Gonococcal Vaccine Preferred Product Characteristics PDVAC Discussion

Virtual PDVAC Session
4 December 2020

World Health Organization

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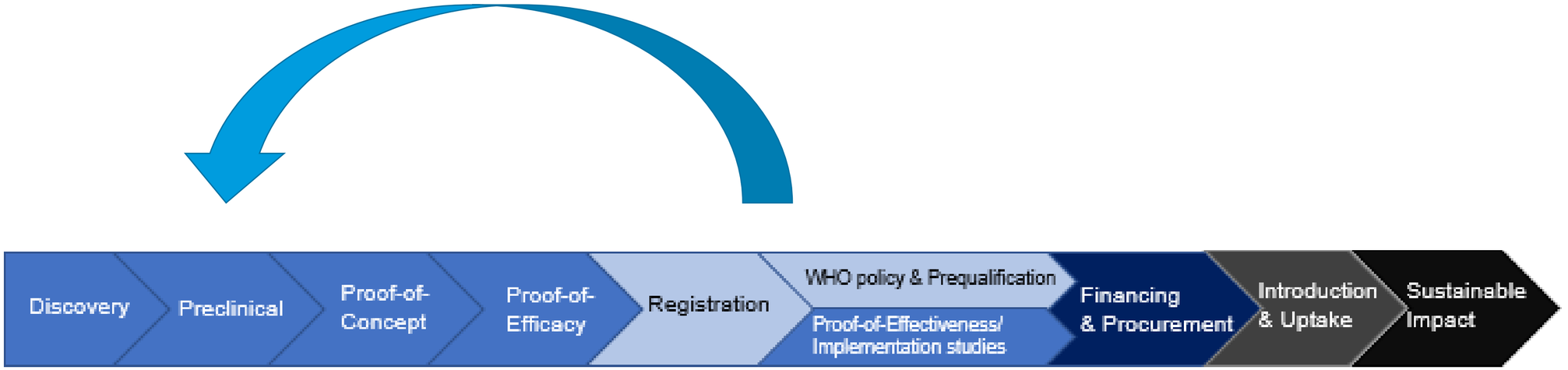
The purpose of WHO Preferred Product Characteristics

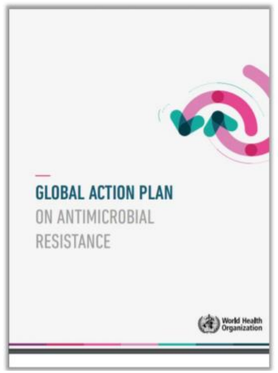


Source: WHO's PPCs and TPPs (IVB)

PPCs aim to provide EARLY guidance to:

- articulate the preferences for vaccines, considering their potential use in LMIC contexts
- increase the likelihood of programmatic fit and benefit, and decrease the delay in implementation
- initiate the considerations for policy considerations, i.e. what data is needed to demonstrate population benefit?
- Increase the probability that emerging candidates will be suitable for LMICs as well as HICs

Development of PPCs for Gonococcal vaccines



- Development of this PPC is early in product development – many unknowns in terms of potential correlates or duration of protection, feasible delivery strategies
- Extent of overlapping epidemiology with MenB incidence, and potential effectiveness of MenB vaccine wrt to gonorrhoea is unclear
- A stand alone gonococcal vaccine will likely need a dual market, i.e. use in both HIC and LMIC to be economically feasible for developers
- Intent was to keep characteristics broad, but where possible (and where we know them) to articulate preferences for LMIC use
- PPCs are refined when data becomes available

Objectives for this session

- Review the rationale and context for developing gonococcal vaccine PPCs
- Evaluate the draft GC PPC and specifically to discuss the following gonococcal vaccine attributes for an ideal gonococcal vaccine:
  - vaccine indication(s)
  - target population(s)
  - vaccine delivery strategy(ies)
  - route of administration
  - duration of protection
- Review additional considerations related to potential use of MenB vaccines for gonococcal infection if they are found to provide some cross-protection

Agenda

Time (Geneva CEST)	Topic	Duration	Detail	Moderators, speakers
14.00 – 14.10	Introduction	10’	• Welcome remarks, roll call, agenda and objectives	Martin Friede (WHO)/ Ruth Karron (JHSPH) / Birgitte Giersing (WHO)
14.10 – 14.35	The rationale and context for development of PPCs for gonococcal vaccines	15 + 10’	• Public health need for gonococcal vaccines • Update on gonococcal vaccine development • Modeling of gonococcal vaccine impact • Gonococcal vaccine PPC process	Sami Gottlieb (WHO) / Carolyn Deal (NIAID)
14.35 – 15.10	Facilitated discussion on selected PPCs for an ideal gonococcal vaccine	35’	• Vaccine indication • Target populations • Vaccine delivery strategies, related to target populations • Route of administration • Duration of protection	Sinead Delany-Moretlwe (Wits RHI) / Sami Gottlieb (WHO)
15.10 – 15.30	Facilitated discussion on additional considerations for MenB vaccines	20’	• MenB vaccines and target populations • MenB vaccines and vaccine delivery strategies • Other considerations related to MenB vaccines	Sinead Delany-Moretlwe (Wits RHI) / Sami Gottlieb (WHO)
15.30 – 16.30	**Discussion (closed session) – PDVAC only** What are PDVAC’s recommendations with respect to the draft text for the product attributes listed above			

Gonococcal infection: range of adverse effects on sexual and reproductive health (SRH)

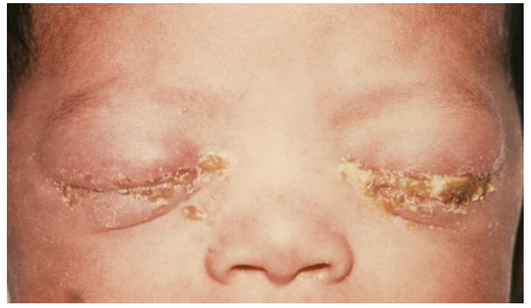
World Health Organization

Gonorrhoea: common bacterial STI caused by *Neisseria gonorrhoeae*

- **Often asymptomatic** or symptoms of urethritis, cervicitis

Whether symptomatic or asymptomatic, infection can lead to:

- Pelvic inflammatory disease (PID), **infertility**, ectopic pregnancy, chronic pelvic pain
- Adverse **pregnancy outcomes** and neonatal conjunctivitis
- Increased **risk of HIV** acquisition and transmission



Disproportionate disease burden in LMICs

87 million new cases of gonococcal infection

World Health Organization

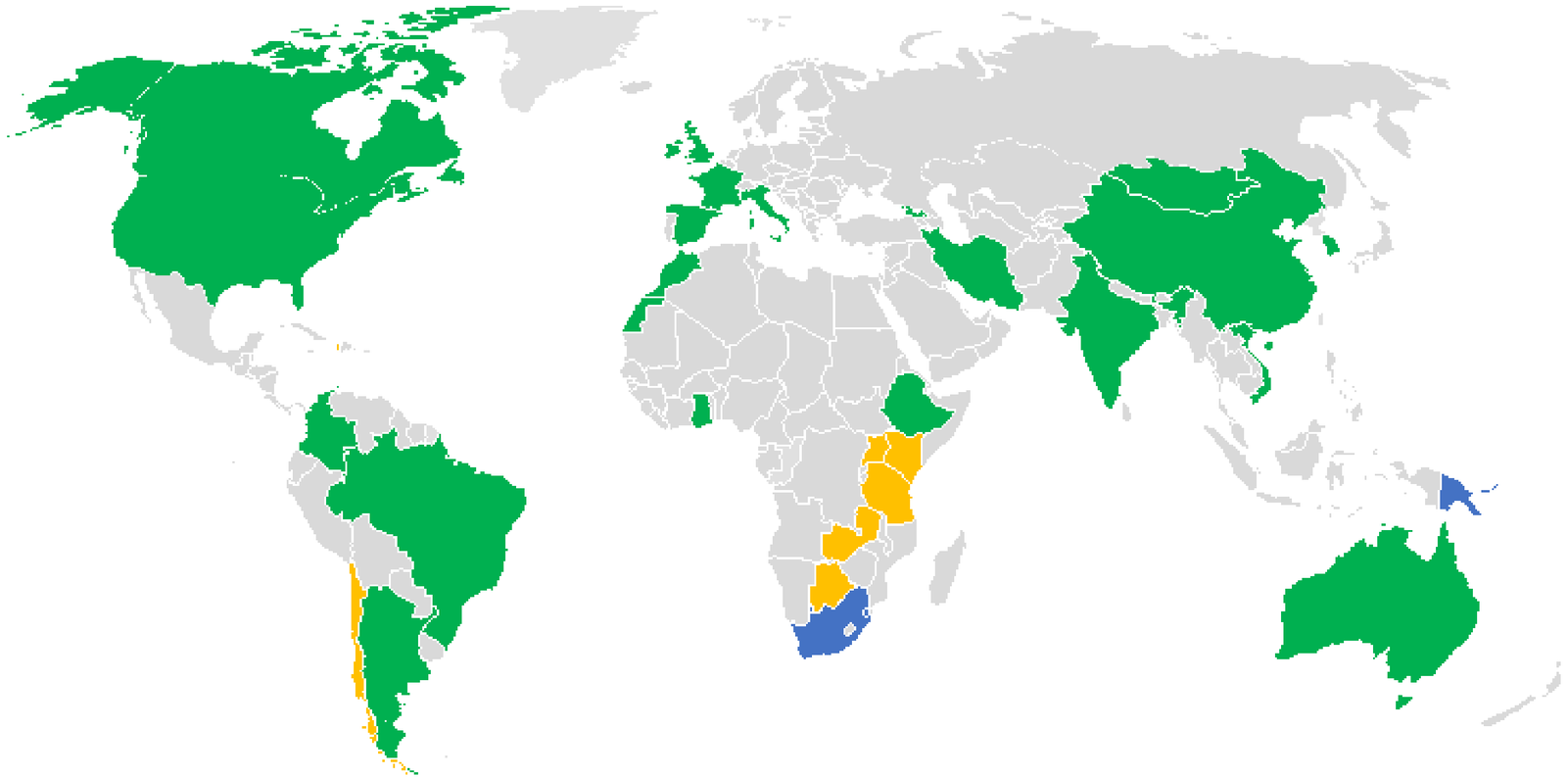
WHO estimates for 2016, among 15-49 year-olds

- Majority of infections in LMICs
- Wide variation in epidemiology between and within countries
  - Access to healthcare/testing
  - Sexual behavior/networks

Source: Rowley et al, Bull WHO, 2019.

Some countries have relatively high gonococcal infection prevalence in general populations

World Health Organization



Gonorrhoea prevalence in women age 15-49.

ND 0 - 0.99 % 1.0 - 5.0 % > 5.0 %

Can still vary widely; many countries without data

Higher in specific sub-populations in ALL settings

Rowley et al, manuscript in preparation.

Studies from general populations; samples collected in 2010 or later.

In many countries: low general population rates, but high rates in specific subpopulations

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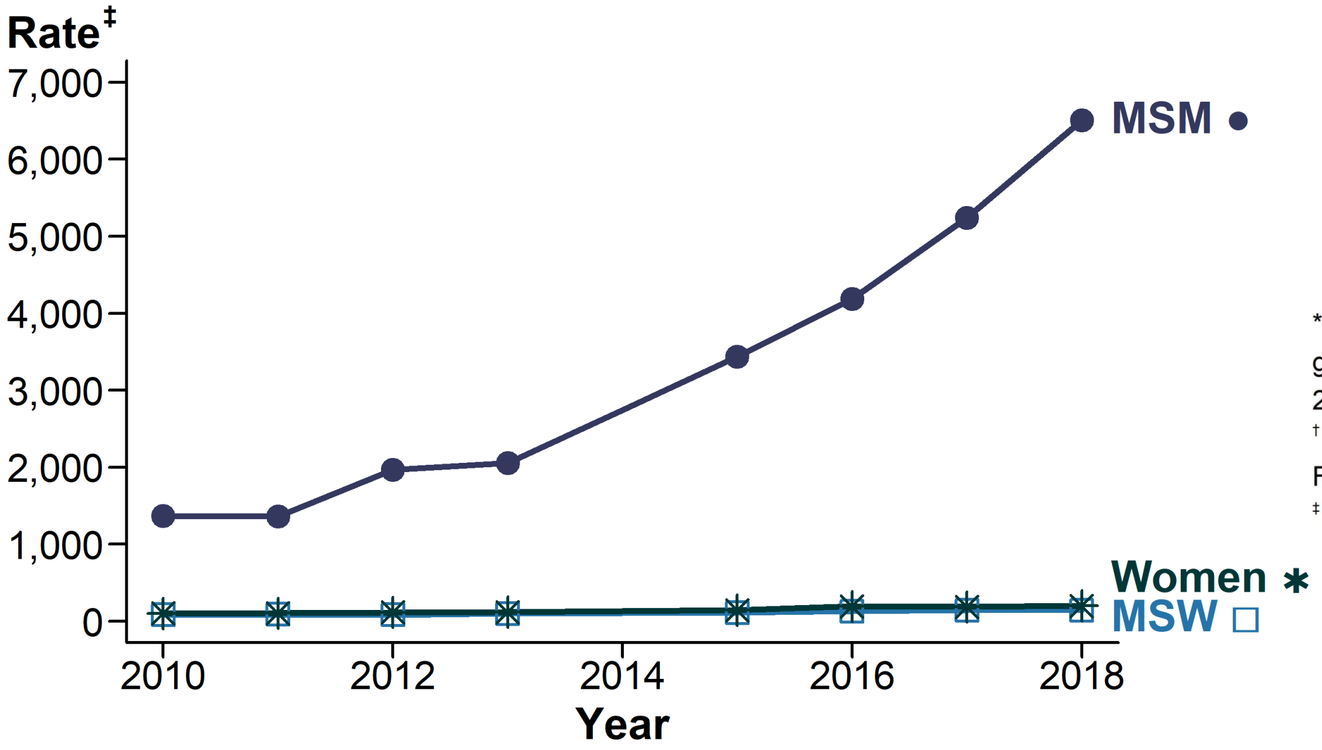
Figure 26. Gonorrhea — Estimated* Rates of Reported Gonorrhea Cases by MSM, MSW, and Women, STD Surveillance Network (SSuN)†, 2010–2018 , USA



MSM = men who have sex with men
MSW = men who have sex with women

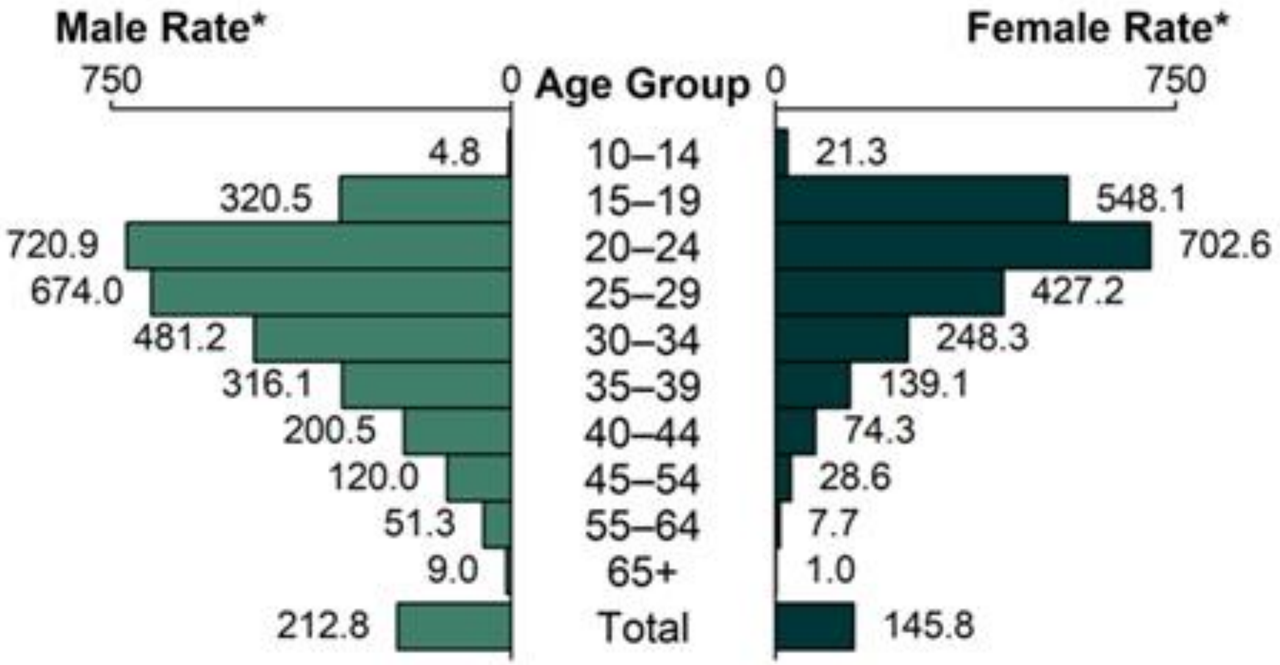
Source: https://www.cdc.gov/std/stats18/default.htm

* Estimates based on interviews among a random sample of reported cases of gonorrhea (n=21,417); cases weighted for analysis. Data not available for 2014; 2013–2015 trend interpolated; trends lines overlap for MSW and women in this figure.
† Sites include Baltimore, Philadelphia, New York City, Washington State, San Francisco, and California (excluding San Francisco).
‡ Per 100.000.

Age and sex distribution of reported gonococcal infections

World Health Organization

Figure 19. Gonorrhea — Rates of Reported Cases by Age Group and Sex, United States, 2018



* Per 100,000.

Source: https://www.cdc.gov/std/stats18/default.htm

- In general populations, peak incidence typically at age 20-24 yrs
- Incidence can extend into older age groups for higher-risk populations

Gonorrhoea control threatened by gonococcal antimicrobial resistance (AMR)

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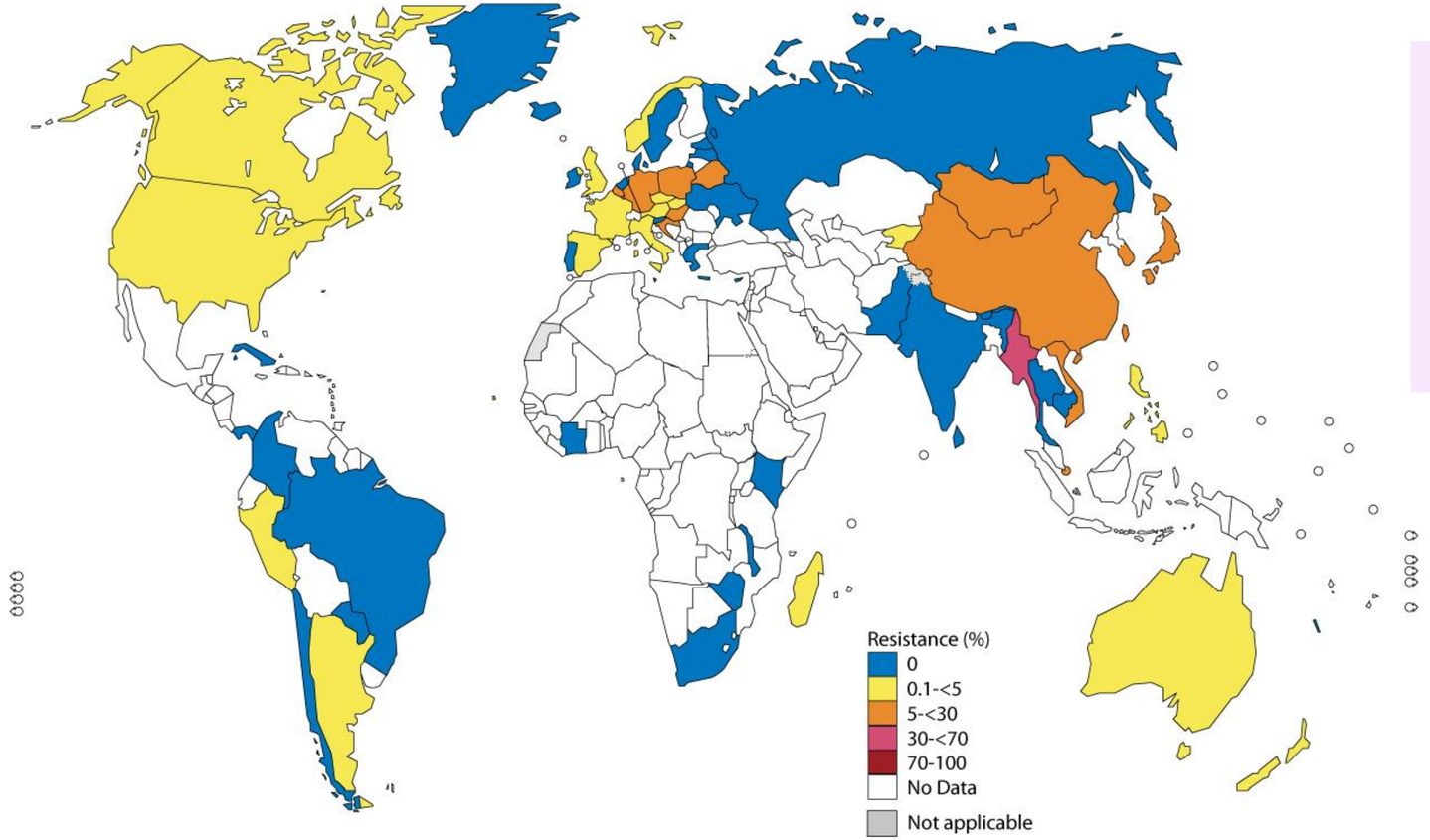
Reported decreased susceptibility/resistance to extended-spectrum cephalosporins in *N. gonorrhoeae*, WHO Gonococcal Antimicrobial Surveillance Project 2015-2016



50% (32/64) countries in GASP with decreased susceptibility/resistance to cefixime or ceftriaxone

Documented clinical treatment failures with multi-drug resistant gonococcal strains

Source: Unemo et al, Sex Health 2019. WHO/GASP data 2015-16

Global Health Sector Strategy on Sexually Transmitted Infections (STIs)

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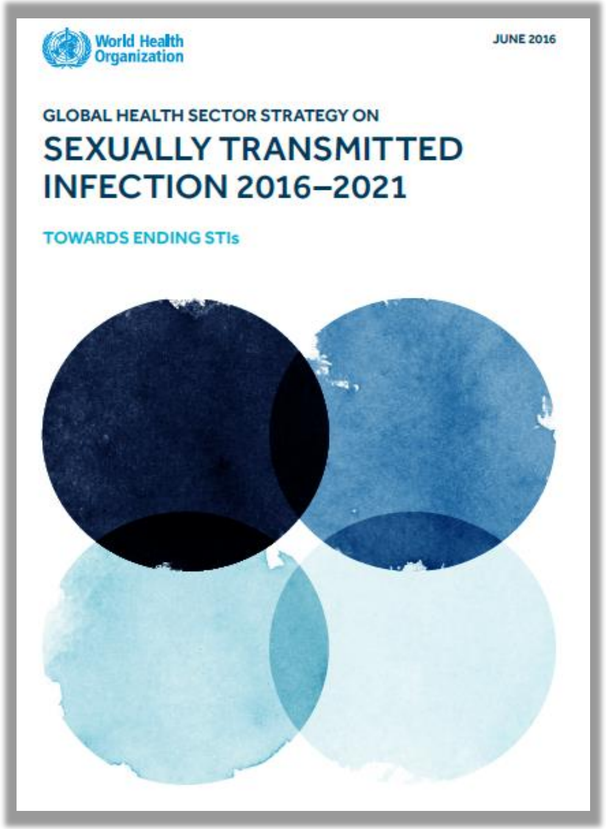
Vision, Goal and Targets

Frameworks for action: Universal health coverage; the continuum of services; and, a public health approach

Strategic Direction 1:	Strategic Direction 2:	Strategic Direction 3:	Strategic Direction 4:	Strategic Direction 5:
Information for focused action	Interventions for impact	Delivering for equity	Financing for sustainability	Innovation for acceleration
The who and the where	*The what*	*The how*	*The financing*	*The future*

Strategy Implementation: …dership, Partnership, Accountability, Monitori… Evaluation



Reduce gonococcal infection incidence by 90% by 2030

Vaccine development

Historically gonococcal vaccine development has been challenging

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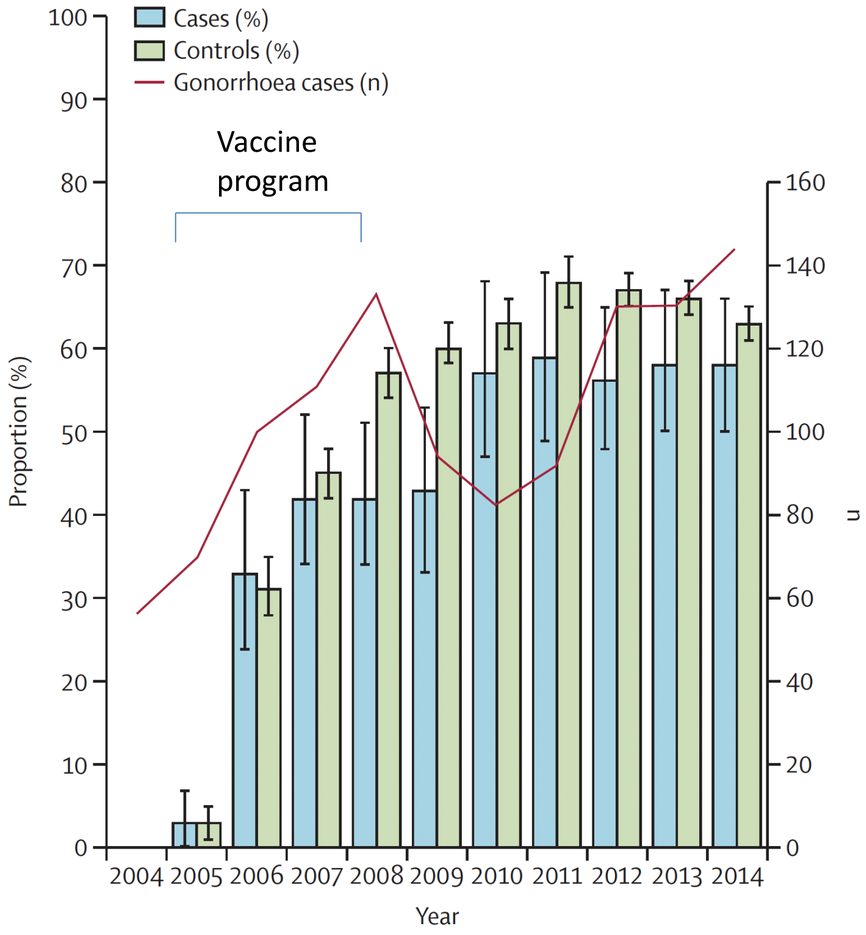
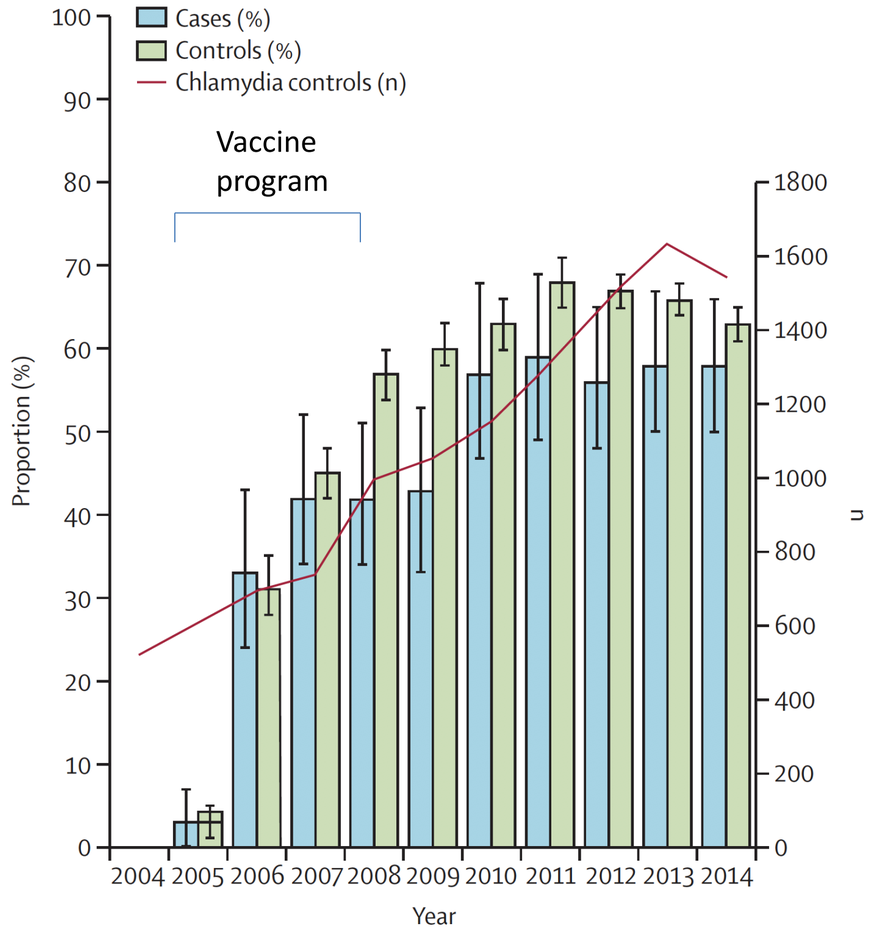
- Antigenic variability of *N. gonorrhoeae* has been well documented
- Repeated infections do not appear to induce immunity therefore provide little insight to vaccine design
- Vaccine efficacy based on naïve versus history of prior gonococcal infection for an individual is currently an unknown for choice of target population
- Early trials of gonococcal vaccines not successful
- Historically, a lack of commercial interest

Mounting data suggesting that gonococcal vaccines are biologically feasible

New Zealand: Meningococcal B outer membrane vesicle (OMV) vaccines and gonorrhoea





In New Zealand, after mass vaccination campaign with group B meningococcal OMV vaccine (MeNZB), gonorrhoea cases appeared to decline

Large case-control study: estimated vaccine effectiveness
31% (21%-39%)

Source: Petousis-Harris et al, Lancet, 2017

Group B meningococcal OMV vaccines and gonorrhoea

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- The New Zealand case-control study retrospectively suggested effectiveness against gonococcal infection
- Licensed meningitis B vaccine 4CMenB (Bexsero®) contains OMVs plus 3 additional antigens
- Meningococcal OMV vaccines accelerate clearance of N. gonorrhoeae in mouse genital tract infection model
- Antibodies from people vaccinated with meningococcal OMV vaccines recognize gonococcal antigens

Sources: Petousis-Harris et al. Lancet 2017; Connolly, abstract 21st IPNC 2018; Semchenko, CID 2018.

Renewed interest in gonococcal vaccines: current candidates and approaches

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Range of vaccine candidates, main approaches:

OMV vaccines

- Meningococcal OMVs
  - 4CMenB (Bexsero®)
  - MC58ΔABR (FDA/CBER)
- Gonococcal OMVs

Purified protein subunit vaccines

- Antigens involved in:
  - physiology or metabolism
  - evasion of innate effectors
  - bacterial structure

LOS epitope (peptide mimetic)

- Synthetic peptide-based

Reviewed in Rice et al. Annu Rev Microbiol 2017; Matthias et al, IPNC 2018 abstract #0113; Connolly et al, IPNC 2018 abstract #0110

Randomized controlled trials of 4CMenB vaccination to prevent gonococcal infection

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Country	Phase	Population	n	Primary Outcome	Timing	Sponsor	Identifier
Australia	III	MSM	130	Time to infection (oropharyngeal, urogenital, anorectal)	2020 Start date	Gold Coast University Hospital	ACTRN12619001478101
Australia	III	MSM	730	Time to infection (oropharyngeal, urogenital, anorectal)	2020 Start date	Kirby Institute	NCT04415424
USA and Thailand	II	Men and women (18-50 y.o.)	2200	Incidence of Infection (urogenital or anorectal)	2020 Start date	National Institute of Allergy and Infectious Diseases	NCT04350138

Other studies of 4CMenB to assess immune response to *N.gonorrhoeae*

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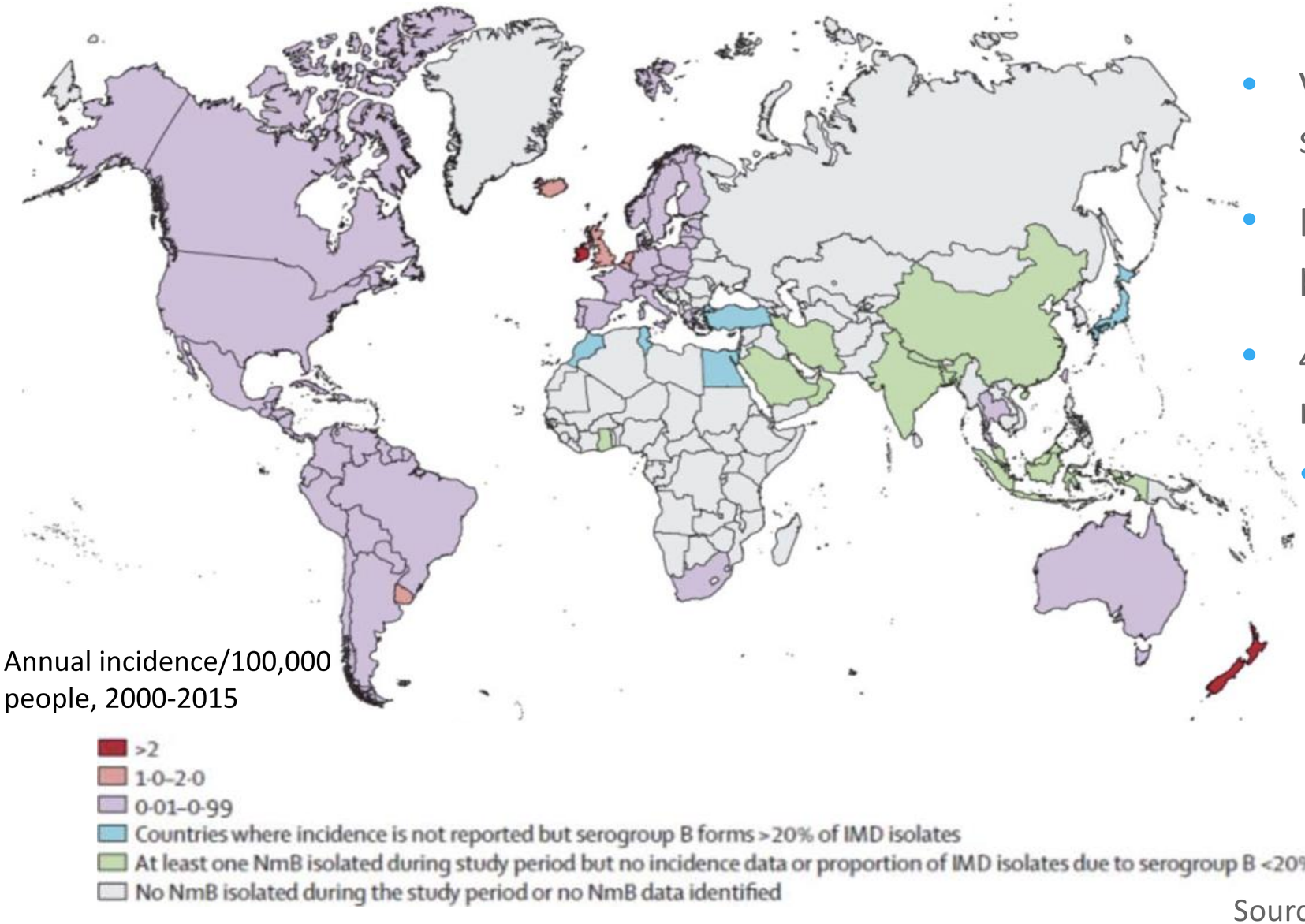
Country	Population	n	Primary Outcome	Timing	Sponsor	Identifier
USA	Young People (18-25 y.o.)	15	Change in anti-*N. gonorrhoeae* OMV-specific IgG, IgM, IgA concentrations; change in frequency of CD4+ T cells expressing at least two different activation markers	Results expected in early 2021	University of North Carolina, Chapel Hill	NCT04094883
Kenya	Young People (18-25 y.o.)	50	Cross-reactive humoral and T cell responses against *N. gonorrhoeae*	Results expected in 2021	University of Oxford	NCT04297436

Global epidemiology of invasive MenB disease

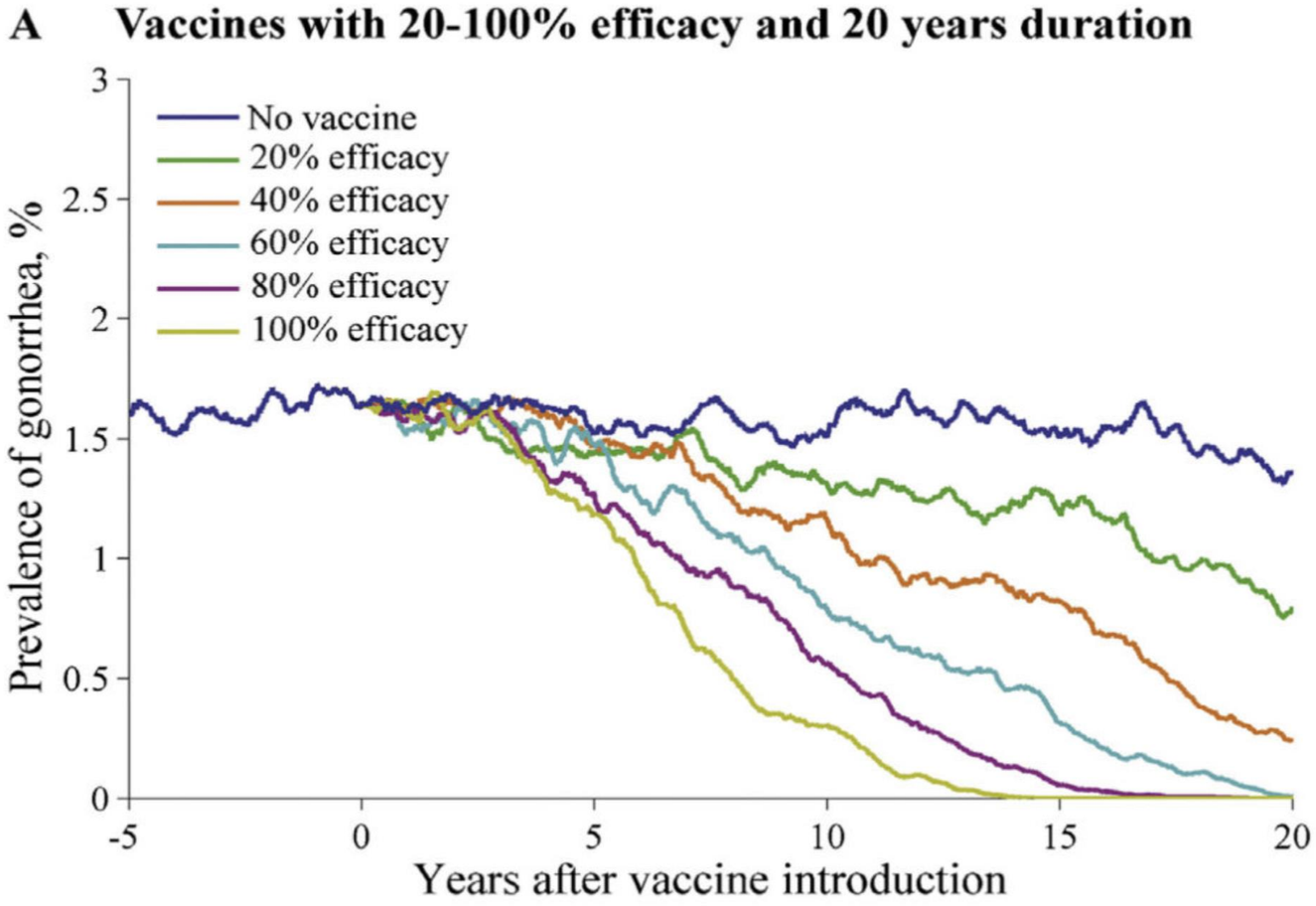


Annual incidence/100,000 people, 2000-2015

- Variability by location and over time; some unpredictable outbreaks
- Highest incidence in infants, smaller peak in adolescence; occurs at all ages
- 4CMenB licensed in 40 countries, mostly HICs
  - Only a fraction of these have it in NIPs or strong recommendations for use

Source: Sridhar et al, Lancet ID, 2015.

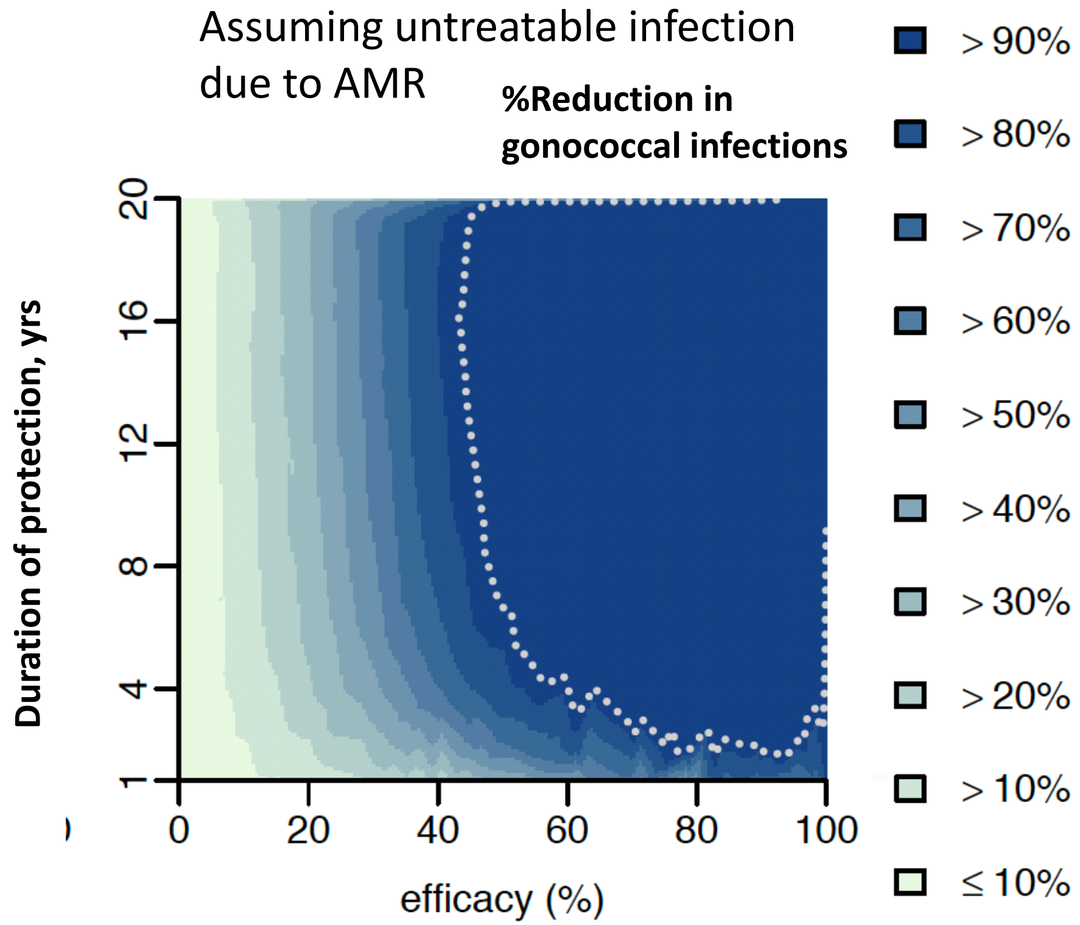
Gonococcal vaccine models: vaccinating all general population 13 year-olds



- Even partially effective vaccine could have substantial impact
- Depends on duration of protection: with shorter duration, need higher efficacy

Source: Craig et al, Vaccine, 2015.

Gonococcal vaccine models: vaccinating all MSM attending UK sexual health clinics



- If can access a large proportion of the group, can have benefits with lower efficacy and duration
- Can achieve 90% reduction in incidence by 2030:
  - 45% protection for 4 years OR
  - 60% protection for 2 years
- Numbers needed to vaccinate may be lower

Source: Whittles et al. Clin Infect Dis, 2020.

Development of PPC document

Vaccine

WHO Report

Gonococcal vaccines: Public health value and preferred product characteristics; report of a WHO global stakeholder consultation, January 2019

Sami L. Gottlieb, Francis Ndowa, Edward W. Hook III, Carolyn Deal, Laura Bachmann, Laith Abu-Raddad, Xiang-Sheng Chen, Ann Jerse, Nicola Low, Calman A. MacLennan, Helen Petousis-Harris, Kate L. Seib, Magnus Unemo, Leah Vincent, Birgitte K. Giersing, Gonococcal Vaccine PPC Expert Advisory Group

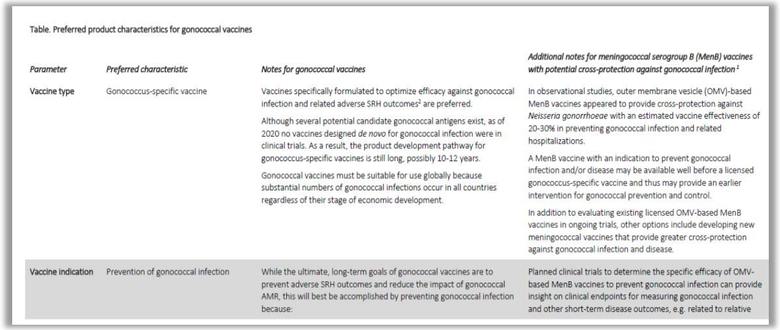


Table. Preferred product characteristics for gonococcal vaccines

Parameter	*Preferred characteristic*	*Notes for gonococcal vaccines*	*Additional notes for meningococcal serogroup B (MenB) vaccines with potential cross-protection against gonococcal infection*
Vaccine type	Gonococcus-specific vaccine	Vaccines specifically formulated to optimize efficacy against gonococcal infection and related adverse SRH outcomes are preferred. Although several potential candidate gonococcal antigens exist, as of 2020 no vaccines designed *de novo* for gonococcal infection were in clinical trials. As a result, the product development pathway for gonococcus-specific vaccines is still long, possibly 10-12 years. Gonococcal vaccines must be suitable for use globally because substantial numbers of gonococcal infections occur in all countries regardless of their stage of economic development.	In observational studies, outer membrane vesicle (OMV)-based MenB vaccines appeared to provide cross-protection against *Neisseria gonorrhoeae* with an estimated vaccine effectiveness of 20-30% in preventing gonococcal infection and related hospitalizations. A MenB vaccine with an indication to prevent gonococcal infection and/or disease may be available well before a licensed gonococcus-specific vaccine and thus may provide an earlier intervention for gonococcal prevention and control. In addition to evaluating existing licensed OMV-based MenB vaccines in ongoing trials, other options include developing new meningococcal vaccines that provide greater cross-protection against gonococcal infection and disease.
Vaccine indication	Prevention of gonococcal infection	While the ultimate, long-term goals of gonococcal vaccines are to prevent adverse SRH outcomes and reduce the impact of gonococcal AMR, this will best be accomplished by preventing gonococcal infection because:	Planned clinical trials to determine the specific efficacy of OMV-based MenB vaccines to prevent gonococcal infection can provide insight on clinical endpoints for measuring gonococcal infection and other short-term disease outcomes, e.g. related to relative

First expert consultation January 2019

Several rounds input Meeting report

Second consultation May 2020

Several rounds input Draft PPC document

Public consultation September 2020

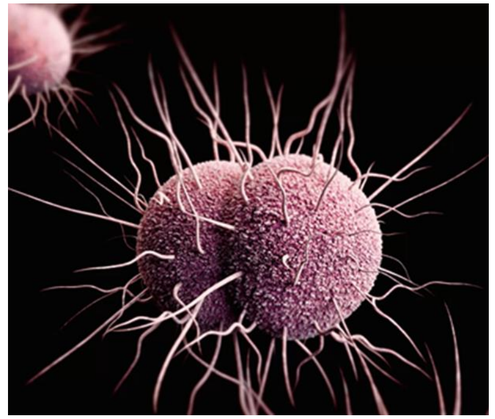
PDVAC Input Nov 2020

Finalization for WHO publication

PDVAC meeting objectives

We would greatly appreciate PDVAC feedback on:

- Selected PPCs for **ideal gonococcal vaccines**
  - **Indications**
  - **Target populations**
  - **Vaccine delivery strategy**
  - Route of administration
  - Duration of protection
- **Additional considerations** if licensed **MenB vaccines** show efficacy against gonococcal infection



Questions on the background?

Many thanks to all of you for lending your time and expertise to this work in the midst of such uncertain and busy times!

Questions?

Does PDVAC agree with the rationale for prevention of infection as the indication?

PPC	Summary of key notes and rationale

Indication:
Prevention of gonococcal infection
	• **Most gonococcal infections asymptomatic** but can still lead to adverse outcomes, particularly in women
	• A vaccine may show efficacy against a disease endpoint but leave **residual asymptomatic infections** that **could still lead to disease or propagate AMR**
	• Existing assays **can easily and accurately measure gonococcal infection** as an outcome in trials
	  • Many **disease outcomes**, such as upper-genital tract sequelae in women, **more difficult to measure**
	  • **Impact on AMR** will likely require **post-licensure studies**

Does PDVAC agree that both young people and specific high-risk populations are priority target populations?

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PPC	Summary of key notes and rationale

Target populations:
Young people
AND/OR
Specific populations at higher risk for gonococcal infection
	• Young people = **adolescents (ages 10-19 years)** and **young adults (ages 20-24 years)**
	• Specific populations at higher risk include:
	  • **Key populations:** those disproportionately affected in most contexts, eg. MSM
	  • **Vulnerable populations:** at higher risk in certain contexts, may vary between/within countries, eg. incarcerated people, subpopulations with historical barriers to healthcare access, AGYW in communities with known high rates of HIV and STIs
	• Key rationale for having either or both as options is **widely varying epidemiologic and programmatic scenarios**

Does PDVAC agree with the factors guiding choice of priority target population(s) in different settings?

PPC	Summary of key notes and rationale

Target populations:
Young people
AND/OR
Specific populations at higher risk for gonococcal infection
	• Choice of **broad-based vaccination of young people** and/or **targeted vaccination of specific higher-risk populations** will depend on factors such as:
	  • **Epidemiology**: general pop prevalence often higher in LMICs but varies; higher-risk pops high in both
	  • **Efficacy in those with prior infection**: may not be an issue as with HPV
	  • **Duration of protection**: unknown
	  • **Cost-effectiveness**: models show each could have impact but at different numbers needed to vaccinate
	  • **Programmatic** delivery: HPV vaccine delivery vs. expanding HIV prevention programmes as platforms
	• Key rationale for **vaccinating both sexes:** infections in both contribute to and are affected by **AMR**

Does PDVAC agree that the ideal vaccine delivery strategy for young people in LMICs is to align with existing (eg. HPV) infrastructure? Does that restrict the ideal target age?

PPC	Notes
Vaccine delivery strategy:	• **Universal vaccination** of young people **may be more straightforward** than targeted delivery

Young people: alignment with existing vaccine delivery infrastructure, eg. for HPV vaccine	• Aligning target age with that for HPV vaccine would allow **use of a similar delivery infrastructure**
	  • Vaccination would occur before first sexual exposure
	  • However, effectiveness **would depend on duration of vaccine protection**
	• Communication should be considered in advance. **Gonococcal vaccines will be more clearly associated with an STI**, which may affect acceptability, esp to parents of adolescents

Does PDVAC agree with the vaccine delivery considerations for people at higher risk? Do they adequately reflect the needs of LMICs?

PPC	Notes

Vaccine delivery strategy:
 	
Populations at higher risk: integration with HIV prevention programmes and other SRH services
	• Specific higher-risk populations **may be harder to reach**
	
	• Where gonococcal incidence is low in general population but concentrated in higher-risk groups:
	  • A **focused vaccination programme** might more **efficiently interrupt community transmission**
	  • Depends on how easily these populations can be reached for delivery
	
	• **Expansion of HIV prevention programmes**, such as PrEP and outreach for key populations, offer novel opportunities for delivery

Should the word ‘mucosal’ be added to the PPC? Are mucosal routes viable for LMICs? Which types?

PPC	Current notes
Route of administration: **Oral or parenteral delivery**	• Local mucosal immunity likely plays an important role in protection against gonococcal infection. An **oral mucosal route is preferred** for ease of administration in LMIC settings. • **Mucosal delivery via other routes**, e.g. intra-nasal, might induce appropriate immune responses but **will be more difficult to deploy**, particularly in resource constrained settings. • Parenteral routes of administration include intramuscular and subcutaneous injections and intra-dermal routes, which can be needle-free, e.g. via a transdermal or microarray patch. **Needle-free methods are preferred** for ease of administration.

Does PDVAC agree with specifying an ideal DoP of 15 yrs for adolescents? And with the caveats for higher-risk pops?

PPC	Summary of key notes and rationale

Duration of protection:
 	
Ideally, at least 15 years duration for vaccinating young adolescents
 	
Shorter durations of protection might still provide benefits for older age groups and specific populations at higher risk
	• Ideally, **vaccine-induced protection should last throughout period of highest risk**
	
	• **Peak incidence** is typically in **young adults (ages 20-24 years)**
	  • For **young adolescents**, duration **might need to be ≥15 years** to avoid booster
	  • For **older young people**, **only 5-10 years** of protection could cover highest-risk period
	
	• For some **pops at higher risk, a duration of only 3-5 years** may still have substantial benefits, eg. in few years after starting PrEP for HIV prevention
	
	• Duration of protection will likely not be known at licensure

Does PDVAC agree with the key considerations for MenB vaccines? Are they useful in the PPC table alongside the gonococcus-specific considerations?

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Related to PPC:	Notes for MenB considerations
Indication	• A **MenB vaccine** with an indication to prevent gonococcal infection may be available well before a gonococcus-specific vaccine and thus **may provide an earlier intervention** for gonococcal control
Target populations	• If preferred target populations in a setting comprise only a small proportion of the population, **expanding an existing licensed vaccine may be more favourable economically** than developing a de novo vaccine for them
Efficacy	• A **lower efficacy could be acceptable** for broadening use of MenB vaccines for gonococcal infection compared with use of a standalone gonococcal vaccine, **given an existing indication** for MenB disease prevention
Vaccine delivery strategy	• **Expanding the indication** of an existing MenB vaccine to include gonococcal prevention could make it more cost-effective and **may affect decisions to introduce MenB vaccines** in more countries and populations

Does PDVAC agree with the considerations for MenB vaccines related to target populations & vaccine delivery?

Related to PPC:	Notes for MenB considerations
Target populations	• Incidence of **invasive MenB disease has substantial geographic variability**. The highest incidence is among infants, and most HICs using MenB vaccines emphasize infant vaccination. However, it occurs at all ages.
Vaccine delivery strategy	• A **few countries recommend MenB vaccines for young people** in areas with frequent close contact (e.g. people entering university or military). This **may overlap** with potential target populations for gonococcal vaccines. • Where MenB vaccine target populations already include young people, vaccinating to also prevent gonococcal infection would be relatively straightforward. • **Many LMICs with high gonorrhea prevalence have little MenB disease** or don't use MenB vaccines due to cost. Better data are needed on epidemiologic overlap and factors affecting MenB vaccine use in different settings. • **Meningitis may be perceived as less stigmatizing** than gonorrhoea. Initial promotion of MenB vaccines with some potential to prevent gonococcal infection may increase acceptability of a specific gonococcal vaccine later.