponsiveness
- They are about to be supplanted by meningococcal polysaccharide <u>conjugate</u> vaccines, which correct the shortcomings of the polysaccharide vaccines (a polysaccharide is conjugated to a protein carrier: e.g., tetanus toxoid)
 - o as and if they become more affordable
- Multivalent meningococcal conjugate vaccines (quadrivalent ACWY and pentavalent ACWYX vaccines) are rapidly replacing monovalent, bivalent and trivalent vaccines
 - o given the great variability in the distribution of different serogroups over time and by country

Multivalent meningococcal conjugate vaccines



Manufacturer	Vaccine*	Ps	Carrier	Age indication	Price per dose ¹
Sanofi Pasteur	Menactra	ACWY	DT	2 months - 55 years	\$20 - \$109
GSK (ex Novartis)	Menveo	ACWY	CRM	2 months - 55 years	\$25 UN procurement limited number of doses
Pfizer (ex GSK)	Nimenrix	ACWY	TT	≥ 6 weeks	\$20 PAHO revolving fund
Sanofi Pasteur	MenQuadfi to gradually replace Menactra	ACWY	TT	≥ 12 months ≥ 6 weeks, 2025	\$111 (US-CDC cost)
Serum Institute of India	MenFive	ACWYX	TT and CRM	9 months – 85 years	\$3 (UNICEF)

^{*} All are WHO prequalified

In development

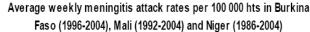
Eubiologics Korea: ACWYX - CRM carrier

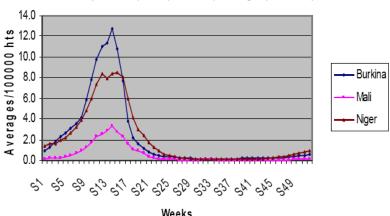
^{1.} Rounded and approximate indicative median prices, based on the following sources consulted on 14 May 2024: (a) WHO Market Information for Access to Vaccines (MI4A), Meningococcal Vaccines Global Market Public Summary August 2019; (b) WHO MI4A Vaccine purchase data; (c) CDC Vaccine Price List: CDC cost/ dose; d) UNICEF Vaccine Price data: awarded price/dose

The meningitis belt

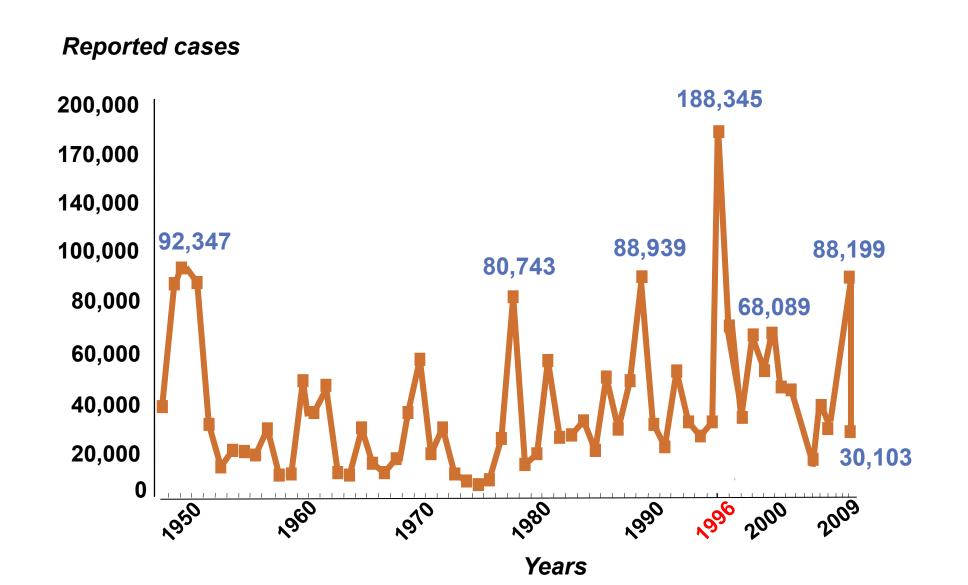
- Epidemic susceptible area corresponding to the 300-1100 mm annual rainfall isohyets
- Dry winter, dominated by northern wind, the Harmattan
- Focal or countrywide outbreaks, with incidence reaching 1000/100 000
- Owercrowding, large population displacements and gatherings
- 26 countries; >500 million people





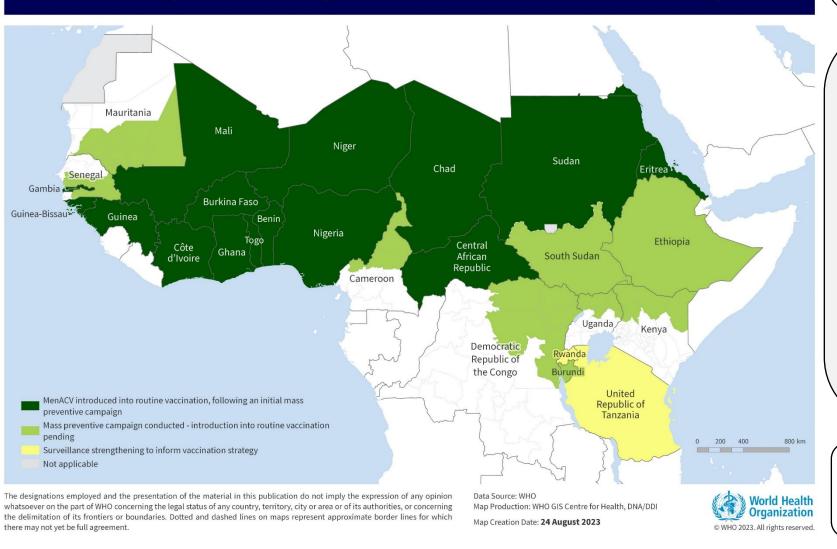


Epidemic meningitis in the African belt



MenACV roll out as of September 2023

Status of meningococcal A conjugate vaccine (MenACV) roll out in the meningitis belt



NmA accounted for more than 80% of seasonal meningitis epidemics before the introduction of MenACV

24 countries conducted MenACV mass vaccination campaigns

350+ million 1-29 year-olds vaccinated since Dec. 2010

through initial mass and catch-up campaigns

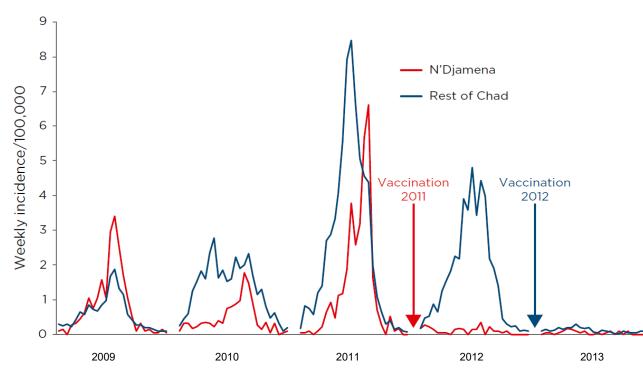
15 countries introduced into national routine programmes

July 2016 – May 2023

at 9 - 18 months of age

No confirmed cases of NmA in countries of the meningitis belt since 2017

Impact of MenACV roll-out in the meningitis belt



Incidence of reported cases of meningitis in Chad 2009–2013. Vaccination with MenAfriVac® targeted persons 1–29 years of age at the end of 2011 and in 2012 (2)

- 1. Novak et al. 2012; Lancet Infect Dis 12: 757-64
- 2. Daugla et al 2014; Lancet 383: 40-7
- 3. Trotter et al 2017; Lancet Infect Dis 17:867-72

Analysis of surveillance data, Burkina Faso 1997-2011¹

- 71% decline in risk of meningitis (suspected cases)
- >99% decline in risk of NmA meningitis (confirmed cases)

Community trial, Chad 2009-2012²

 94% reduction in incidence of meningitis in vaccinated vs. unvaccinated districts (suspected cases)

Analysis of surveillance data, 9 countries, 2005-2015³

- 57% decline in incidence of meningitis (suspected cases)
 in vaccinated compared with unvaccinated populations
- >99% decline in incidence of NmA meningitis (confirmed cases)
- 59% decline in the risk of a district reaching the epidemic threshold

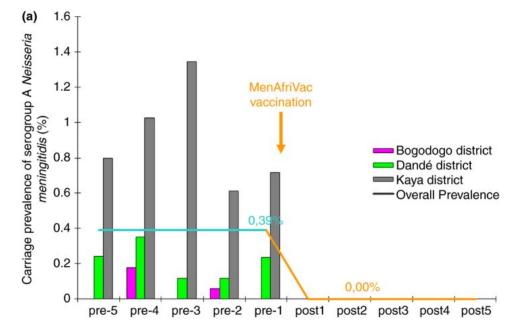
MenACV induces herd protection

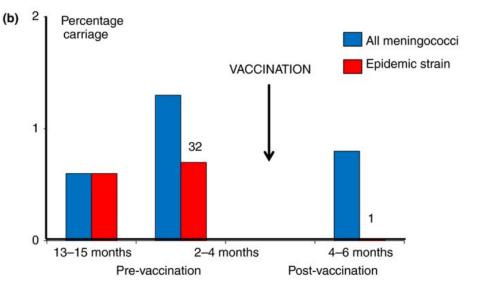


Elimination of NmA carriage in vaccinated

& unvaccinated population up to 13 months after mass vaccination in Burkina Faso,^a when comparing pre- and post-vaccination carriage prevalence

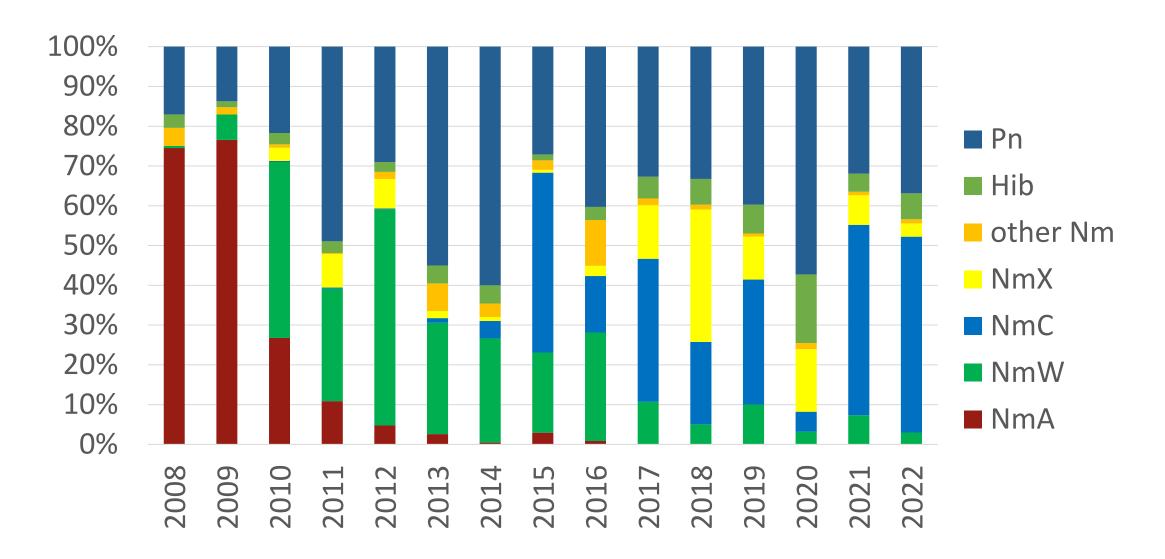
98% decrease in NmA carriage prevalence 4-6 months after mass vaccination vs. pre-vaccination in Chad^b



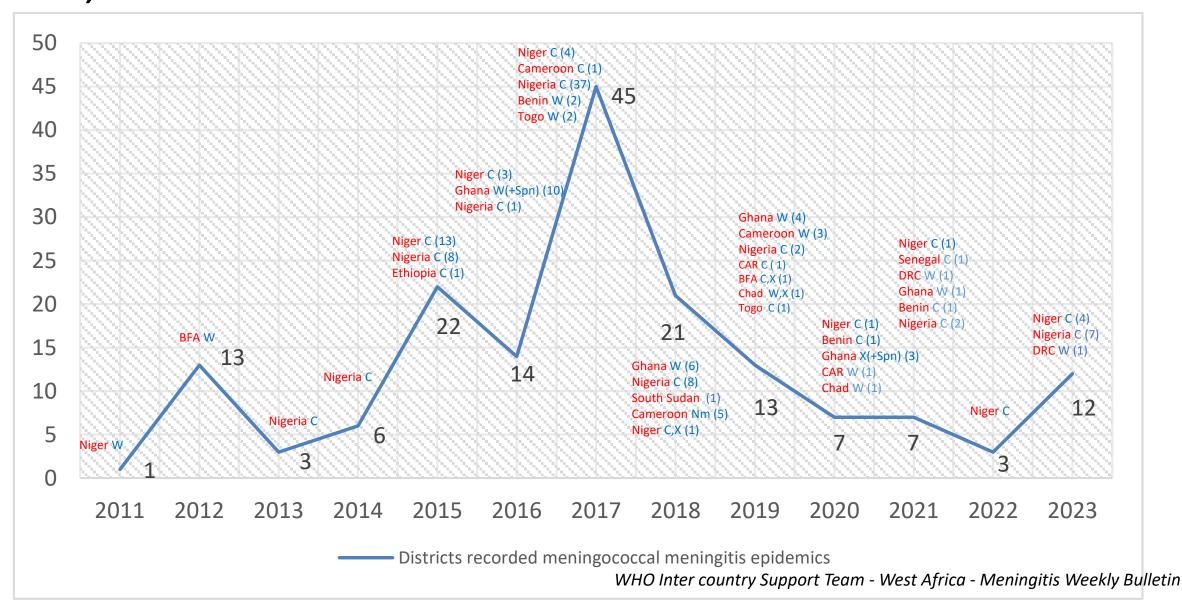


⁽a) Kristiansen et al., 2013; Clin Infect Dis 56:354-63 (b) Daugla et al., 2014; Lancet 383:40-7

Meningitis pathogens in the meningitis belt, 2008-2022

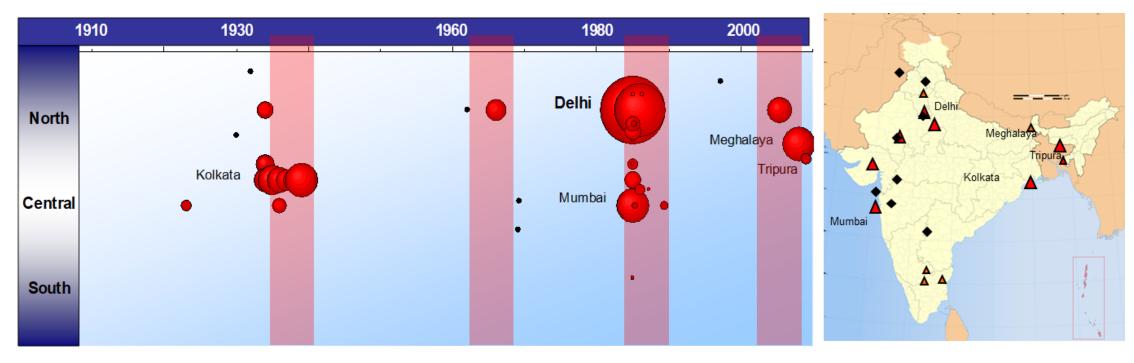


Meningococcal epidemics reported in the meningitis belt, 2011-2023





Recurrent epidemics also happen in other regions ...overview of epidemics in India



Sinclair D et al. Epidemiology of meningococcal disease in India. Trop Med Int Health 2010;15:1421-35

Meningococcal B vaccines



- Due to molecular mimicry, serogroup B capsular polysaccharide is poorly immunogenic, and its use is precluded by theoretical considerations of autoimmunity and potential fetal damage
- Outer membrane vesicle (OMV) vaccines were first developed, and OMV-based vaccines shown to be effective in particular in clonal outbreaks
 - o but poor protection in young children, short-term effectiveness and no evidence of major impact on carriage
- Subcapsular, surface-exposed, conserved protein antigens were then shown to induce bactericidal activity through two different approaches
 - Reverse vaccinology (GSK/Novartis) or fractionation, protein purification, and proteomics steps (Pfizer)
- Licensed meningococcal B protein-based vaccines have some shared components
- Implemented in routine childhood immunization programmes in some countries

Meningococcal B protein-based vaccines



Manufacturer	Vaccine*	Antigens	Age indication	Price per dose ¹
GSK	Bexsero 4CMenB	B fHbp, B NHBA, B NadA, OMV	2 months - 50 years	\$82 - \$150
Pfizer	Trumenba MenB-FHBP	B fHbp A + B	≥ 10 years	\$82- \$136

^{*} None are WHO prequalified

In development

- Sanofi: fHbp A+B/NadA/OMV, licensure 2028/29
- GSK: second generation Bexsero, TBC
- DCVMN manufacturer PDP: TBC

^{1.} Rounded and approximate indicative median prices, based on the following sources consulted on 14 May 2024: (a) WHO Market Information for Access to Vaccines (MI4A), Meningococcal Vaccines Global Market Public Summary August 2019; (b) WHO MI4A Vaccine purchase data; (c) CDC Vaccine Price List: CDC cost/dose



Contents lists available at ScienceDirect

Vaccine

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





A comparison of national vaccination policies to prevent serogroup B meningococcal disease

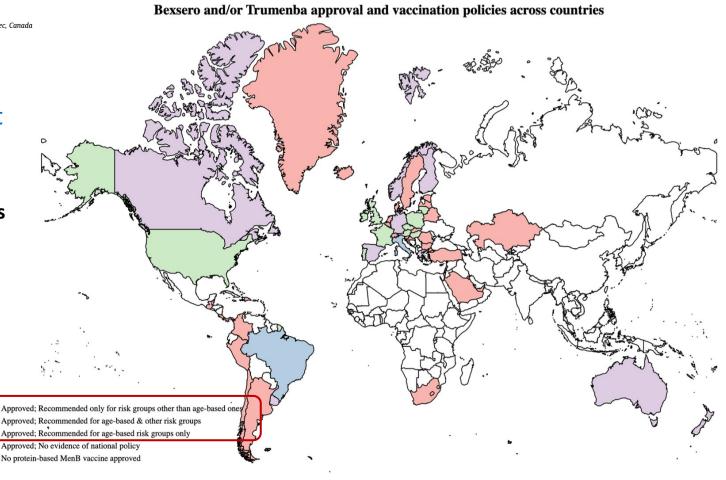


Giorgia Sulis a,*, Miranda Horn a, Ray Borrow b, Nicole E. Basta a

^a Department of Epidemiology, Biostatistics and Occupational Health, School of Population and Global Health, McGill University, Montreal, Quebec, Canada ^b UK Health Security Agency, Meningococcal Reference Unit, Manchester Royal Infirmary, Manchester, United Kingdom

15 countries have recommendations for at least one **age-based risk group**

- Infant vaccination recommended in 14 countries (+ select groups/areas of Spain and Australia):
- Other age-based risk groups
 - Brazil (2015)
 all toddlers, children and adolescents (not publicly funded)
 - South Australia (2019)
 all individuals aged 15-16 years
 - US (2020)
 all individuals aged 16-23 years



Meningococcal B vaccines



- Population-based effectiveness studies against NmB in countries where 4CMenB vaccine has been introduced and evaluated (mostly Europe and Australia) predicted that vaccination could reduce the risk of invasive meningococcal disease caused by 66% to 100% of NmB isolates
- More data are required on population-wide effectiveness of other MenB vaccines, as well as
 effectiveness data on long-term protection after vaccination to refine vaccination strategies
- No impact on carriage
- Evidence on the effect of MenB vaccines containing OMV against Neisseria gonorrhoeae
 infection, to be documented further -> a public health opportunity, especially given
 antimicrobial resistance -> UK recommended a targeted vaccination programme with 4CMenB
 vaccine for the prevention of gonorrhea in November 2023 (high-risk people)

Combination vaccines 5-in-1 MenABCWY



Manufacturer	Vaccine*	Antigens	Age indication	Price per dose ¹
Pfizer combining MenACWY-nimenrix and MenB-trumenba antigens	Penbraya	ACWY B	10 - 25 years	\$189
GSK combining MenACWY- menveo and 4CMenB- bexsero antigens prior to administration	GSK3536819 Men ABCWY (1st Gen)	ACWY B	10 - 25 years	N/A Registration Phase

In development

• Sanofi: combination product in fully liquid format, licensure 2030/2031

^{1.} Rounded and approximate indicative median prices, based on the following sources consulted on 14 May 2024: CDC Vaccine Price List: CDC Cost/ Dose

Current and future perspectives





Strategic Goal 3. develop evidence-based policy on Nm, Spn, Hi and GBS vaccination strategies that result in optimal individual protection and, where possible, herd protection

Men5CV vaccine ACWYX -TT & CRM

July 2023 WHO Prequalification

WHO recommendation on use of MMCVs in countries of the African meningitis belt

September 2023

Strategic Advisory Group on Immunization (SAGE) meeting

WHO recommendation on overall use of meningococcal vaccines globally, including both MMCV and MenB vaccines

March 2025
SAGE meeting

Mid year 2025
Updated WHO Position paper
on meningococcal
vaccines and vaccination



May 2023

Guideline Development Group(GDG)

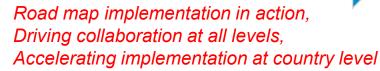
on meningitis diagnosis, treatment
& care guidelines meeting



Mid year 2024

Publication of WHO Guidelines

on meningitis diagnosis, treatment & care



Strategic Goal 9. Provide and implement appropriate, context specific, quality-assured guidelines and tools for treatment and supportive care to reduce the risk of mortality, sequelae and antimicrobial resistance

Important related global initiatives

Decision WHA73(9)

Immunization Agenda 2030: A global strategy to leave no one behind

http://www.immunizationagenda2030.org/

Resolution WHA73.10
Global actions on epilepsy and other neurological disorders

https://apps.who.int/gb/ebwha/pdf files/WHA73/A73 R10-en.pdf; https://www.who.int/news-room/articles-detail/Web-based-consultation-on-the-first-draft-of-the-Intersectoral-global-action-plan-on-epilepsy-and-other-neurological-disorders

Resolution EB148.R6

The highest attainable standard of health for persons with disabilities

https://apps.who.int/gb/ebwha/pdf_files/EB148/B148_R6-en.pdf; https://www.who.int/news/item/27-05-2021-a-new-landmark-resolution-on-disability-adopted-at-the-74th-world-health-assembly

