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Meningococcal vaccines

Progress, Challenges and Opportunities in Africa

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Medical Head English Speaking Sub-Saharan Africa – Sanofi Vaccines

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Introduction to IMD (Invasive Meningococcal Disease)

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Meningococcal infections are caused by the bacterium *Neisseria meningitidis* [1]

- An **aerobic, gram-negative**, oxidase-positive, **diplococcus** bacterium[1]
- Exclusively **human pathogen**[1]
- Obligate commensal organism- **nasopharynx** [2]
- Can be **capsulated or non-capsulated**[1]
- 12 known capsular serogroups based on the biochemical structure of the capsule[1]
- Most meningococcal disease is caused by *N. meningitidis* serogroups:[1]

A B C W X Y

- Invasive disease is dependent on the **virulence** of the strain and various **host characteristics**[2]

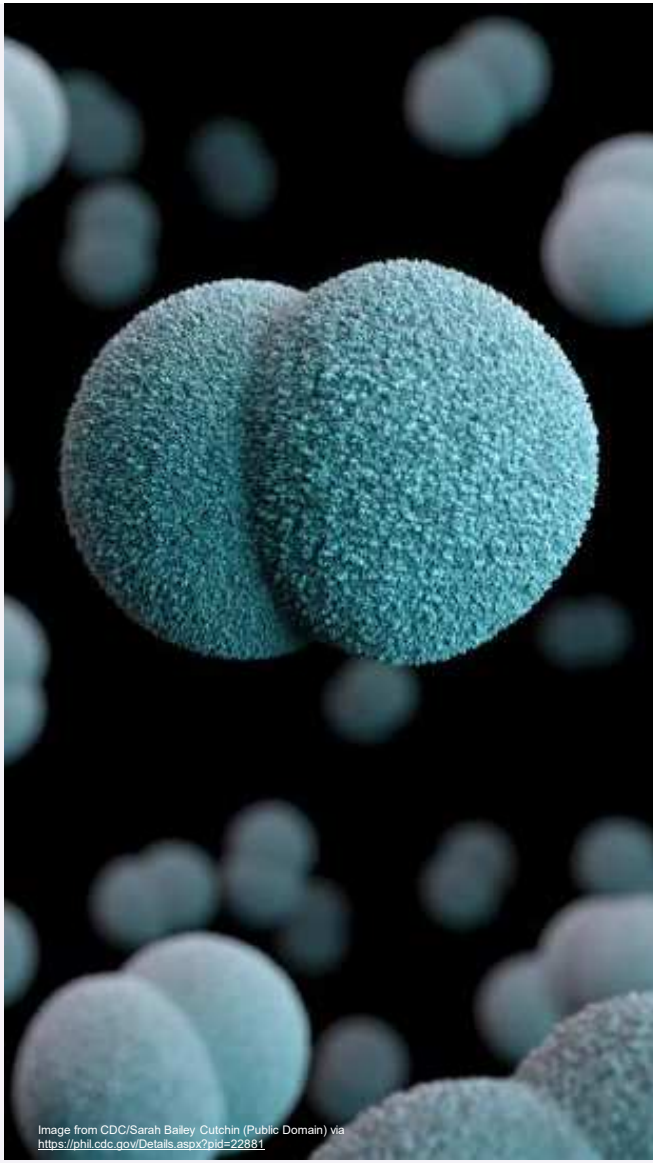

Image from CDC/Sarah Bailey Cutchin (Public Domain) via https://phil.cdc.gov/Details.aspx?pid=22881

3D image based on scanning electron microscopy

References: 1. McNamara LA, Pollard AJ, Harrison LH. Meningococcal Capsular Group A, C, W, and Y Conjugate Vaccines. In: Orenstein W, Offit P, Edwards KM, Plotkin S, editors. Plotkin's Vaccines. 8th ed. Elsevier; 2023. p. 664-689.e12. ISBN 9780323790581. 2. Van Deuren M, Brandtzaeg P, van der Meer JW. Update on meningococcal disease with emphasis on pathogenesis and clinical management. Clinical microbiology reviews. 2000 Jan 1;13(1):144-66.

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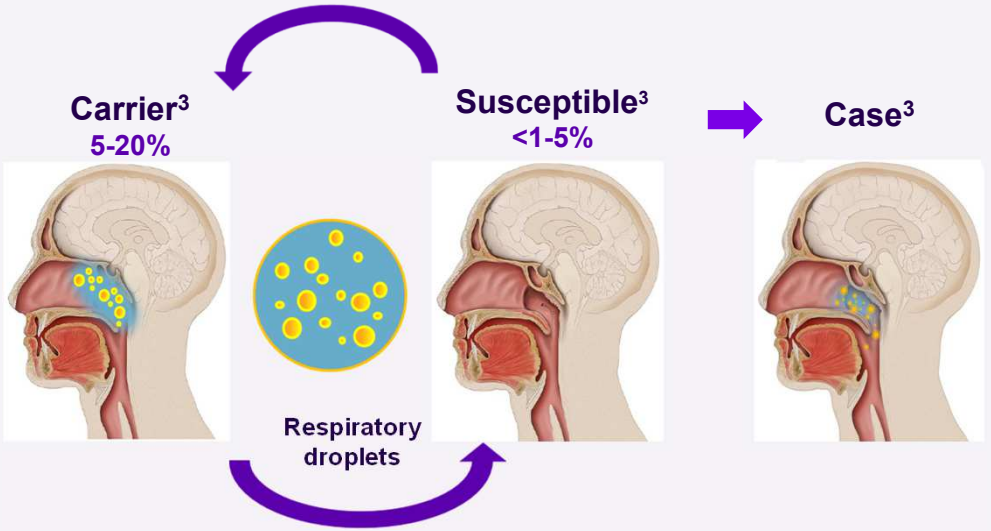
Invasive Meningococcal Disease (IMD)

- Meningococcal infection is a **global problem** with a varying distribution ranging from sporadic disease to epidemics[1]
- Between **4.5% - 25%** of the general population are **asymptomatic nasopharyngeal carriers** at any given time[2,3]
- Only a **small proportion** (<1%-5%) of carriers progress to IMD[3,4]
- Transmission occurs through **contact with respiratory droplets** from a colonised person[1]

Carriage Is Essential for Transmission of IMD



Reducing carriage is critical for preventing transmission [5]

Respiratory tract image: adapted from Patrick J. Lynch, medical illustrator; C. Carl Jaffe, MD, cardiologist (CC BY-2.5)
References: **1.**Rouphael NG, Stephens DS. Neisseria meningitidis: biology, microbiology, and epidemiology. Neisseria meningitidis: advanced methods and protocols. 2012:1-20. **2.** Balmer P, Burman C, Serra L, York LJ. Impact of meningococcal vaccination on carriage and disease transmission: a review of the literature. Human vaccines & immunotherapeutics. 2018 May 4;14(5):1118-30. **3.** Borrow R, Findlow J. The important lessons lurking in the history of meningococcal epidemiology. Expert Review of Vaccines. 2024 Dec 31;23(1):445-62. **4.** European Centre for Disease Prevention and Control. Factsheet about meningococcal disease. https://ecdc.europa.eu/en/meningococcal-disease/factsheet. Updated 7 January 2019 [accessed April 2023. **5.** Clark SA, Borrow R. Herd protection against meningococcal disease through vaccination. Microorganisms. 2020 Oct 28;8(11):1675.

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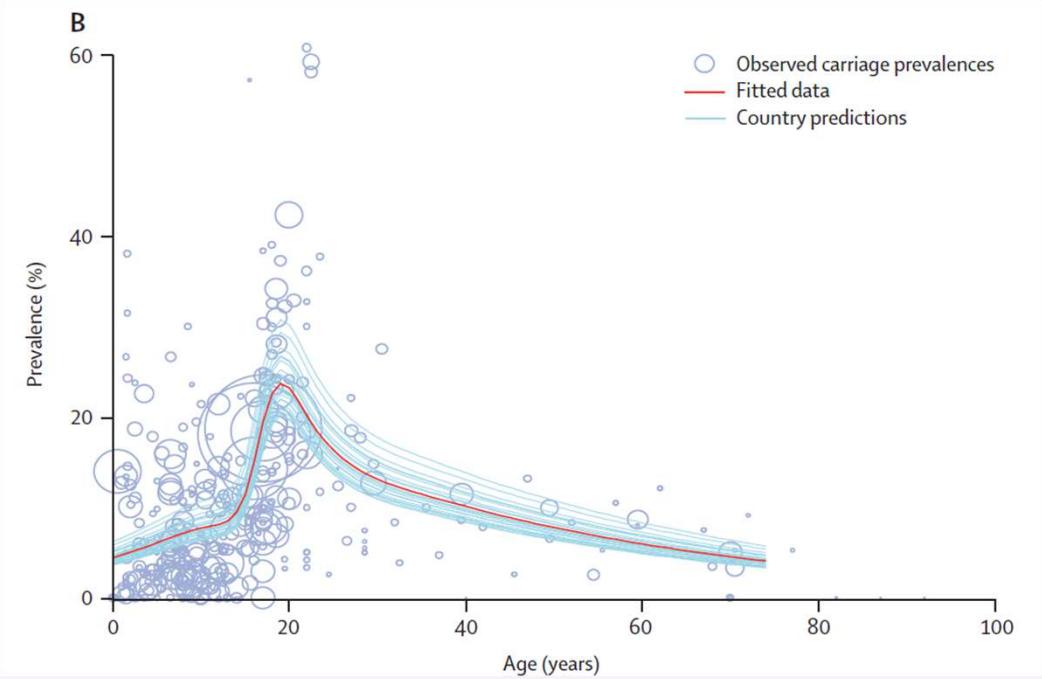
Invasive Meningococcal Disease (IMD)

Meta-analysis of 89 Studies in 28 Countries[1]

- **Low in Children**: Carriage is low in infants (**4.5%**) and rises slowly through childhood.
- **Peak in Adolescents**: Carriage peaks at **23.7% in 19-year-olds** due to social behaviors.
- **Decline with Age**: Carriage decreases after adolescence, reaching **7.8% by age 50**.



Targeting **adolescents** in vaccination **reduces transmission** and supports **herd immunity**.

References: 1. Christensen H, May M, Bowen L, Hickman M, Trotter CL. Meningococcal carriage by age: a systematic review and meta-analysis. The Lancet infectious diseases. 2010 Dec 1;10(12):853-61.

Role of the Capsule and Surface Proteins in Immune Evasion and Host Invasion by *Neisseria meningitidis* [1]

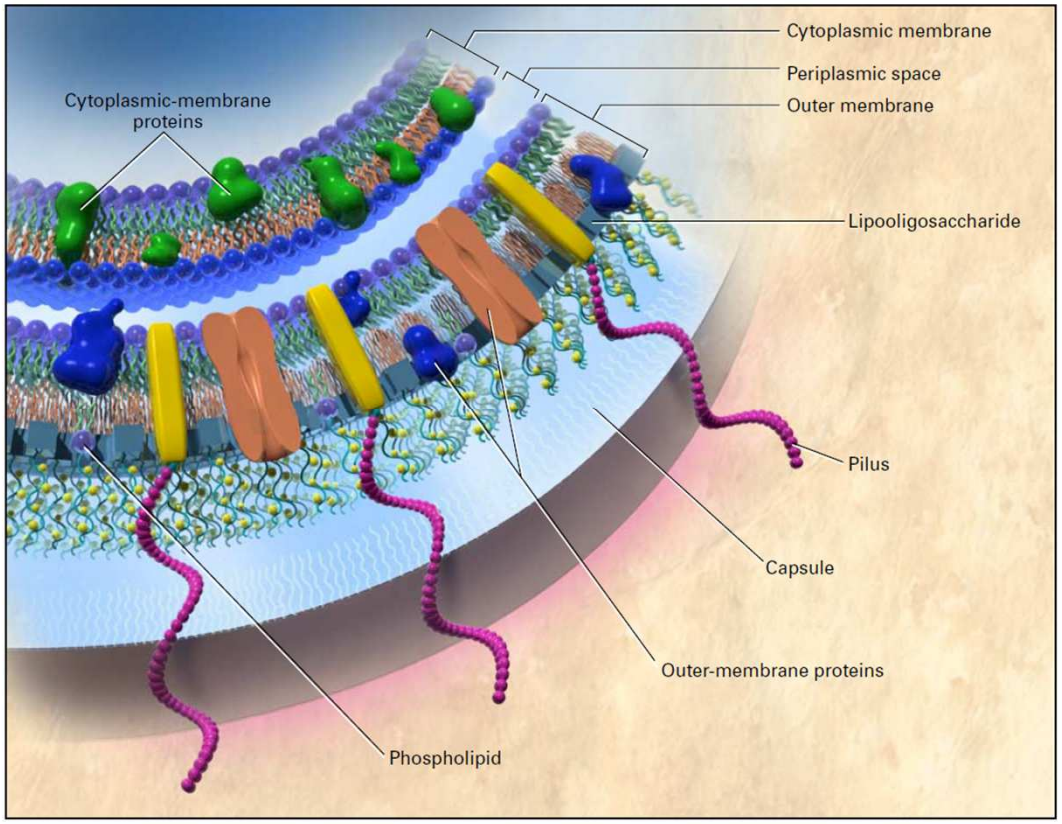


TABLE 1. FUNCTION AND CLASSIFICATION OF THE OUTER-MEMBRANE COMPONENTS OF *NEISSERIA MENINGITIDIS*.

COMPONENT	FUNCTION	CLASSIFICATION
Capsule	Protects against host-mediated, complement-dependent bacteriolysis and phagocytosis	13 Serogroups (A, B, C, E-29, H, I, K, L, M, W-135, X, Y, Z)
Outer-membrane proteins		
Porins	Create pores through which small hydrophilic solutes pass, cation-selective or anion-selective	
PorA		Class 1 outer-membrane protein (serosubtyping)
PorB		Class 2 or 3 outer-membrane protein (serotyping)
Opacity-associated proteins		
Opa	Promotes adherence to host cells and leukocytes	Class 5 outer-membrane proteins
Opc	Promotes adherence to host cells	
Reduction-modifiable protein	Unknown	Class 4 outer-membrane protein
Lipooligosaccharide	Has potent endotoxic activity	13 Immunotypes*
Pili	Promote initial adherence to epithelial and endothelial cells and erythrocytes	Class I and II*

*The classification is based on differences in antigenicity.

Reference: 1. Figure 2 and Table 1 - Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM. Colonization of Neisseria meningitidis in the Nasopharynx and Entry into the Bloodstream and Cerebrospinal Fluid. New Eng J Med. 2001 May 3;344(18):1383

Immune Evasion Mechanisms of *Neisseria meningitidis*[1]

Capsular Polysaccharides:

- **Shield** the bacterium from immune detection, preventing recognition by the host's immune system.
- **Inhibit complement-mediated destruction** and **block phagocytosis**, allowing the bacteria to survive in the host.

IgA-1 Protease:

- **Cleaves host antibodies (IgA)** at mucosal surfaces, neutralizing the immune response and promoting bacterial survival.

Mechanisms of Host Entry

- *Neisseria meningitidis* uses **pili** to bind to **CD4 receptors** on epithelial cells, enabling initial attachment to the host.
- **Opa and Opc proteins** further facilitate bacterial entry by binding to host receptors, allowing the bacteria to penetrate deeper tissues.
- Once inside, the bacteria release **endotoxins**, which trigger a strong immune response and help the pathogen cross the blood-brain barrier (BBB), leading to invasive disease.

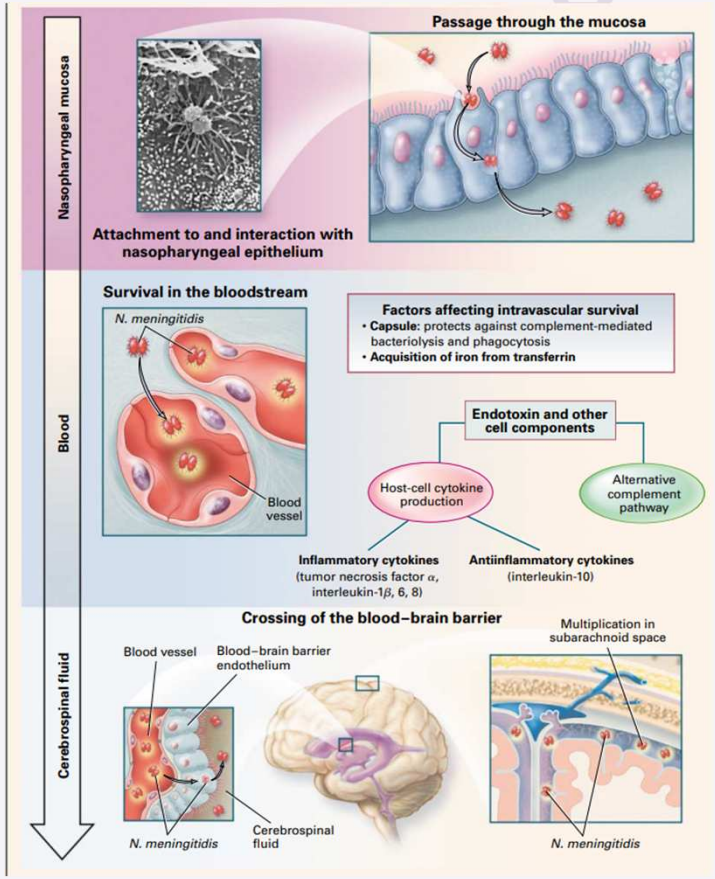


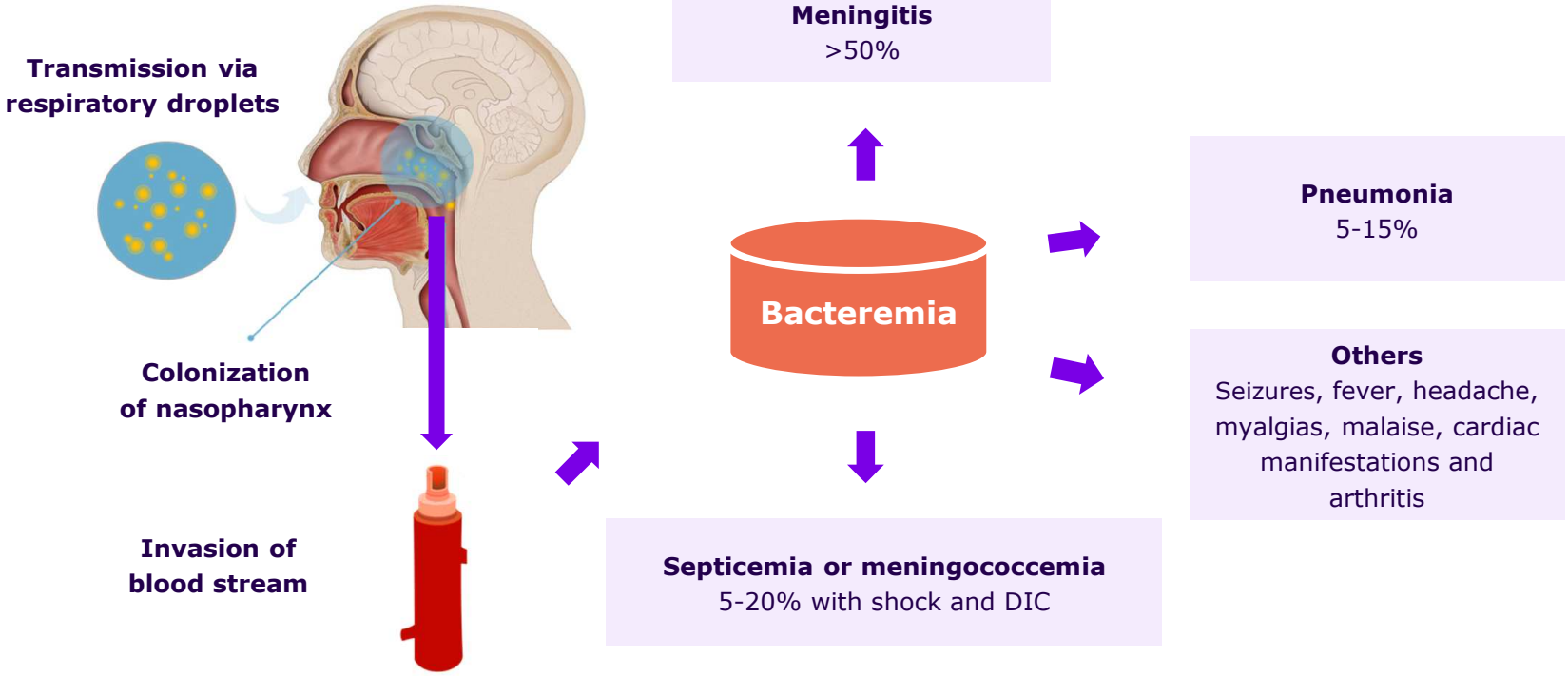
Figure 3 - Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM. New Eng J Med. 2001;344(18):1383

Reference: 1. Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM. Colonization of Neisseria meningitidis in the Nasopharynx and Entry into the Bloodstream and Cerebrospinal Fluid. New Eng J Med. 2001 May 3;344(18):1383

Invasive Meningococcal Disease (IMD)

There are several clinical manifestations of IMD, which may present independently or in combination[1,2]

Non-specific and variable features of IMD[1,2]



Vessel image: adapted from Kelvinsong (CC BY-SA 3.0) via Wikimedia. Respiratory tract image: adapted from Patrick J. Lynch, medical illustrator; C. Carl Jaffe, MD, cardiologist (CC BY-2.5)

References: 1. McNamara LA, Pollard AJ, Harrison LH. Meningococcal Capsular Group A, C, W, and Y Conjugate Vaccines. In: Orenstein W, Offit P, Edwards KM, Plotkin S, editors. Plotkin's Vaccines. 8th ed. Elsevier; 2023. p. 664-689.e12. ISBN 9780323790581. **2.** Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM. Meningococcal disease. New England journal of medicine. 2001 May 3;344(18):1378-88.

Invasive Meningococcal Disease (IMD)

There are several clinical manifestations of IMD, which may present independently or in combination[1,2]

Meningitis is an acute inflammation of the protective membranes covering the brain.

- Fever, headache, photophobia, neck stiffness, and altered mental status[1,4,5]

Meningococcemia (i.e., meningococcal sepsis or "blood poisoning"), even though *N. meningitidis* can be isolated from the bloodstream in up to three-fourths of those patients[3]

Meningococcal septic shock, is the main determinant of the burden of IMD and is associated with high morbidity and mortality[4,6]

Meningococcal pneumonia, it may be underdiagnosed due to the inability to distinguish *N. meningitidis* in sputum samples as being invasive in origin or due to carriage[1]

- Less common manifestations of IMD include **conjunctivitis**, **otitis media, meningococcal septic arthritis (2%), epiglottitis**, **arthritis**, **urethritis**, and **pericarditis**[1,7,8]
- In infants, children, and young adults, IMD usually presents as meningitis or meningococcal septic shock, either alone or in combination[4]

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References: **1.**Martinón-Torres F, J Adolesc Health. 2016;59(2 Suppl):S12-S20; **2.** Bosis S et al., J Prev Med Hyg. 2015;56(3):E121-E124; **3.**Rosenstein NE et al., N Engl J Med. 2001;344(18):1378-1388; **4.** Nadel S et al., Front Pediatr. 2018;6:321; **5.**National Health Service, UK. Overview: meningitis. https://www.nhs.uk/conditions/meningitis/. Updated 25 October 2022 [accessed April 2023]; **6.** Stoof SP et al., Clin Infect Dis. 2015;61(8):1281-1292; **7.** Government of Canada. Pathogen safety data sheets: infectious substances–Neisseria meningitidis. https://www.canada.ca/en/public-health/services/laboratory-biosafetybiosecurity/pathogen-safety-data-sheets-risk-assessment/neisseria-meningitidis.html. Updated 15 May 2019 [accessed 12 November 2019]; **8.**MacNeil J, Patton M., CDC, VPD surveillance manual. Meningococcal disease 2017.

Invasive Meningococcal Disease (IMD)

IMD is associated with risk of death in approximately 24 hours, and even appropriate treatment is often insufficient to avoid severe sequelae among survivors[1-3]

High fatality

- Even when the disease is diagnosed early and adequate treatment is started, between **10% and 15%** of IMD patients will die[5]
- IMD is fatal in **50%** of cases if left untreated[4]
- The case-fatality ratio of IMD among patients with meningococcemia is up to 40%[5]
- The **elderly** have the highest case-fatality rates among all the age groups[6-8]
- **Serogroup W** is associated with the highest case-fatality rate (12.8%), followed by serogroup C (12.0%), serogroup Y (10.8%), and serogroup B (6.9%)[8]

Severe sequelae in survivors

- Severe **physical** sequelae are experienced by 10% to 20% of IMD survivors[4,9]
- Permanent and potentially devastating sequelae among IMD survivors include **neurological** damage and hearing loss[9]
- IMD is associated with significant **behavioral** problems and **psychological** sequelae among the survivors[1,6]

References: 1. Nadel S et al., Front Pediatr. 2018;6:321; **2.** Bosis S et al., J Prev Med Hyg. 2015;56(3):E121-E124; **3.** Vyse A et al., Expert Rev Anti Infect Ther. 2013;11(6):597-604, **4.** World Health Organization. Meningococcal meningitis. Meningitis (who.int) Updated 17 April 2023 [accessed April 2023]; **5.** CDC. Meningococcal disease. Pink Book 13th edition. 2015:231-246; **6.** Martinón-Torres F. J Adolesc Health. 2016;59(2 Suppl):S12-S20; **7.** CDC. Surveillance data tables: incidence rates (per 100,000 persons) of meningococcal disease by age group from 2007 to 2017. https://www.cdc.gov/meningococcal/surveillance/surveillance-data.html#figure02. Last reviewed 6 March 2023 [accessed April 2023]; **8.** Wang B et al., Vaccine. 2019;37(21):2768-2782; **9.** Sadarangani M et al., Clin Infect Dis. 2015;60(8):e27-e35.

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Diagnosis and management of IMD

IMD diagnosis [1,2]

Gold standard: isolation, culture and gram staining of *N. meningitidis* from a normally sterile body site (eg, CSF and blood)[1,2]

N. meningitidis may be identified and serogrouped through molecular genetic methods (eg, PCR)- particularly if antibiotics have already been started [1,2]

IMD management[1]

Antibiotics Treatment
Ceftriaxone or cefotaxime

Chemoprophylaxis
Close contacts -rifampin, ciprofloxacin, or ceftriaxone, to prevent secondary infections

Supportive Treatment
fluid resuscitation and management of shock or organ failure, is essential for severe cases

Vaccination
For infection prevention and outbreak control

IMD can be fatal within 24–48 hours of symptom onset.
Early diagnosis and treatment is critical for disease prognosis[1]

References: 1. McNamara LA, Pollard AJ, Harrison LH. Meningococcal Capsular Group A, C, W, and Y Conjugate Vaccines. In: Orenstein W, Offit P, Edwards KM, Plotkin S, editors. Plotkin's Vaccines. 8th ed. Elsevier; 2023. p. 664-689.e12. ISBN 9780323790581. **2**. Borrow R, Findlow J. The important lessons lurking in the history of meningococcal epidemiology. Expert Review of Vaccines. 2024 Dec 31;23(1):445-62.

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Meningococcal Vaccines

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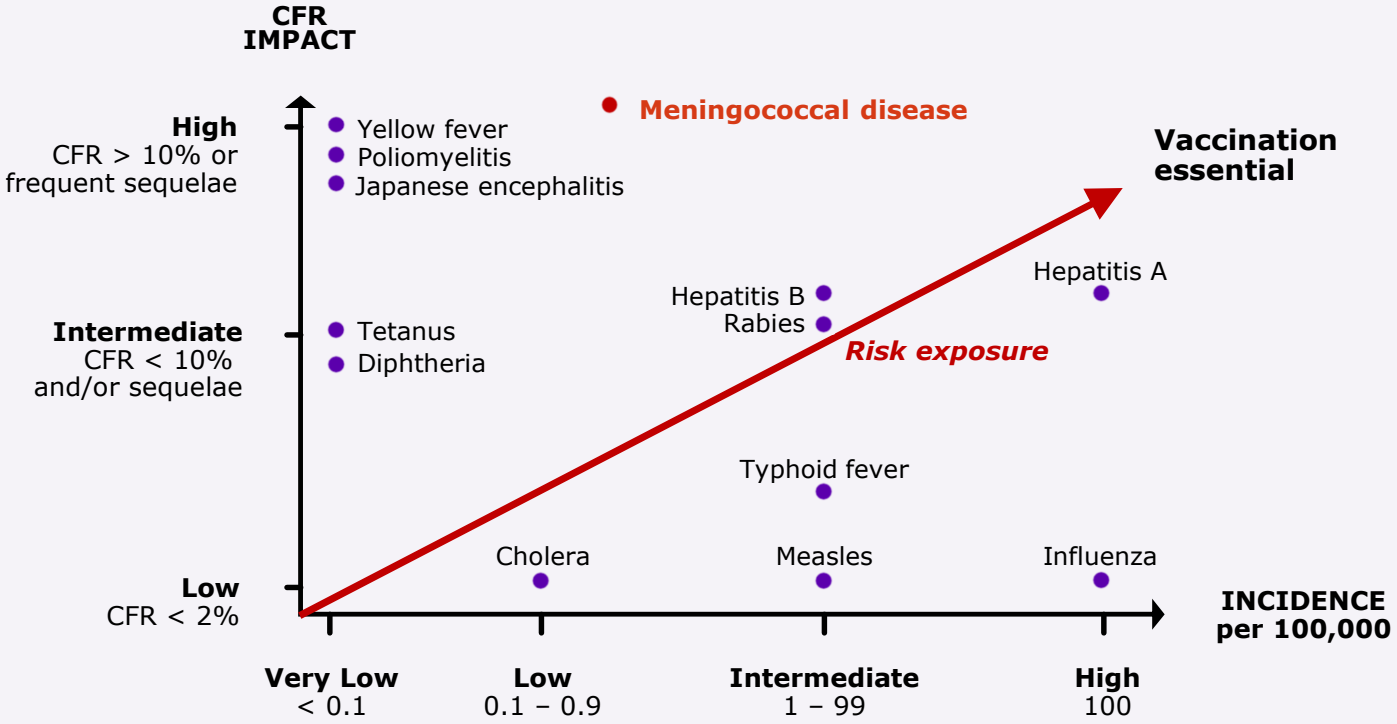
IMD is an infectious global disease that can place all segments of the population at risk for death or devastating sequelae[1,2]

Incidence and Case Fatality Rate Impact of Vaccine-Preventable Diseases [1]

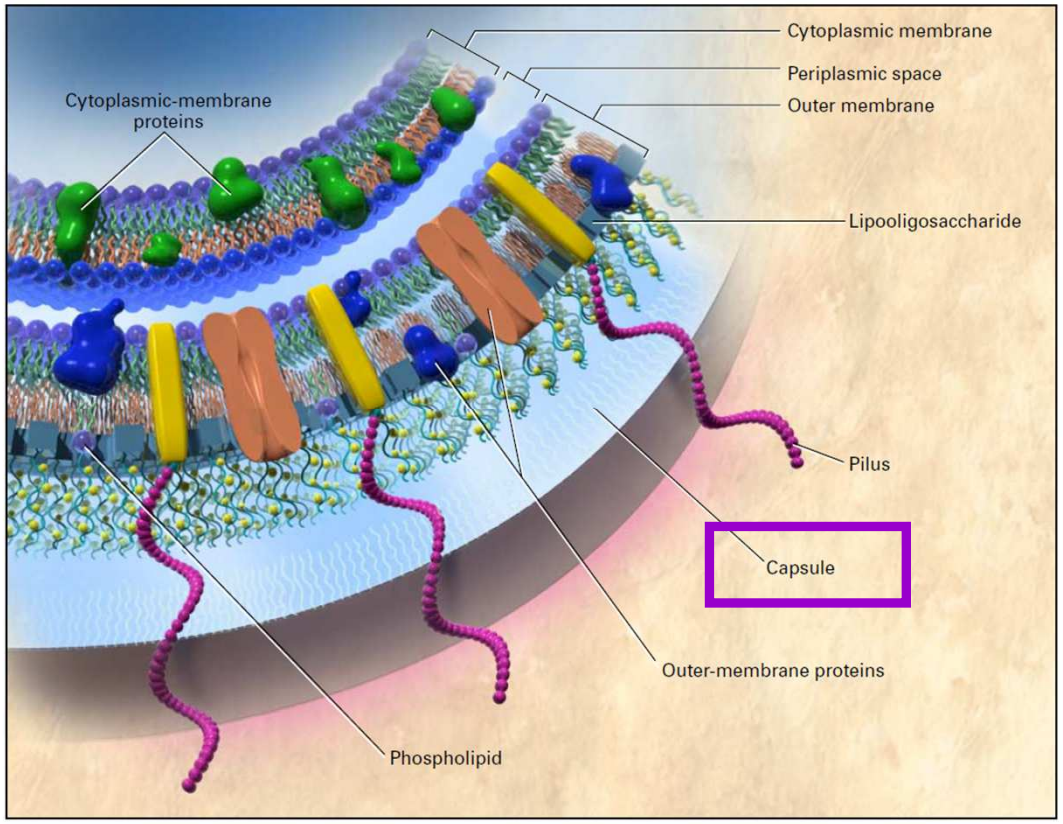


- IMD is **difficult to diagnose** and has a rapid course of progression that can lead to death in a matter of hours[2,3]
- **Severe physical sequelae** are experienced by up to approx. 30% of IMD survivors[2,3]
- Compared with other diseases, meningococcal disease has **low incidence rates** but **high fatality rates**[1]

Image reproduced from Steffen R et al., J Travel Med. 2005;12(1):26-35

References: 1. Steffen R, Connor BA. Vaccines in travel health: from risk assessment to priorities. J Travel Med. 2005 Jan-Feb;12(1):26-35. doi: 10.2310/7060.2005.00006. PMID: 15996464. **2** Bosis S, Mayer A, Esposito S. Meningococcal disease in childhood: epidemiology, clinical features and prevention. Journal of preventive medicine and hygiene. 2015 Aug;56(3):E121. **3.** Nadel S, Ninis N. Invasive meningococcal disease in the vaccine era. Frontiers in Pediatrics. 2018 Nov 9;6:321.

Meningococcal Vaccines for A, C, W and Y serogroups



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Outer-membrane proteins		
Porins	Create pores through which small hydrophilic solutes pass, cation-selective or anion-selective	
PorA		Class 1 outer-membrane protein (serosubtyping)
PorB		Class 2 or 3 outer-membrane protein (serotyping)
Opacity-associated proteins		
Opa	Promotes adherence to host cells and leukocytes	Class 5 outer-membrane proteins
Opc	Promotes adherence to host cells	
Reduction-modifiable protein	Unknown	Class 4 outer-membrane protein
Lipooligosaccharide	Has potent endotoxic activity	13 Immunotypes*
Pili	Promote initial adherence to epithelial and endothelial cells and erythrocytes	Class I and II*

*The classification is based on differences in antigenicity.

Reference: 1. Figure 2 and Table 1 - Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM. Colonization of Neisseria meningitidis in the Nasopharynx and Entry into the Bloodstream and Cerebrospinal Fluid. New Eng J Med. 2001 May 3;344(18):1383

Meningococcal Vaccines for A, C, W and Y serogroups

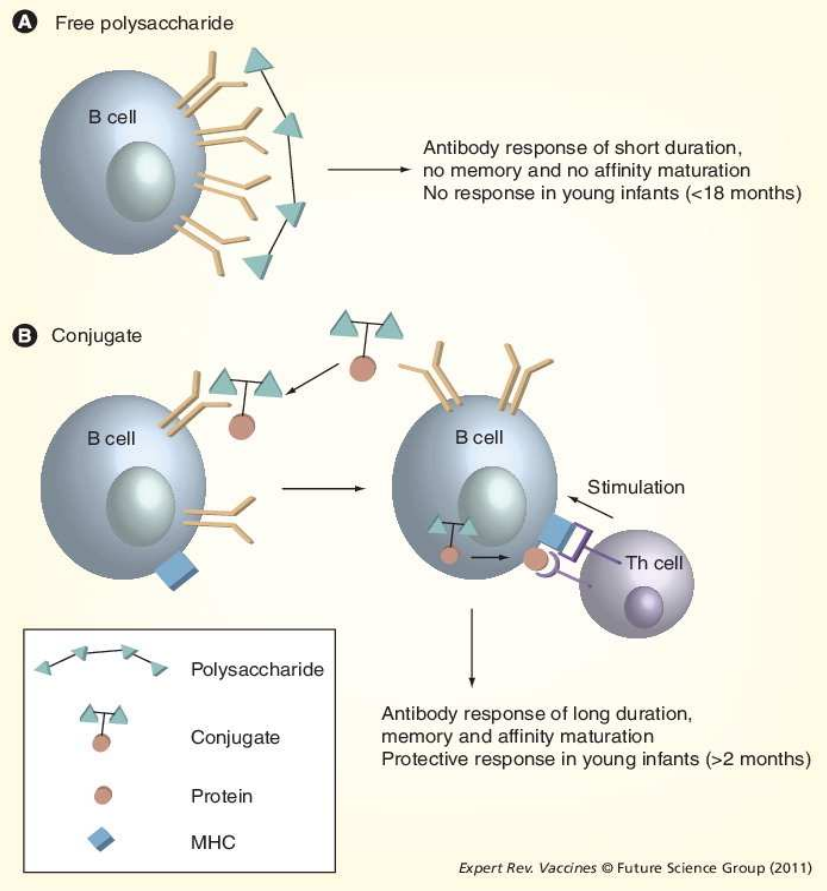

Figure 1 - Poolman J, Borrow R. *Expert Rev Vaccines*. 2011;10(3):307-22. doi: 10.1586/erv.11.8.

Polysaccharide vaccines (plain) introduced in the 1960s provided protection but had limitations:[1,2]

- Short-lived immunity
- Poorly immunogenic in infants
- Do not offer a booster response
- T-cell independent response
- Do not substantially reduce carriage, limiting herd protection
- Can induce "immunological hyporesponsiveness"

They are still used at times for **outbreak control**, particularly in the meningitis belt of Africa but it is likely that they will phased out soon.

Conjugate vaccines developed to improve immune response:[1]

- T-cell dependent antigen
- Longer-lasting immunological memory
- Reduction in nasopharyngeal carriage (herd immunity).

Widespread use of conjugate vaccines has led to dramatic reductions in disease burden, particularly in Africa's meningitis belt.

References: **1.** McNamara LA, Pollard AJ, Harrison LH. Meningococcal Capsular Group A, C, W, and Y Conjugate Vaccines. In: Orenstein W, Offit P, Edwards KM, Plotkin S, editors. Plotkin's Vaccines. 8th ed. Elsevier; 2023. p. 664-689.e12. ISBN 9780323790581. **2.** Borrow R, Findlow J. The important lessons lurking in the history of meningococcal epidemiology. Expert Review of Vaccines. 2024 Dec 31;23(1):445-62

Meningococcal Vaccines for A, C, W and Y serogroups

Manufacturer	Other Designation	Active Constituents Per Dose	Adjuvant	Other Excipients	Presentation and Administration	Storage and Stability	Reference
Pfizer	P-MenC-CRM[a]	10 μg *O*-acetylated group C oligosaccharide conjugated to ~15μg CRM_{197}	$AlPO_4$	Sodium chloride	Single-dose, liquid suspension in a pre-filled syringe	2–8°C	283
GlaxoSmithKline vaccines	G-MenC-CRM	10 μg group C oligosaccharide conjugated to 12.5–25 μg CRM_{197}	$Al(OH)_3$	Histidine, sodium chloride, water for injection	Single-dose, liquid suspension in vial or syringe	2–8°C	410
Pfizer	MenC-TT	10 μg de-*O*-acetylated group C oligosaccharide conjugated to 10–20 μg tetanus toxoid	$Al(OH)_3$	Sodium chloride	Single-dose, prefilled syringe	2–8°C, or up to 9 months at room temperature (up to 25° C)	285
GlaxoSmithKline vaccines	Hib-MenC	5 μg Hib polysaccharide conjugated to ~12.5 μg tetanus toxoid and 5 μg group C polysaccharide conjugated to ~5 μg tetanus toxoid	None	Tris, sucrose, sodium chloride	Single-dose, freeze-dried vial reconstituted with prefilled syringe	2–8°C. If not used immediately after reconstitution, vaccine should be stored at 2–8°C and used within 24 hours	286
Serum Institute of India	MenA-TT	10 μg group A polysaccharide conjugated to 10–33 μg tetanus toxoid	$AlPO_4$	Thimerosal, mannitol, sucrose, Tris	Single or ten-dose, lyophilized group A component and ampoule of diluent	2–8°C; can be exposed to temperature up to 40° C for up to 4 days prior to reconstitution	287
GlaxoSmithKline vaccines	MenACWY-CRM	5 μg each of groups C, W, and Y oligosaccharide and 10 μg of group A oligosaccharide conjugated to a total of 33–64 μg CRM_{197}	None	Sucrose, potassium dihydrogen phosphate, sodium phosphate buffer, sodium chloride	Single-dose vial with lyophilized group A component; single-dose vial with the three other components in liquid form	2–8°C. If not used immediately after reconstitution, should be stored at 2–25°C and used within 8 hours.	288, 289
Sanofi Pasteur	MenACWY-DT	4 μg each of groups A, C, W, and Y polysaccharide conjugated to ~48 μg of diphtheria toxoid	None	Phosphate buffered saline	Single dose vial	2–8°C	290
Pfizer	P-MenACWY-TT	5 μg each of groups A, C, W, and Y polysaccharide conjugated to 44 μg of tetanus toxoid	None	Sucrose, trometamol, sodium chloride	Single-dose vial with lyophilized powder and diluent ampoule or pre-filled syringe	2–8°C. If not used immediately after reconstitution, can be stored at up to 30°C for use within 8 hours.	291
Sanofi pasteur	S-MenACWY-TT	10 μg each of groups A, C, W, and Y polysaccharide conjugated to ~55 μg of tetanus toxoid	None	Sodium chloride, sodium acetate	Single-dose vial of sterile solution	2–8°C	292

Adapted Table 39.2 - McNamara LA, Pollard AJ, Harrison LH. In: Plotkin's Vaccines. 8th ed. Elsevier; 2023. p. 664-689.e12.

Meningococcal Vaccines for B serogroup

- **Group B** capsular polysaccharide is poorly immunogenic and risk of auto-antibody production (due to its similarity to human neural cell adhesion molecules), has made **polysaccharide-based vaccines ineffective** for group B [1,2]
- **Protein-based vaccines** were developed to overcome challenges with the polysaccharide capsule [1,2]
- **Strain variability**: Group B strains are highly diverse, with variability in key surface proteins[1]
- Initial MenB vaccines utilized **outer membrane vesicles (OMVs),** which limited protection to the specific vaccine strain[2]
- Later replaced by **recombinant subcapsular MenB vaccines** that target multiple antigens to increase coverage[2]
- Both vaccines use SBA (**Serum Bactericidal Assay**) titers as a measure of protection, but not all strains are equally susceptible [1]
- RWE: Effective in preventing disease but limited efficacy on nasopharyngeal carriage[1]

References:. Stephens DS, Granoff DM, Pollard AJ, Harrison LH. Meningococcal vaccines directed at capsular group B. In: Orenstein W, Offit P, Edwards KM, Plotkin S, editors. Plotkin's Vaccines. 8th ed. Elsevier; 2023. p. 690-710.e7 . **2.** Borrow R, Findlow J. The important lessons lurking in the history of meningococcal epidemiology. Expert Review of Vaccines. 2024 Dec 31;23(1):445-62

Meningococcal Vaccines for Serogroup B[1]

TABLE 40.2 Composition of Licensed Group B Vaccines

MenB-4C Vaccine	Quantity Per 0.5-mL IM Dose	MenB-FHbp Vaccine	Quantity Per 0.5-mL IM Dose
Antigens		Antigens	
Recombinant GNA2091-FHbp (Subfamily B) fusion protein[a]	50 µg	Recombinant FHbp (Subfamily A)[b]	60 µg
Recombinant NHba-GNA130 fusion protein	50 µg	Recombinant FHbp (Subfamily B)[c]	60 µg
Recombinant NadA	50 µg		
OMV (strain NZ98/254, PorA P1.4)	25 µg		
Other		Other	
Aluminum	0.519 mg of Al^{+3} as aluminum hydroxide	Aluminum	0.25 mg of Al^{+3} as aluminum phosphate
Sucrose	10 mg	Polysorbitol 80 (PS80)	0.018 mg
Histidine	0.776 mg	Histidine buffered saline	10 mM
NaCl	3.125 mg	NaCl	Amount not reported
pH	6.4-6.7	pH	6.0

[a]FHbp peptide ID 1, as described in the public database http://pubmlst.org/neisseria/fHbp/. This sequence variant is assigned to variant group 1 in an alternative classification system.[88]
[b]FHbp ID 45 (called A05 by Pfizer using an alternative classification of amino acid sequence variants (98).
[c]FHbp ID 55 (called B01 by Pfizer; see above).

- **MenB-4C** includes single variants of 3 surface-exposed antigens: nonlipidated FHbp (Factor H binding protein), Neisseria adhesion A, and Neisserial Heparin Binding Antigen (Nhba). It also includes OMV (Outer Membrane Vesicle)[2]
- **MenB-FHbp** includes 2 lipidated FHbp variants from different subfamilies[2]

References:. Stephens DS, Granoff DM, Pollard AJ, Harrison LH. Meningococcal vaccines directed at capsular group B. In: Orenstein W, Offit P, Edwards KM, Plotkin S, editors. Plotkin's Vaccines. 8th ed. Elsevier; 2023. p. 690-710.e7 . **2.** Borrow R, Findlow J. The important lessons lurking in the history of meningococcal epidemiology. Expert Review of Vaccines. 2024 Dec 31;23(1):445-62

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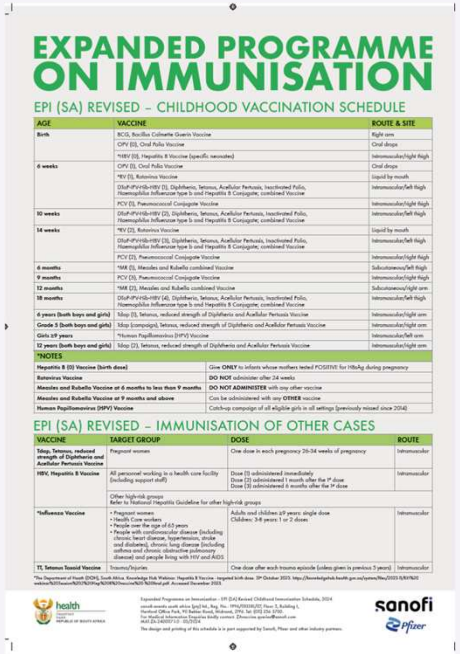
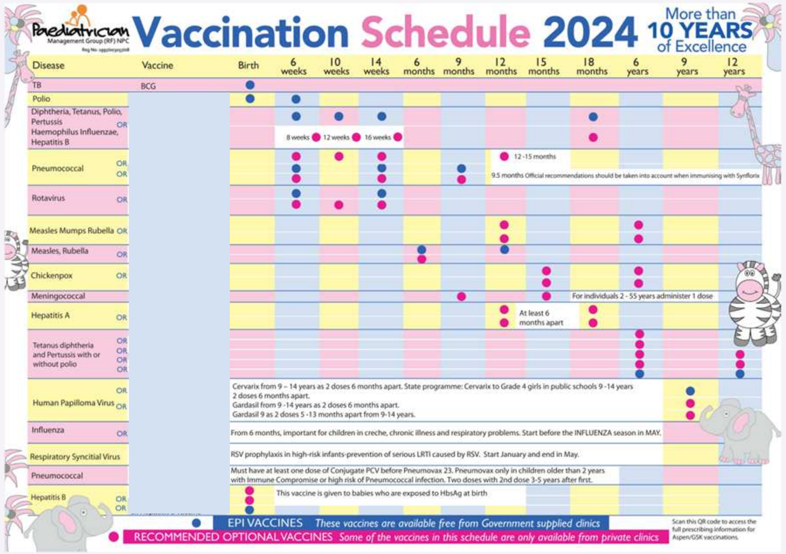
South Africa: Recommendations for use of meningococcal vaccines





Recommendations for the use of meningococcal vaccines in South Africa

Susan Meiring[a*i], Gregory Hussey[b], Prakash Jeena[c], Salim Parker[d] and Anne von Gottberg[e]

Table 1: Suggested recommendations of use of meningococcal vaccine in South Africa

Population Group	Vaccine choice	Recommendation	Primary dosing	Booster
Healthy children and infants	Quadrivalent conjugate vaccine (MCV4)	Should be considered	Children 9 months to 23 months: 2 doses 12 weeks apart Children ≥24 months: 1 dose	
Healthy adolescents or young adults entering university or college (particularly if staying in hostels)	Quadrivalent conjugate vaccine (MCV4)	Should be considered	Single dose prior to entry into university or college	
Military recruits on training or deployment	Quadrivalent conjugate vaccine (MCV4)	Should be considered	Single dose prior to commencing training or deployment	Booster dose required if risk remains high 5 years after primary dose
Miners	Quadrivalent conjugate vaccine (MCV4)	Should be considered	Single primary dose	
Research/reference laboratory workers routinely exposed to *N. meningitidis*	Quadrivalent conjugate vaccine (MCV4)	Recommended	Single primary dose	Booster dose every 5 years if risk remains
Travellers to meningitis belt or other areas where disease is hyperendemic/epidemic	Quadrivalent conjugate vaccine (MCV4)	Recommended	Single primary dose	Booster dose every 5 years should be considered for repeated travel to highly endemic areas
Hajj pilgrims and travellers to Saudi Arabia	Quadrivalent conjugate vaccine	Required	Single primary dose	A booster dose every 3 years for MPSV4 or 5 years for MCV4 is required for repeated travel as per current Saudi regulations
Attendees of mass gatherings	Quadrivalent conjugate vaccine (MCV4)	Should be considered	Single primary dose	
Persons with medical conditions at high risk of acquiring infection: Complement component deficiencies	Quadrivalent conjugate vaccine (MCV4)	Recommended	Two-dose primary schedule 12 weeks apart	Booster every 5 years
Anatomical or functional asplenia	Quadrivalent conjugate vaccine (MCV4)	Recommended	Two-dose primary schedule 12 weeks apart	Booster every 5 years
HIV infection	Quadrivalent conjugate vaccine (MCV4)	Should be considered	Two-dose primary schedule 12 weeks apart	Booster every 5 years
Other immunocompromising conditions	Quadrivalent conjugate vaccine (MCV4)	Should be considered	Two-dose primary schedule 12 weeks apart	Booster every 5 years

- Meningococcal Vaccines are not included in the SA **EPI schedule**
- Quadrivalent vaccines are available but **under-utilised** in both public and private sectors
- **MenB** is the current leading cause of IMD in South Africa yet MenB vaccines are not yet available in SA

Reference: 1. Meiring S, Hussey G, Jeena P, Parker S, Von Gottberg A. Recommendations for the use of meningococcal vaccines in South Africa. Southern African Journal of Infectious Diseases. 2017 Dec 1;32(3):82-6.

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IMD in Africa

MAT-ZA-2400493 – V1 – 11/2024

Meningococcal Disease: Global epidemiology (2018/2019)

- **Serogroup A:** Historically prominent in the "**meningitis belt**" of sub-Saharan Africa[1]
- **Serogroups B and C:** Common in **Europe, North America, Australia** and **South Africa**. While MenB is less common in Africa, has played a role in sporadic cases and smaller clusters of disease[1,2]
- **Serogroups W and Y:** Increasing in many regions, including **South America** and **Europe**[1]
- Outbreaks often occur in closed settings, such as college dormitories, military barracks, and refugee camps[1]

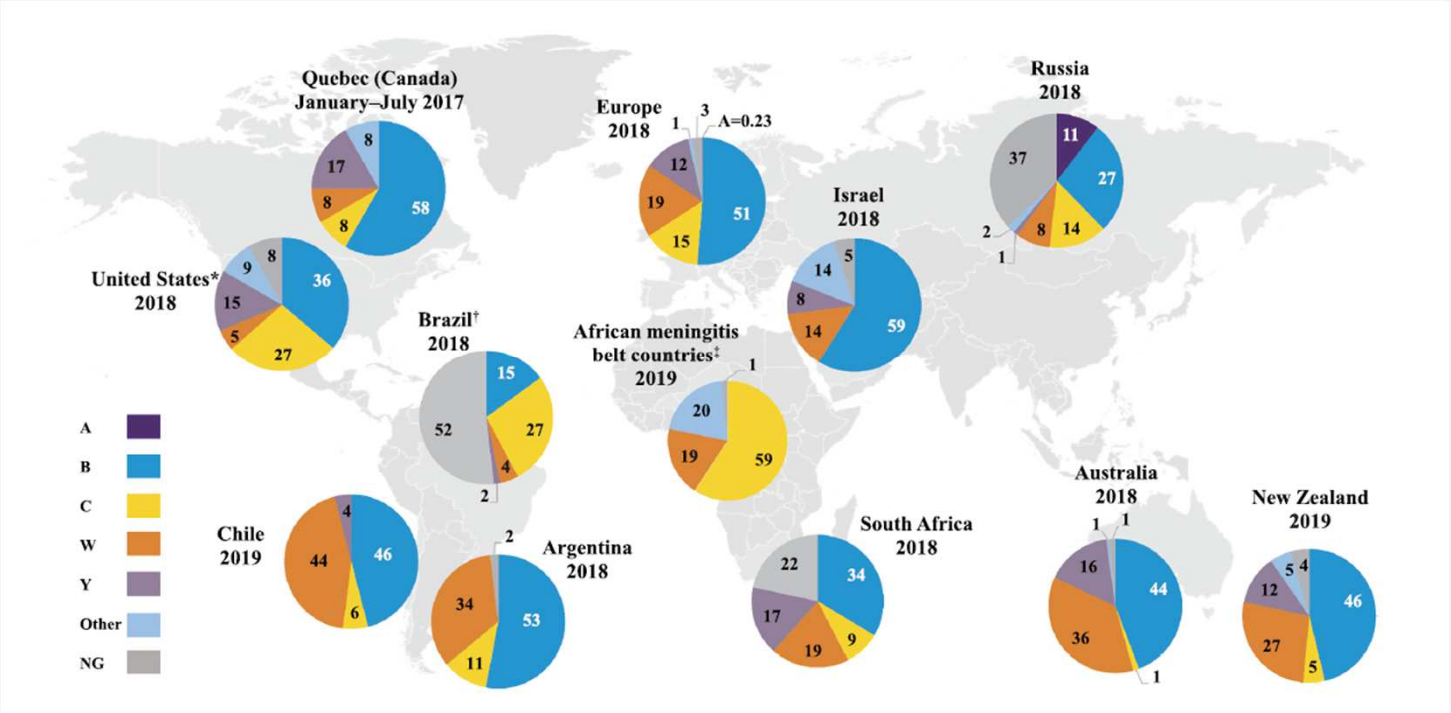

Figure 3 - Borrow R, Findlow J. *Expert Rev Vaccines*. 2024;23(1):445-62.

References: **1.** McNamara LA, Pollard AJ, Harrison LH. Meningococcal Capsular Group A, C, W, and Y Conjugate Vaccines. In: Orenstein W, Offit P, Edwards KM, Plotkin S, editors. Plotkin's Vaccines. 8th ed. Elsevier; 2023. p. 664-689.e12. ISBN 9780323790581. 2. Borrow R, Findlow J. The important lessons lurking in the history of meningococcal epidemiology. Expert Review of Vaccines. 2024 Dec 31;23(1):445-62.

Meningitis Belt and Serogroup Epidemiology

- ***Neisseria meningitidis*** is historically the leading cause of **epidemic meningitis** in Africa[1]
- The highest burden of disease is concentrated in the **Meningitis Belt**, which stretches across 26 countries from Senegal to Ethiopia[2]
- Region is home to approx. **430 million** people[2]
- **High endemic rates** of meningitis, annual seasonal outbreaks and explosive epidemics every 5-12 years[2]
- Peak epidemic incidence of disease would **exceed 1000 per 100,000 population**[3]

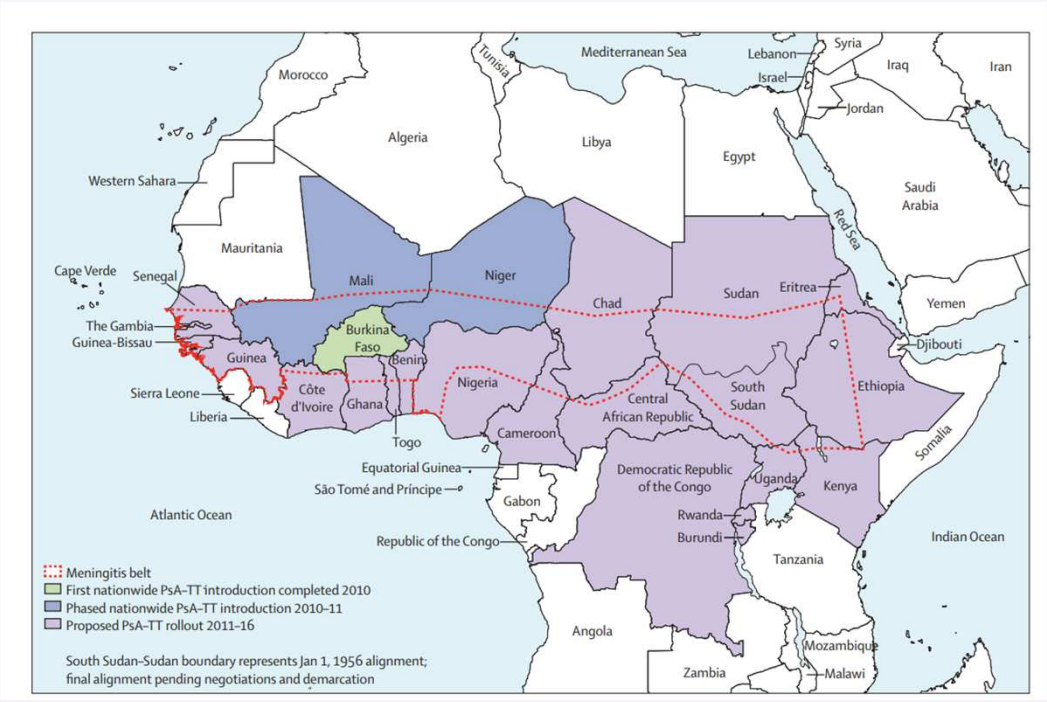

Figure 1 - Novak RT, Kambou JL, Diomandé FV, et al. *Lancet Infect Dis*. 2012;12(10):757-64.

References: **1.** Sinumvayo JP, Munezero PC, Tope AT, Adeyemo RO, Bale MI, Mutsaka-Makuvaza MJ, Daba TM, Nyandwi JB, Nzungize L, Mutumwinka D, Omotayo MO. Vaccination and vaccine-preventable diseases in Africa. Scientific African. 2024 Mar 29:e02199. **2.** Novak RT, Kambou JL, Diomandé FV, Tarbangdo TF, Ouédraogo-Traoré R, Sangaré L, Lingani C, Martin SW, Hatcher C, Mayer LW, LaForce FM. Serogroup A meningococcal conjugate vaccination in Burkina Faso: analysis of national surveillance data. **3.** .McNamara LA, Pollard AJ, Harrison LH. Meningococcal Capsular Group A, C, W, and Y Conjugate Vaccines. In: Orenstein W, Offit P, Edwards KM, Plotkin S, editors. Plotkin's Vaccines. 8th ed. Elsevier; 2023. p. 664-689.e12. ISBN 9780323790581

Meningitis Belt and Serogroup Epidemiology

- **Cyclical outbreaks of meningitis** are experienced across the continent – predominately in **winter season** (dry, dusty conditions)[1]
- **Serogroup A** historically responsible for the majority of cases before the introduction of the monovalent group A conjugate vaccine in 2010[1,2]
- By 2021, **>350 million** people across 24 countries had been immunized[3]
- Subsequently dramatic decline in NmA disease (>99%) but increase in **serogroups W, X** and more recently **serogroup C**[1,2]

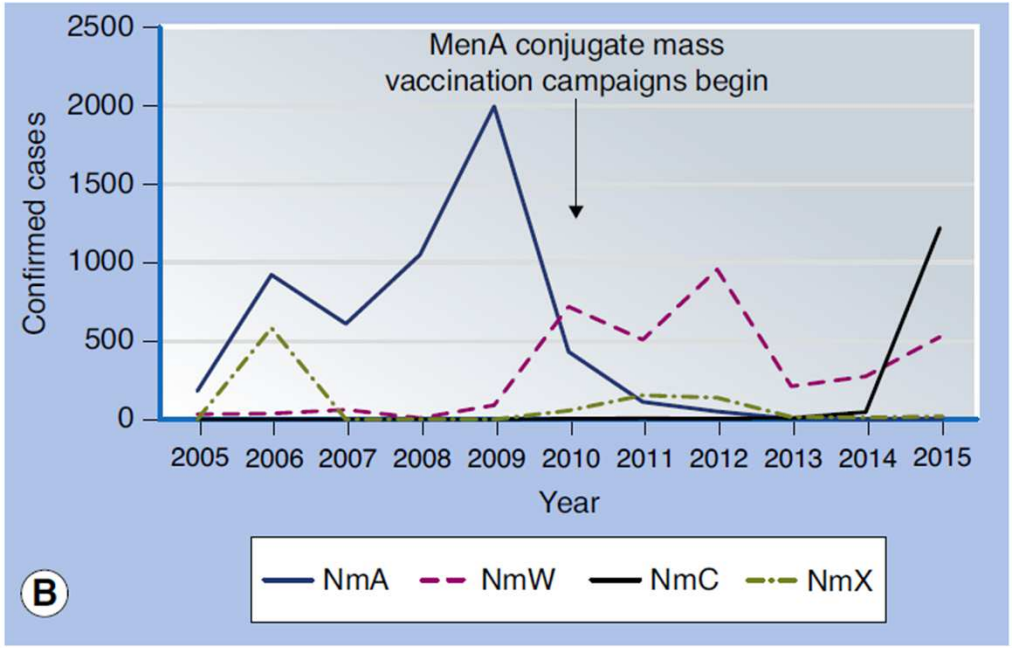

Figure 39.2B - McNamara LA, Pollard AJ, Harrison LH. In: Plotkin's Vaccines. 8th ed. Elsevier; 2023. p. 664-689.e12.

References: 1. Clark SA, Borrow R. Herd protection against meningococcal disease through vaccination. Microorganisms. 2020 Oct 28;8(11):1675. **2 .** McNamara LA, Pollard AJ, Harrison LH. Meningococcal Capsular Group A, C, W, and Y Conjugate Vaccines. In: Orenstein W, Offit P, Edwards KM, Plotkin S, editors. Plotkin's Vaccines. 8th ed. Elsevier; 2023. p. 664-689.e12. ISBN 9780323790581.3. **.** Sinumvayo JP, Munezero PC, Tope AT, Adeyemo RO, Bale MI, Mutsaka-Makuvaza MJ, Daba TM, Nyandwi JB, Nzungize L, Mutumwinka D, Omotayo MO. Vaccination and vaccine-preventable diseases in Africa. Scientific African. 2024 Mar 29:e02199

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Meningococcal Disease in South Africa

- South Africa presents a **distinct epidemiological profile** compared to the rest of the Meningitis Belt, with **four serogroups** responsible for the majority of IMD cases (2016-2021): **B, W, Y** and **C**[1]
- Shift in prevalence of different serogroups from previous IMD surveillance data (2003–2016) largely believed to be due to the **introduction of vaccines** that controlled specific serogroup outbreaks[1]
- The **highest carriage rate** likely found in adolescents and linked with relative behaviours [2]
- The highest incidence of IMD in South Africa was found in: [1]
  - **in infants** (<1 year old) followed by children (<5 years)
  - Predominance in **males** (53%)
  - **Western Cape** (ave incidence 0.62*) followed by **Gauteng** (ave incidence 0.22*)

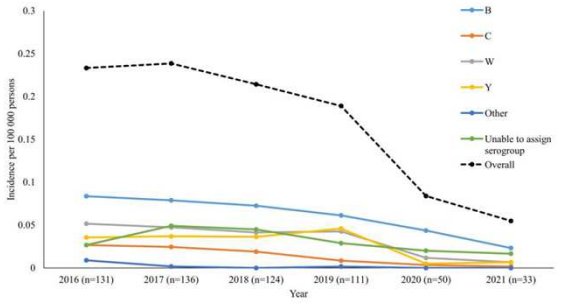


Figure 1. Incidence of invasive meningococcal disease by serogroup and year, South Africa, 2016–2021 (N = 585). "Other" includes Z (n = 1), nongroupable (n = 5), and E (n = 1). Isolates in the "unable to assign serogroup" category were 108 of 585 (18%).

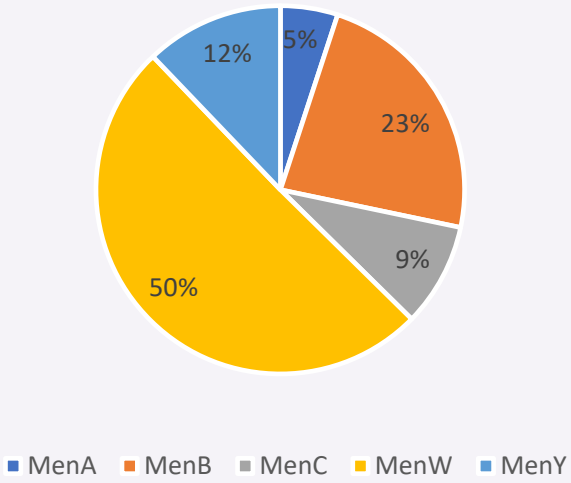
Figure 1 - Mikhari RL, Meiring S, de Gouveia L, et al. *J Infect Dis*. 2024 Apr 30; jiae225.

* Annual IMD incidence per 100 000 persons

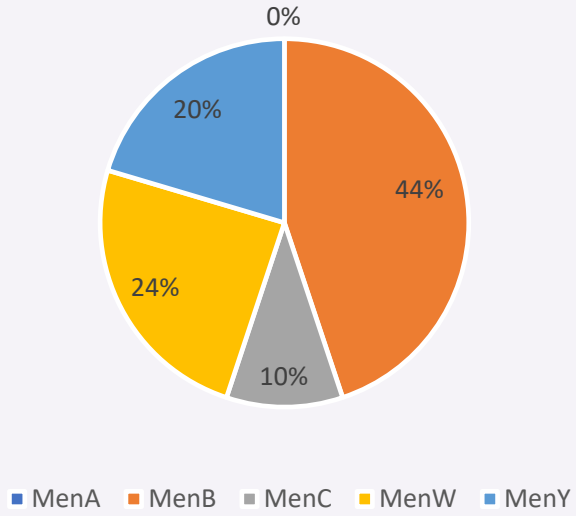
References **1.** Mikhari RL, Meiring S, de Gouveia L, Chan WY, Jolley KA, Van Tyne D, Harrison LH, Marjuki H, Ismail A, Quan V, Cohen C. Genomic Diversity and Antimicrobial Susceptibility of Invasive Neisseria meningitidis in South Africa, 2016–2021. The Journal of Infectious Diseases. 2024 Apr 30:jiae225. 2. Christensen H, May M, Bowen L, Hickman M, Trotter CL. Meningococcal carriage by age: a systematic review and meta-analysis. The Lancet infectious diseases. 2010 Dec 1;10(12):853-61

Meningococcal Disease in South Africa

Invasive Meningococcal Disease Surveillance
2004- 2016



Invasive Meningococcal Disease Surveillance
2016-2021



Serogroup	2016-2021
MenA	0%
MenB	44%
MenC	10%
MenW	24%
MenY	20%

References **1.** Mikhari RL, Meiring S, de Gouveia L, Chan WY, Jolley KA, Van Tyne D, Harrison LH, Marjuki H, Ismail A, Quan V, Cohen C. Genomic Diversity and Antimicrobial Susceptibility of Invasive Neisseria meningitidis in South Africa, 2016–2021. The Journal of Infectious Diseases. 2024 Apr 30:jiae225.

Unpredictability of Meningococcal Epidemiology

- Major challenge in controlling IMD – **unpredictable nature,** with **sporadic outbreaks** occurring across various African regions[1]
- Historical data shows that IMD is prone to periodic surges due to the **emergence of hyperinvasive clones**[1]
- This genomic plasticity adds **complexity to prevention strategies**[1]
- While **serogroups A, B, C, W, and Y** remain the most dominant causes of IMD, **serogroup X** has caused **sporadic outbreaks**, further emphasizing the unpredictability of meningococcal disease across Africa[1]
- **Progressive geographical expansion** of meningitis epidemics outside of the traditional "meningitis belt" with an increasing diversity of Nm strains [2]
- Despite progress in vaccination efforts, the disease is difficult to predict, even in regions with robust healthcare infrastructures[3]. Comprehensive surveillance programs are crucial[1].

References: **1**. Borrow R, Findlow J. The important lessons lurking in the history of meningococcal epidemiology. Expert Review of Vaccines. 2024 Dec 31;23(1):445-62. **2.** Mazamay S, Guégan JF, Diallo N, Bompangue D, Bokabo E, Muyembe JJ, Taty N, Vita TP, Broutin H. An overview of bacterial meningitis epidemics in Africa from 1928 to 2018 with a focus on epidemics "outside-the-belt". BMC Infectious Diseases. 2021 Dec;21:1-3.
3. Martinón-Torres F. Challenges of Unpredictability: Meningitis Prevention Takes Everyone's Continuous Vigilance–Interview with A Key Opinion Leader [Internet]. Available from: https://www.emjreviews.com/wp-content/uploads/2024/09/Challenges-of-Unpredictability-Meningitis-Prevention-Takes-Everyones-Continuous-Vigilance.pdf. Accessed Sept 2024

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Progress:

Meningococcal Vaccination in Africa

MAT-ZA-2400493 – V1 – 11/2024

MenAfriVac: A Transformative Impact in Africa

Historical Context:

- Prior to 2011, **MenA** accounted for approx. 90% of meningitis cases across all ages[1]
- Introduction of a low-cost, temperature-stable **monovalent MenA conjugate vaccine (MACV)** marked a pivotal shift in disease control strategy [1,2]

Vaccine Characteristics (MACV):

- Suitable for challenging transport and storage conditions, is delivered in a **single dose**[1]
- Shown to **maintain elevated antibody titers** for approximately **5 years** post-vaccination[1]

A meningococcal vaccination session in Burkina Faso in 2017. Credit: GAVI/2017/Juliette Bastin

References **1.** Bender RG, Shen J, Aravkin A, Fouda AA, Bwaka AM, Galles NC, Haeuser E, Hay SI, Latt A, Mwenda JM, Rogowski EL. Meningococcal A conjugate vaccine coverage in the meningitis belt of Africa from 2010 to 2021: a modelling study. EClinicalMedicine. 2023 Feb 1;56.**2.** Sinumvayo JP, Munezero PC, Tope AT, Adeyemo RO, Bale MI, Mutsaka-Makuvaza MJ, Daba TM, Nyandwi JB, Nzungize L, Mutumwinka D, Omotayo MO. Vaccination and vaccine-preventable diseases in Africa. Scientific African. 2024 Mar 29:e02199.

MenAfriVac: A Transformative Impact in Africa

Target Population and Strategy:

- The vaccine was strategically administered to **individuals aged 1-29** (represent >90% at risk pop)[1]
- Campaign started in the **highest-risk areas**—Burkina Faso, Mali, and Niger in Dec 2010[1]
- Thereafter leveraged **epidemiological data** to prioritise and sequence country introductions.

Remarkable Outcomes:

By 2021:

- **>350 million people** across 24 of the 26 countries in the meningitis belt were vaccinated[1,2]
- **High vaccination coverage** in **Burkina Faso, Niger, and Togo** (above 85%). [1]
- This wide coverage led to the **near elimination of MenA outbreaks**, significantly disrupting the transmission of serogroup A[1]

References **1.** Bender RG, Shen J, Aravkin A, Fouda AA, Bwaka AM, Galles NC, Haeuser E, Hay SI, Latt A, Mwenda JM, Rogowski EL. Meningococcal A conjugate vaccine coverage in the meningitis belt of Africa from 2010 to 2021: a modelling study. EClinicalMedicine. 2023 Feb 1;56.**2.** Sinumvayo JP, Munezero PC, Tope AT, Adeyemo RO, Bale MI, Mutsaka-Makuvaza MJ, Daba TM, Nyandwi JB, Nzungize L, Mutumwinka D, Omotayo MO. Vaccination and vaccine-preventable diseases in Africa. Scientific African. 2024 Mar 29:e02199.

Image from of WHO - Ayodamola Olufunto Owoseye.

Nigeria: pentavalent MenACWXY-CV campaign and roll out[1]

- Introduction of the MACV vaccine in 2010 has nearly eradicated NmA, shifting the burden to other serogroups such as **C, W, X, and Y**
- Between 1 Oct ’23 – 11 March ’24, there was a devastating **outbreak of MenC** led to **1742 suspected meningitis** cases with **153 deaths**.
- The **pentavalent vaccine (MenACWXY-CV)**was developed to provide protection against five major serogroups (A, C, W, X, and Y), addressing the limitations of earlier vaccines.
- The vaccine was developed through a **13-year collaboration between PATH, the Serum Institute of India Pvt. Ltd,** with funding from the UK government and Gavi, the Vaccine Alliance (Dec ’23)
- **Clinical trials** conducted across countries like **Burkina Faso, Mali, and Ghana** demonstrated the vaccine’s safety and high immunogenicity, particularly for serogroup X, with seroconversion rates exceeding 97%

References: 1. Ukoaka BM, Okesanya OJ, Daniel FM, Affia MO, Emeruwa VE. A perspective on the novel pentavalent Men5CV (NmCV-5) meningitis vaccine and Nigeria’s pioneering rollout campaign. Le infezioni in medicina. 2024 Sep 1;32(3):323-9.

Nigeria: pentavalent MenACWXY-CV campaign and roll out[1]

- In **March 2024**, Nigeria became the **first country** to introduce the **MenACWXY-CV vaccine**
- The vaccine rollout, which occurred over **three days**, successfully **vaccinated over one million people**, targeting individuals aged **1-29 years**.
- Campaigns focused on **high-risk regions in seven states** affected by the outbreak
- The success of this campaign **set a benchmark** for other countries in the meningitis belt, demonstrating Nigeria's commitment to public health innovation.
- Nigeria's rollout of **MenACWXY-CV** showcases **effective collaboration** between the Government, Gavi, healthcare workers, and the Nigeria Centre for Disease Control and Prevention (NCDC).

References: 1. Ukoaka BM, Okesanya OJ, Daniel FM, Affia MO, Emeruwa VE. A perspective on the novel pentavalent Men5CV (NmCV-5) meningitis vaccine and Nigeria's pioneering rollout campaign. Le infezioni in medicina. 2024 Sep 1;32(3):323-9.

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Challenges in Meningococcal Vaccination

MAT-ZA-2400493 – V1 – 11/2024

Challenges in Meningococcal Vaccination in Africa

Vaccine Hesitancy[1]

- Historical Medical Exploitation
- Misinformation Campaigns
- Conspiracy Theories
- Misconceptions About Vaccine Targeting
- Impact of Unverified Information

Funding and Infrastructure[1]

- **Power outages, improper handling & inadequate cold storage** are significant obstacles, especially in rural areas

Conflict and Political Instability[1]

- East African countries face additional barriers due to conflict and instability

Antimicrobial Resistance[2]

- Penicillin resistance increased from **6%** (pre-2008) to **16%** in South Africa (2016-2021), particularly in serogroups **B and W**
- South Africa recommends **third-generation cephalosporins** for initial IMD treatment

Reference 1. Sinumvayo JP, Munezero PC, Tope AT, Adeyemo RO, Bale MI, Mutsaka-Makuvaza MJ, Daba TM, Nyandwi JB, Nzungize L, Mutumwinka D, Omotayo MO. Vaccination and vaccine-preventable diseases in Africa. Scientific African. 2024 Mar 29:e02199. 2. Mikhari RL, Meiring S, de Gouveia L, Chan WY, Jolley KA, Van Tyne D, Harrison LH, Marjuki H, Ismail A, Quan V, Cohen C. Genomic Diversity and Antimicrobial Susceptibility of Invasive Neisseria meningitidis in South Africa, 2016–2021. The Journal of Infectious Diseases. 2024 Apr 30:jiae225.

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Opportunities for future vaccines

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Defeating Meningitis by 2030: A Global Road Map[1]

Global Commitment (Launched 2021):

- **194 WHO member states** have **pledged to defeat meningitis by 2030**, focusing on prevention, early diagnosis, and treatment of meningitis globally.

Visionary Goals:

1. Eliminate bacterial meningitis epidemics

- WHO emphasizes the need to combat hyperinvasive meningococcal serogroups (A, B, C, W, Y) globally.

2. Reduce cases and deaths:

- 50% reduction in cases of vaccine-preventable bacterial meningitis.
- 70% reduction in deaths globally by 2030.

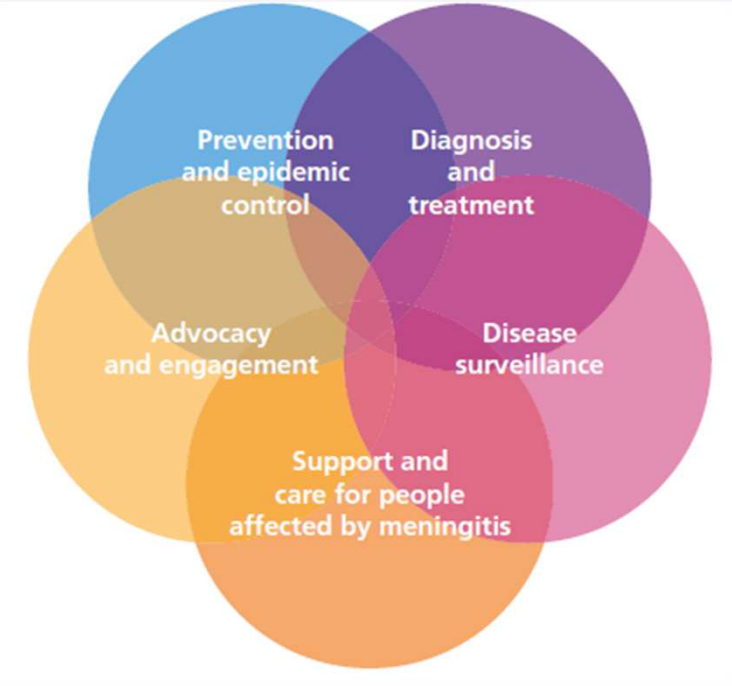
3. Improve quality of life for survivors

- Addressing the long-term disabilities such as neurological damage or hearing loss in meningitis survivors.

Reference: World Health Organization. Investing to defeat meningitis and beyond. World Health Organization; 2024 Apr 24.

Defeating Meningitis by 2030: A Global Road Map[1]

Five Strategic Pillars:



Long-term Impact:

- Prevent **920,000 deaths** by 2030, reduce disability, and save $3.8-$10 billion in healthcare costs.

Reference: World Health Organization. Investing to defeat meningitis and beyond. World Health Organization; 2024 Apr 24.

Ongoing risk in Meningitidis belt

- Despite of the drastic decrease, outbreaks have occured in the sub-Saharan African meningitidis belt:
  - **Meningococcal serogroup C** (MenC) in Benin[1]
  - **Meningococcal serogroup X** (MenX) in Ghana[1]
    - More than 400 confirmed CSM (cerebrospinal meningitis)[2]
    - 50 deaths[2]
    - Case fatality rate = 40%[2]
  - **Meningococcal serogroup W** (MenW) in Congo[3]
    - Suspected cases: 608
    - 161 deaths (case fatality ratio = 26%)
    - 12 confirmed cases of meningitis
  - **Meningococcal serogroup C** (MenC) in Togo[4]

References: 1. Alderson MR, Arkwright PD, Bai X, Black S, Borrow R, Caugant DA, Dinleyici EC, Harrison LH, Lucidarme J, McNamara LA, Meiring S. Surveillance and control of meningococcal disease in the COVID-19 era: A Global Meningococcal Initiative review. Journal of Infection. 2022 Mar 1;84(3):289-96. **2.** Adjorlolo S, Egbenya DL. A twin disaster: Addressing the COVID-19 pandemic and a cerebrospinal meningitis outbreak simultaneously in a low-resource country. Global Health Action. 2020 Dec 31;13(1):1795963. **3.** Meningitis - Democratic Republic of the Congo (who.int) – last accessed on Nov 2022; **4** Feagins AR, Sadji AY, Topaz N, Itsko M, Halatoko JW, Dzoka A, Labite J, Kata Y, Gomez S, Kossi K, Assane H. Neisseria meningitidis serogroup C clonal complex 10217 outbreak in West Kpendjal prefecture, Togo 2019. Microbiology Spectrum. 2022 Apr 27;10(2):e01923-21.

Conclusion

Meningococcal Vaccination in Africa: Key Insights & Future Directions

Progress:

- **Impact of MenACV & subsequent MenACWXY-CV:** dramatically transformed the landscape of meningococcal disease in Africa. **Over 350 million** people have been **vaccinated**, with a **>99% reduction** in **serogroup A** cases [1,2]

- **Vaccine Evolution**: Introduction of the **MenACWXY-CV vaccine** marks a pivotal step towards achieving **comprehensive protection against multiple serogroups** within the African meningitis belt [2]

- **Public Health Milestones**: Over one million people vaccinated in Nigeria's groundbreaking campaign (2024)- has set a new precedent for regional rollouts [2]

A young girl is vaccinated at the MenAfriVac® launch in Burkina Faso. Photo: Gabe Bienczycki/PATH

Ongoing Challenges:

- Despite these advances, Africa still faces significant barriers such as misinformation, vaccine hesitancy, and underdeveloped infrastructure that continue to impede vaccination efforts, particularly in rural and conflict-affected areas [3]

- **Serogroup Gaps:** Despite MenACV vaccine's initial success, new serogroups post ongoing risks, as seen with the Nigeria MenC epidemic(s)[4]

References **1.** Bender RG, Shen J, Aravkin A, Fouda AA, Bwaka AM, Galles NC, Haeuser E, Hay SI, Latt A, Mwenda JM, Rogowski EL. Meningococcal A conjugate vaccine coverage in the meningitis belt of Africa from 2010 to 2021: a modelling study. EClinicalMedicine. 2023 Feb 1;56. **2.** Ukoaka BM, Okesanya OJ, Daniel FM, Affia MO, Emeruwa VE. A perspective on the novel pentavalent Men5CV (NmCV-5) meningitis vaccine and Nigeria's pioneering rollout campaign. Le infezioni in medicina. 2024 Sep 1;32(3):323-9. **3**. Sinumvayo JP, Munezero PC, Tope AT, Adeyemo RO, Bale MI, Mutsaka-Makuvaza MJ, Daba TM, Nyandwi JB, Nzungize L, Mutumwinka D, Omotayo MO. Vaccination and vaccine-preventable diseases in Africa. Scientific African. 2024 Mar 29:e02199. 4. Ukoaka BM, Okesanya OJ, Daniel FM, Affia MO, Emeruwa VE. A perspective on the novel pentavalent Men5CV (NmCV-5) meningitis vaccine and Nigeria's pioneering rollout campaign. Le infezioni in medicina. 2024 Sep 1;32(3):323-9

Meningococcal Vaccination in Africa: Key Insights & Future Directions

Opportunities and the Path Forward:

To meet the WHO's 2030 target of eradicating bacterial meningitis, the focus must be on:[1]

- **Strengthening healthcare infrastructure**, including methods to prevent power outages, improving cold chain storage and increasing surveillance to anticipate emerging strains[2,3]
- **Expanding access to next-generation vaccines** like MenACWXY and future MenB vaccines, leveraging key learnings from Nigeria's vaccine rollout and effective stakeholder collaboration[4]
- **Driving public awareness and education campaigns** to combat misinformation and increase vaccine uptake [2]

References: World Health Organization. Investing to defeat meningitis and beyond. World Health Organization; 2024 Apr 24. 2. Sinumvayo JP, Munezero PC, Tope AT, Adeyemo RO, Bale MI, Mutsaka-Makuvaza MJ, Daba TM, Nyandwi JB, Nzungize L, Mutumwinka D, Omotayo MO. Vaccination and vaccine-preventable diseases in Africa. Scientific African. 2024 Mar 29:e02199. 3. . Borrow R, Findlow J. The important lessons lurking in the history of meningococcal epidemiology. Expert Review of Vaccines. 2024 Dec 31;23(1):445-62. 4. Ukoaka BM, Okesanya OJ, Daniel FM, Affia MO, Emeruwa VE. A perspective on the novel pentavalent Men5CV (NmCV-5) meningitis vaccine and Nigeria's pioneering rollout campaign. Le infezioni in medicina. 2024 Sep 1;32(3):323-9

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Tel: (011) 256 3700.

For Medical Information Enquiries Kindly Contact ZAvaccine.queries@sanofi.com

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For full prescribing information refer to the professional information approved by the medicines regulatory authority.

S4 **MENACTRA** (solution for injection). **QUALITATIVE AND QUANTITATIVE COMPOSITION:** Each 0,5 mL dose contains 4 µg meningococcal (Serogroup A) polysaccharide (monovalent conjugate), 4 µg meningococcal (Serogroup C) polysaccharide (monovalent conjugate), 4 µg meningococcal (Serogroup Y) polysaccharide (monovalent conjugate) and 4 µg meningococcal (Serogroup W-135) polysaccharide (monovalent conjugate). Each of the four polysaccharides is conjugated to diphtheria toxoid protein (approx. 48 µg). **REGISTRATION NUMBER:** 44/30.1/1064.
HOLDER OF CERTIFICATE OF REGISTRATION: sanofi-aventis south africa (pty) ltd., Reg. no.: 1996/010381/07, Floor 5, Building I, Hertford Office Park, 90 Bekker Road, Midrand, 2196. Tel: (011) 256 3700.

S4 **MENQUADFI®** (solution for injection). **QUALITATIVE AND QUANTITATIVE COMPOSITION:** Each 0,5 mL dose contains 10,0 µg *Neisseria meningitidis* group A polysaccharide, 10,0 µg *Neisseria meningitidis* group C polysaccharide, 10,0 µg *Neisseria meningitidis* group Y polysaccharide and 10,0 µg *Neisseria meningitidis* group W polysaccharide, conjugated to 55 µg tetanus toxoid carrier protein. **REGISTRATION NUMBER:** 55/30.2/0612.
HOLDER OF CERTIFICATE OF REGISTRATION: sanofi-aventis south africa (pty) ltd., Reg. no.: 1996/010381/07, Floor 5, Building I, Hertford Office Park, 90 Bekker Road, Midrand, 2196. Tel: (011) 256 3700.

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