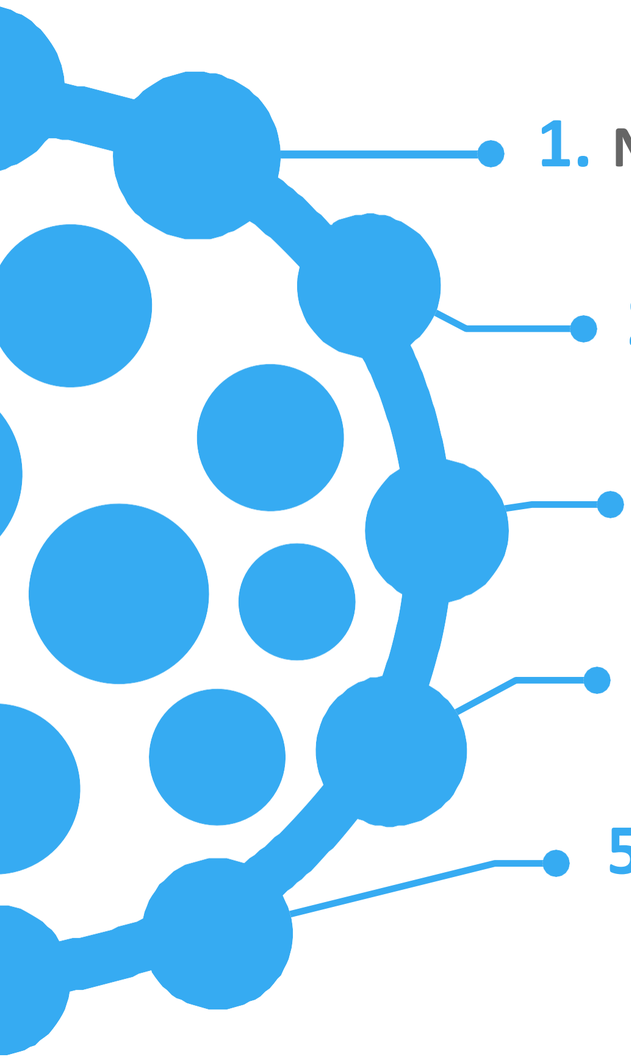
# Advancing vaccine development for gonococcal infections and the Global STI Vaccine Roadmap

Dr Sami Gottlieb
World Health Organization
17 March 2021

World Health Organization

# Outline





1. Need for vaccines against gonococcal infection
2. Can gonococcal vaccines be developed?
3. Global Roadmap to Advance STI Vaccine Development
4. Epidemiology and the use case for gonococcal vaccines
5. Looking to the future

# Global estimates: 87 million new cases of gonococcal infection



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

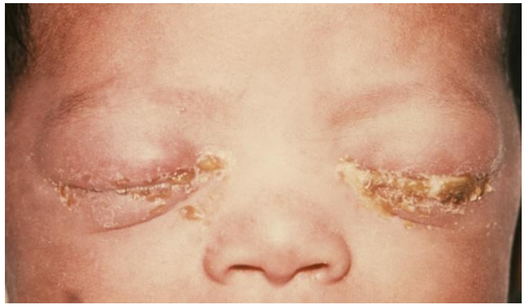

- Majority of infections in low- and middle-income countries (LMICs)
- Variation in epidemiology between and within countries

Source: Rowley et al, Bull WHO, 2019.

# Gonococcal infection: range of adverse effects on sexual and reproductive health



- Lower genital tract symptoms: urethritis, cervicitis
- Pelvic inflammatory disease (PID) → infertility, ectopic pregnancy, chronic pelvic pain
- Adverse pregnancy outcomes and neonatal conjunctivitis
- Increased risk of HIV acquisition and transmission

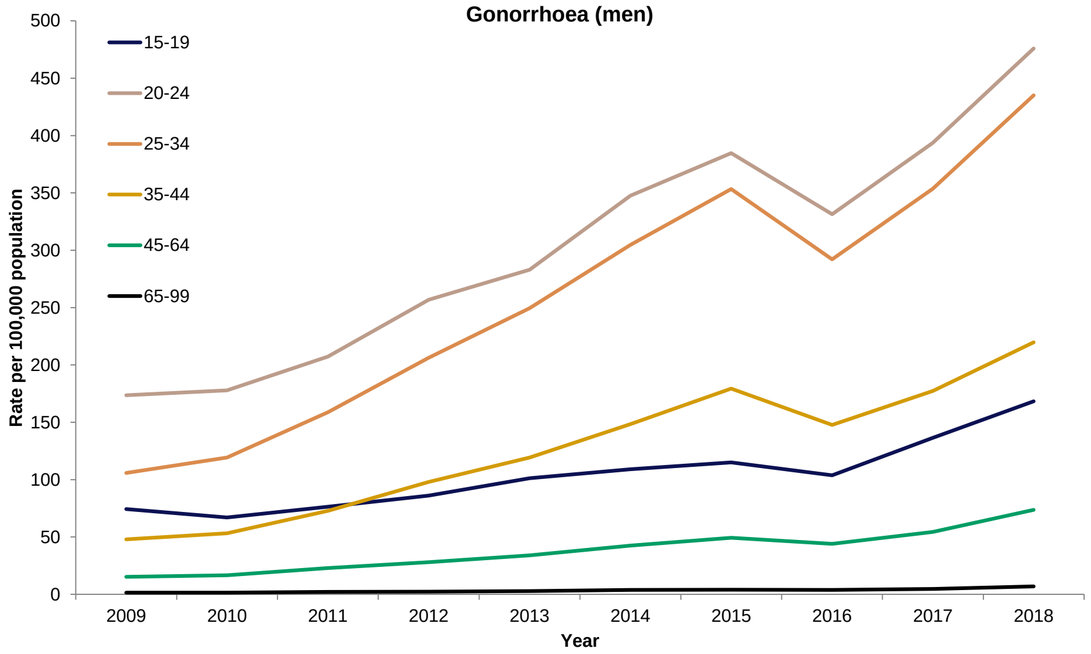


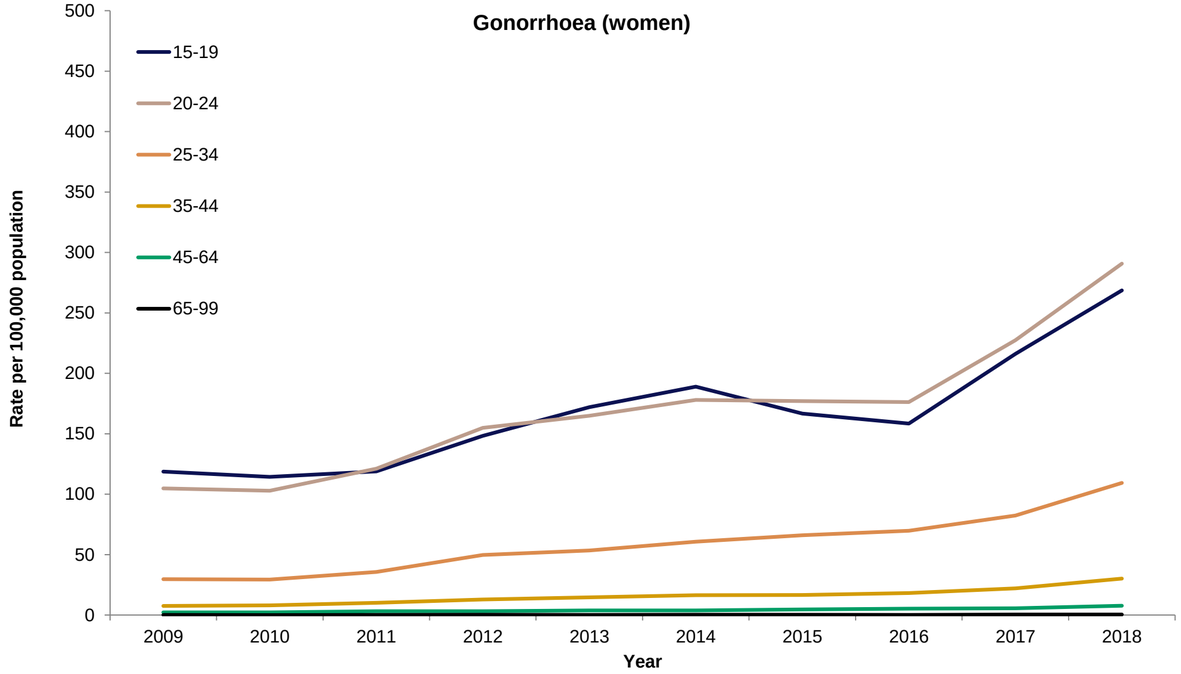
Disproportionate disease burden in LMICs

# Gonococcal infection rates: Losing ground?



- Even in settings with previously good control, recent increases in reported case rates




Source: Public Health England. Sexually transmitted infections and screening for chlamydia in England, 2018. Health Protection Report 13(9), 2019.

# Challenges to gonorrhoea control

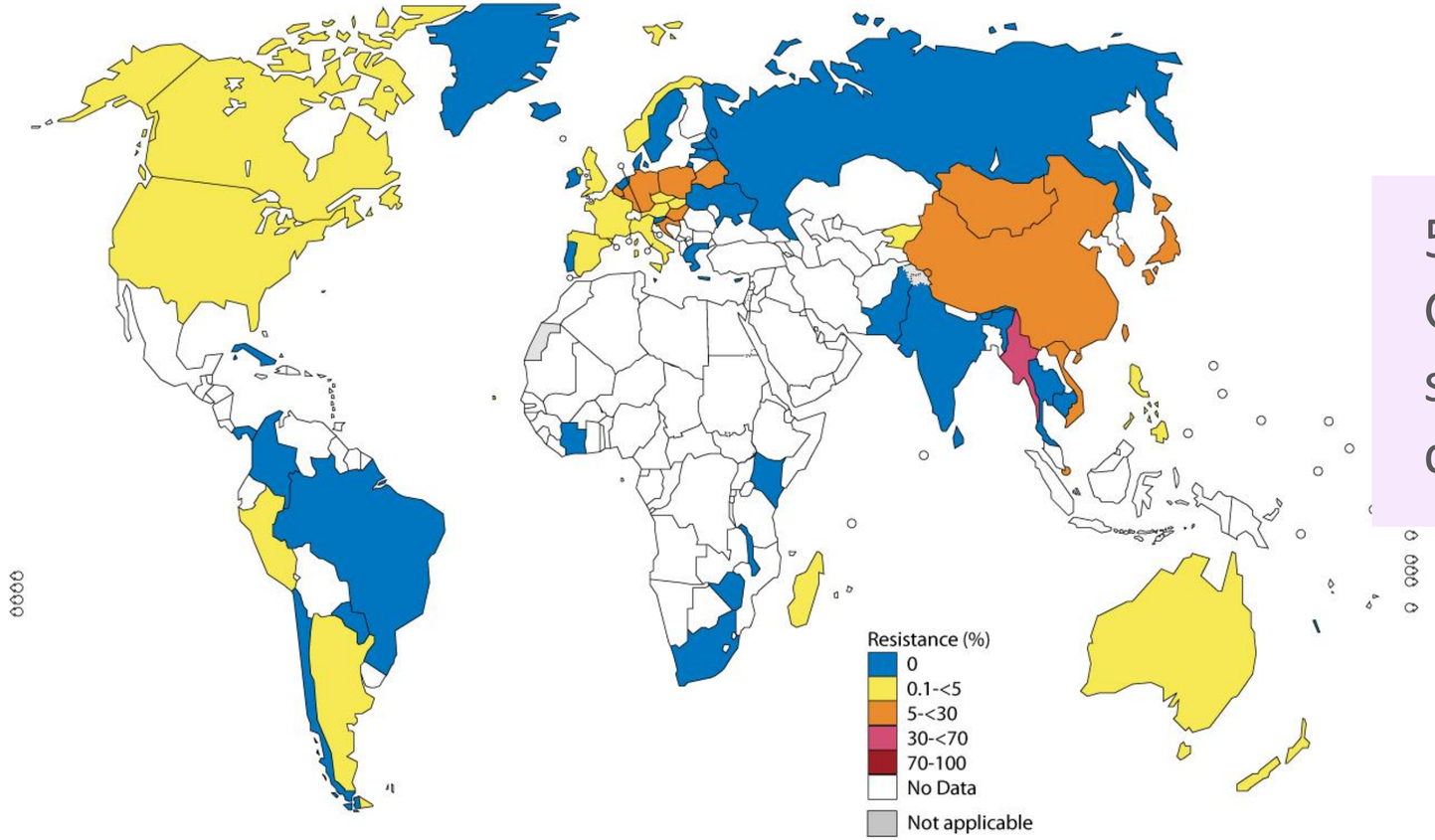


- Limits to progress made with condom promotion
- Most infections asymptomatic
  - Lack of feasible tests in many settings
  - Screening programs difficult to bring to scale
- Stigma and lack of public policy attention: without simple intervention, harder to garner support
- **Antimicrobial resistance**

# Gonorrhoea control threatened by gonococcal antimicrobial resistance (AMR)



## 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

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

# Documented treatment failures with multi-drug resistant gonococcal strains



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The VICE Guide To Right Now

## Super Gonorrhoea Is Coming to Destroy Your Junk

It's coming for us. All of us. All of us who don't wear protection.

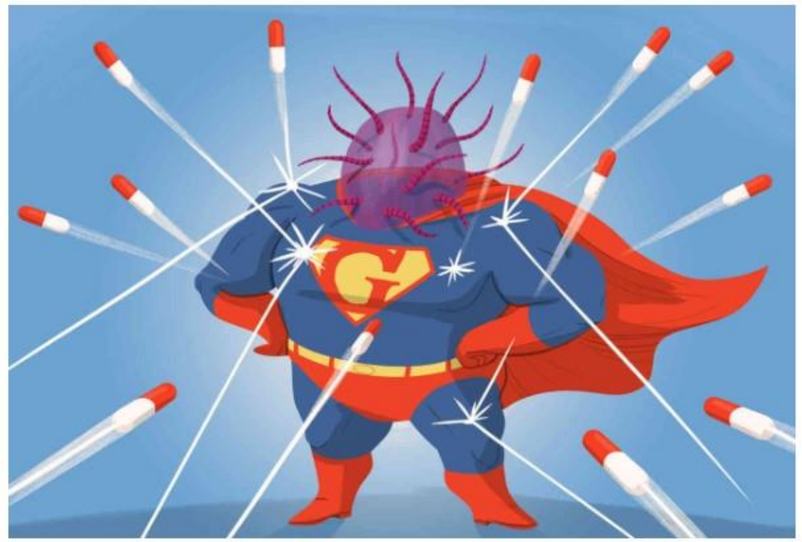
By Carlton Férment

18 April 2016, 12:58pm Share Tweet

THRILLIST WATCH FOOD & DRINK TRAVEL ENTERTAINMENT SHOPPING CITIES

## Uh-Oh: Super Gonorrhea Is Something You Have to Worry About Now

By JOHN MARSHALL
Published On 05/27/2016



Jason Hoffman/Thrillist

# The steady pace of gonococcal AMR



## Antibiotic Introduced

1936: Sulfonamides

Penicillin
Streptomycin

Erythromycin

Spectinomycin
Tetracycline

Fluoroquinolone
Azithromycin

Cephalosporins

1940 | 1950 | 1960 | 1970 | 1980 | 1990 | 2000 | ‘07 | ‘08 | ‘09 | ‘10 | ‘11 | ‘12

Sulfonamides

Erythromycin

Penicillin
Tetracycline
Spectinomycin

Fluoroquinolones
Azithromycin

Oral extended-spectrum cephalosporins

## Antibiotic Removed

Figure courtesy of Ann Jerse

# Global Health Sector Strategy on Sexually Transmitted Infections (STIs)



World Health Organization

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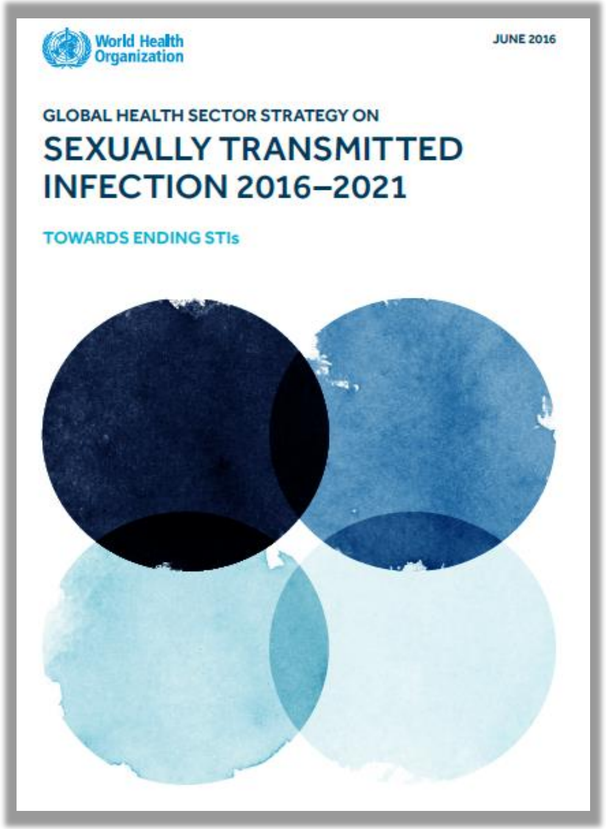
**Vision, Goal and Targets**

**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**



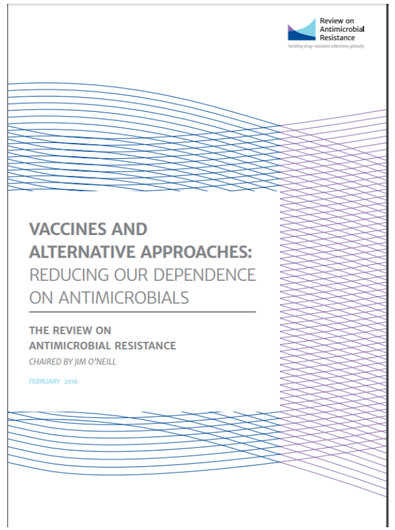

**Reduce gonococcal infection incidence by 90% by 2030**

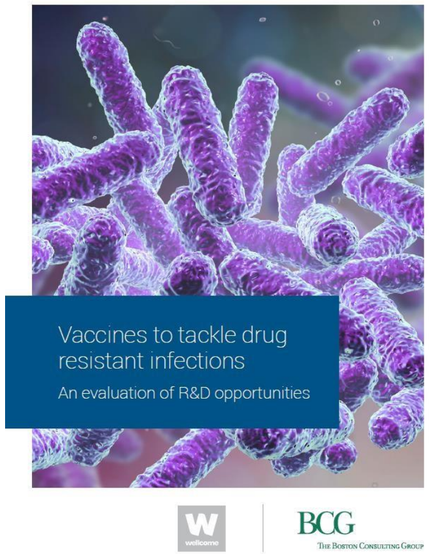
**Vaccine development**

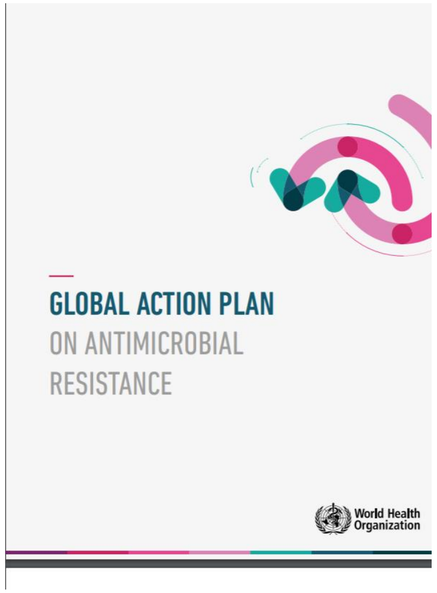
# Global initiatives on AMR and the role of vaccines in fighting AMR



- Several global efforts have recognized the importance of vaccines in fighting AMR
- *Neisseria gonorrhoeae* on WHO's list of "high priority" pathogens for AMR



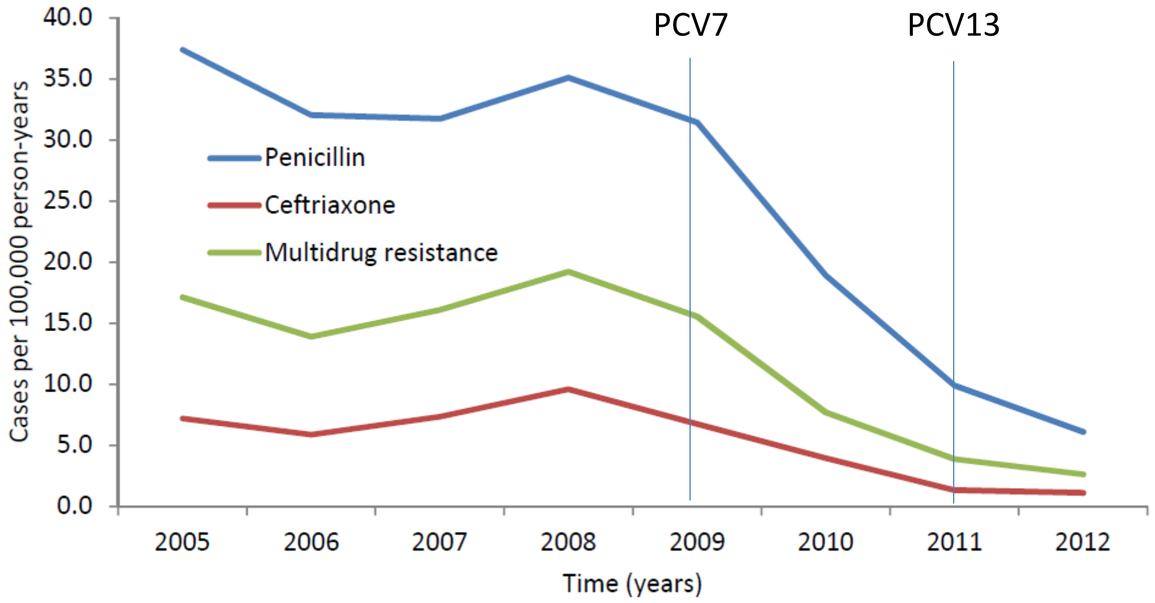




# Vaccines can fight AMR directly and indirectly



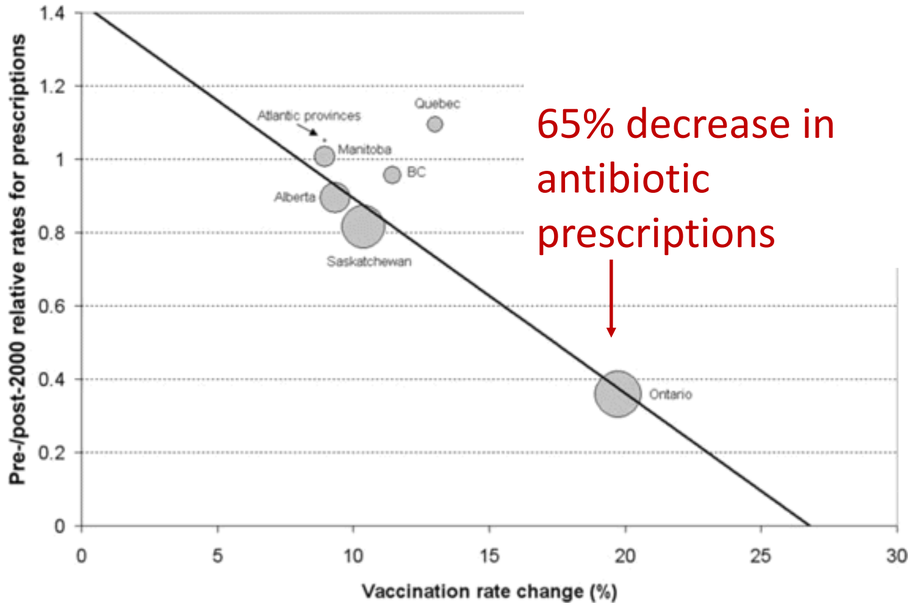
## 1) Decreasing resistant infections directly

Pneumococcal vaccine in South Africa




## 2) Reducing antibiotic use → selective pressure

Influenza vaccine in Canada

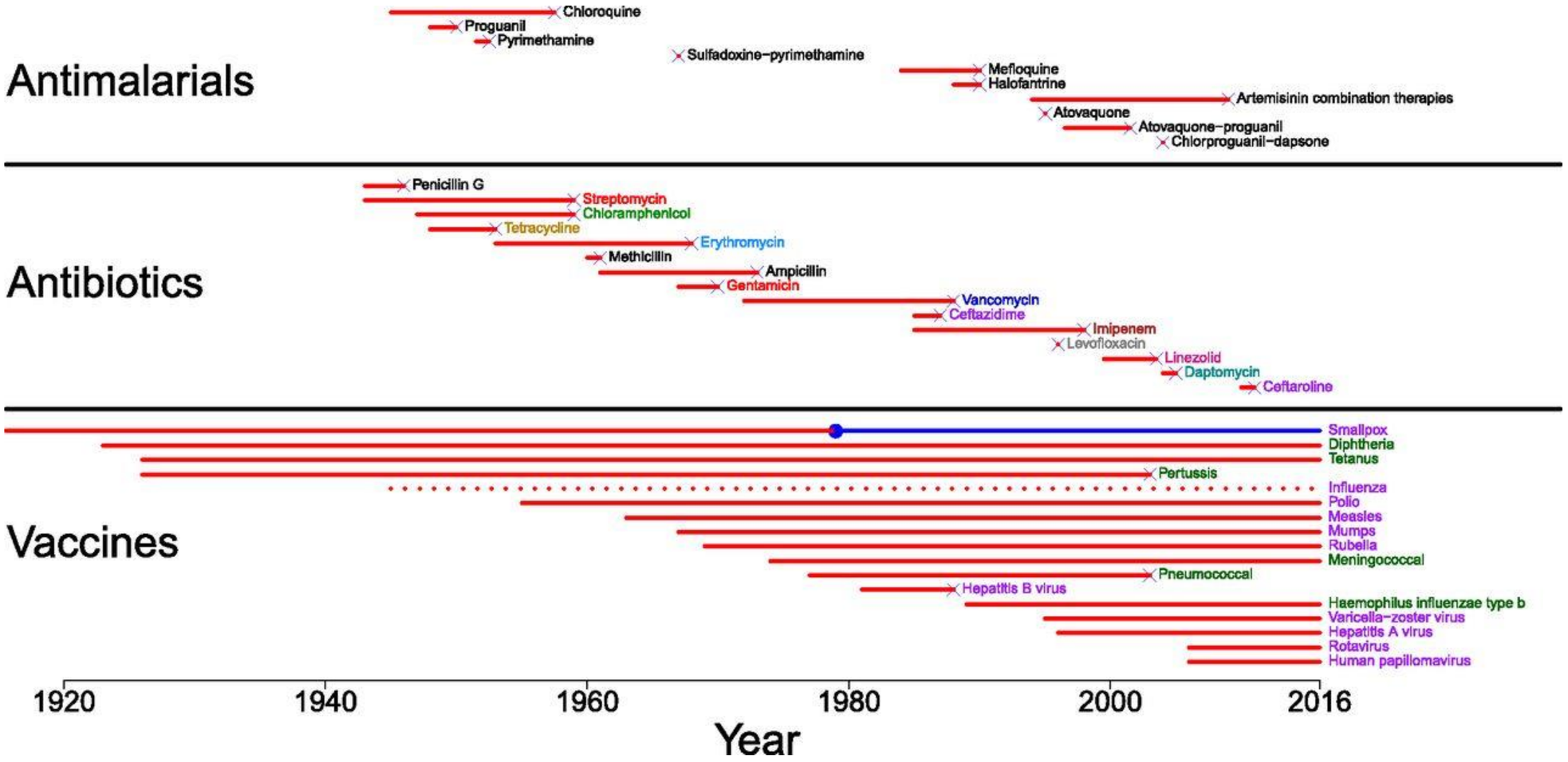



Sources: von Gottberg et al, NEJM 2014; Kwong et al, CID 2009.

# Unlike antimicrobials, vaccines can be used for decades without generating resistance



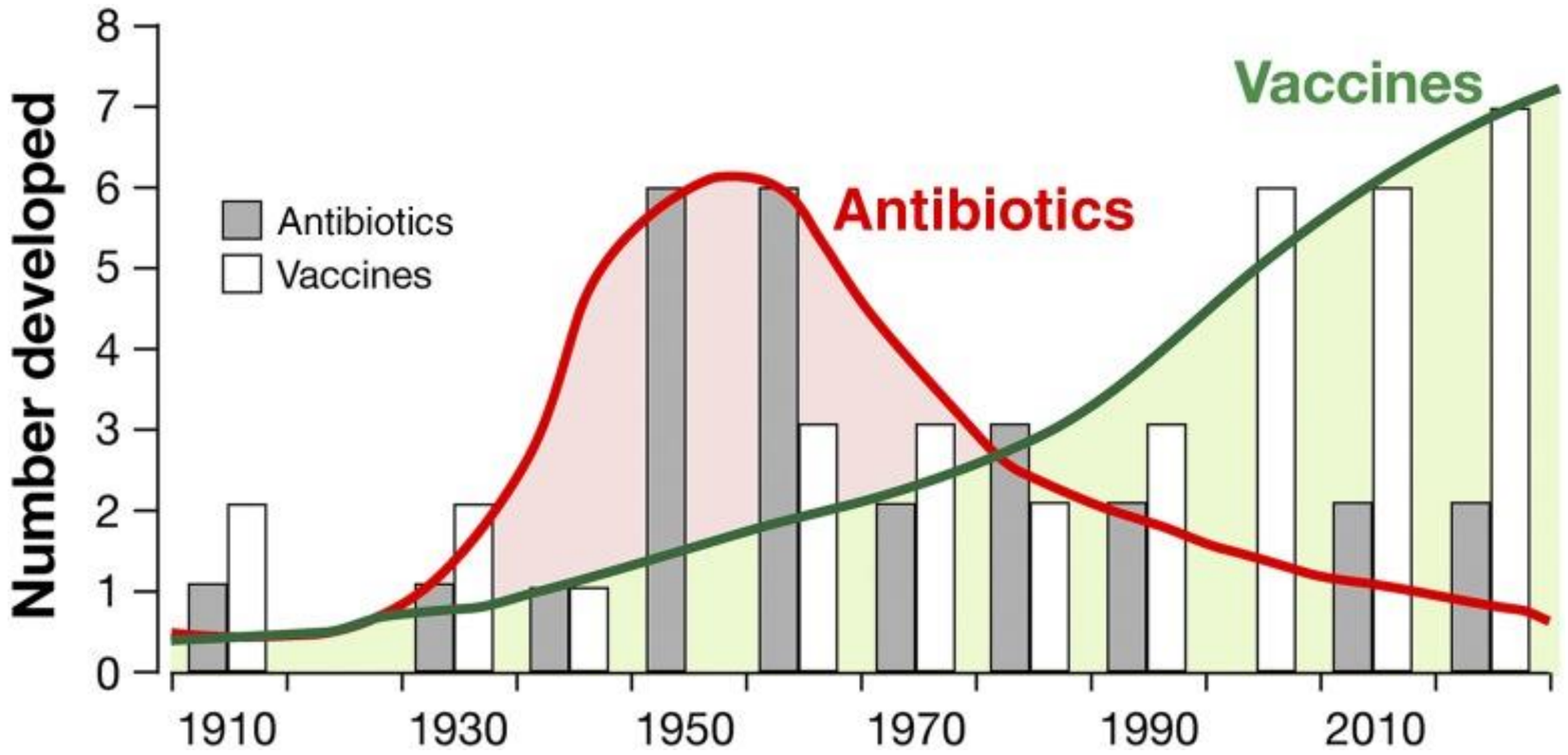
Time between deployment of an intervention and the first documented failure in humans due to resistance (marked with “x”s)




Source: Kennedy and Read, PNAS 2018.

# Technological advances have led to a “golden era” of vaccines

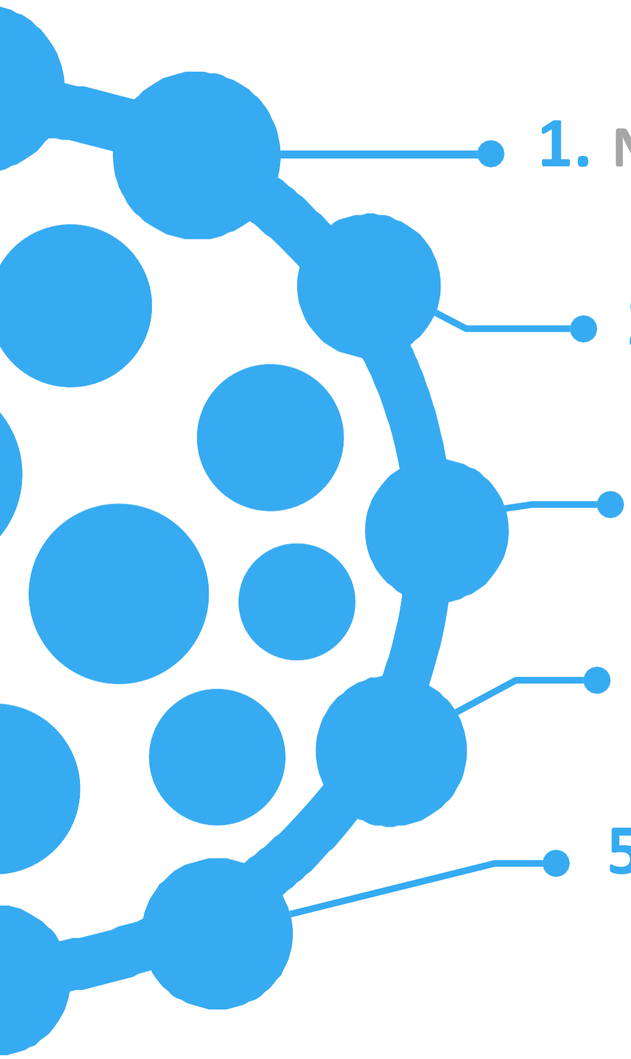





Source: Bloom et al. Antimicrobial resistance and the role of vaccines. PNAS, 2018.

# Outline





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# Historically gonococcal vaccine development has been challenging



- Antigenic variability of *N. gonorrhoeae*
- Repeated infections without inducing immunity
- Early trials of gonococcal vaccines not successful

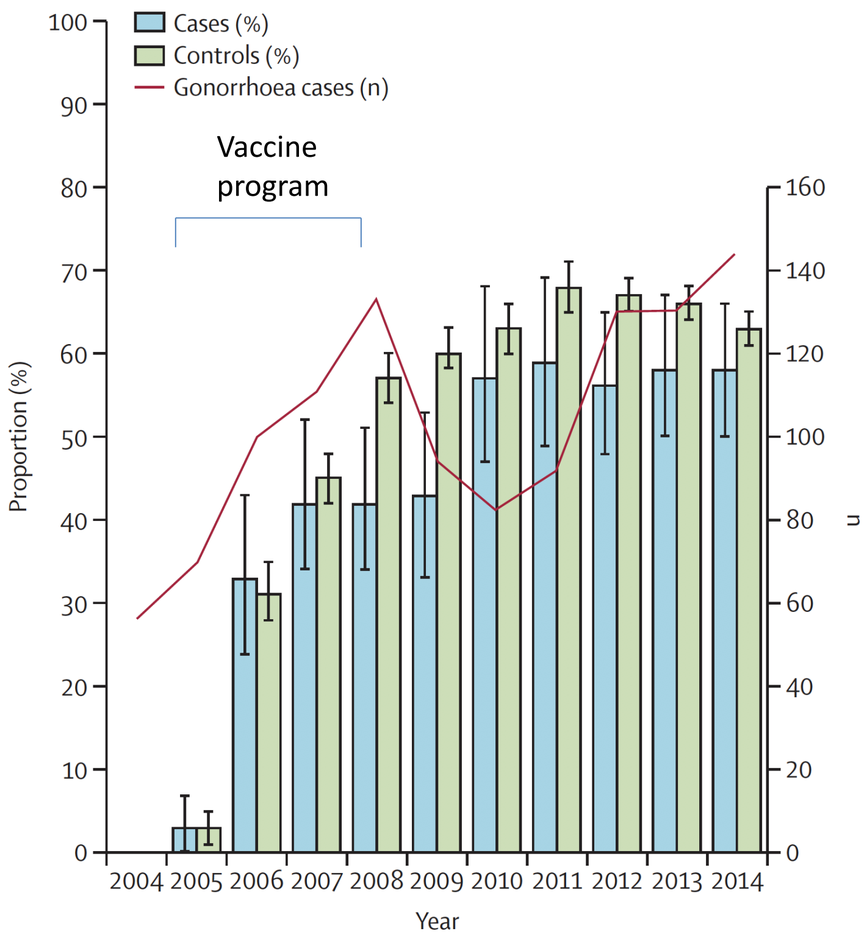

Mounting evidence on group B meningococcal vaccines and gonorrhoea has re-energized the field

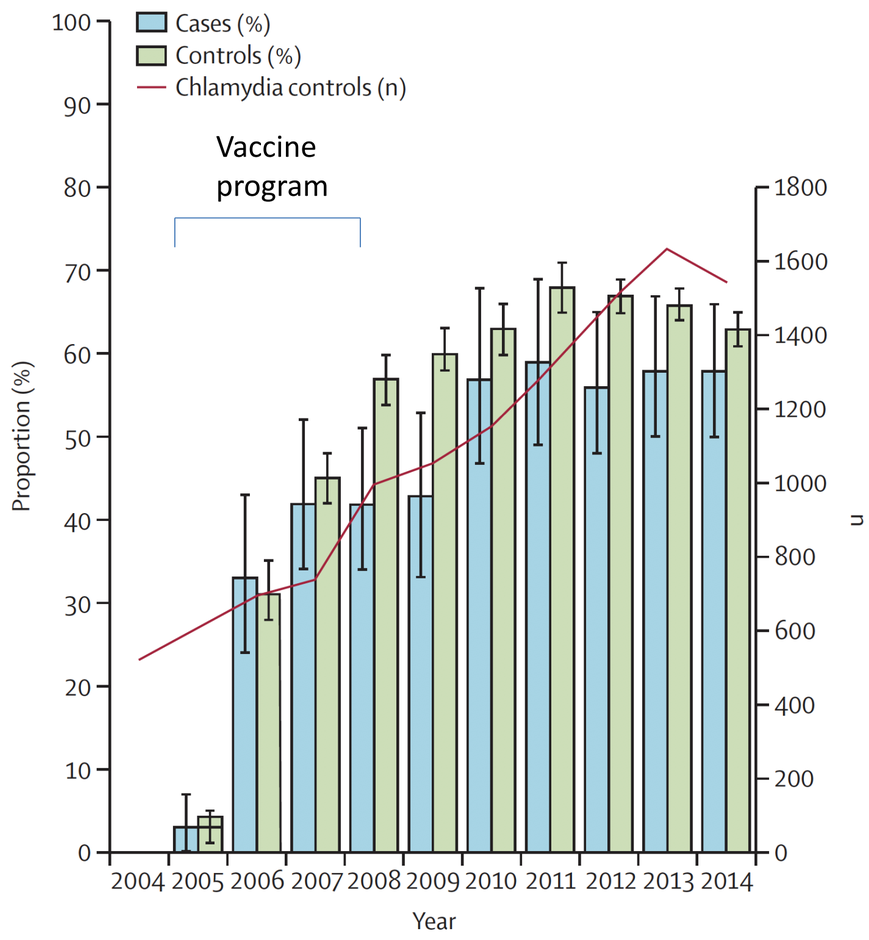
**Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study**

*Helen Petousis-Harris, Janine Paynter, Jane Morgan, Peter Saxton, Barbara McArdle, Felicity Goodyear-Smith, Steven Black*

# *Neisseria meningitidis* group B outer membrane vesicle (OMV) vaccines and gonorrhoea






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

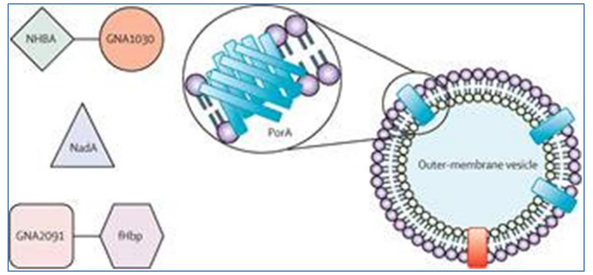
Large case-control study: estimated vaccine effectiveness
31% (21%-39%)

Source: Petousis-Harris et al, Lancet, 2017

# Group B meningococcal OMV vaccines and gonorrhoea – additional data



- Licensed meningitis B vaccine 4CMenB (Bexsero®) contains OMVs plus 3 additional antigens
- Antibodies from people vaccinated with meningococcal B OMV vaccines recognize gonococcal antigens
- Meningococcal B OMV vaccines accelerate clearance of *N. gonorrhoeae* in mouse genital tract infection model






Sources: Semchenko, CID 2018; Connolly, abstract 21st IPNC 2018.

# Current status of the development pathway of vaccines for gonococcal infection



*Ng = N gonorrhoeae*
*Nm = N meningitidis*

Purified protein subunit

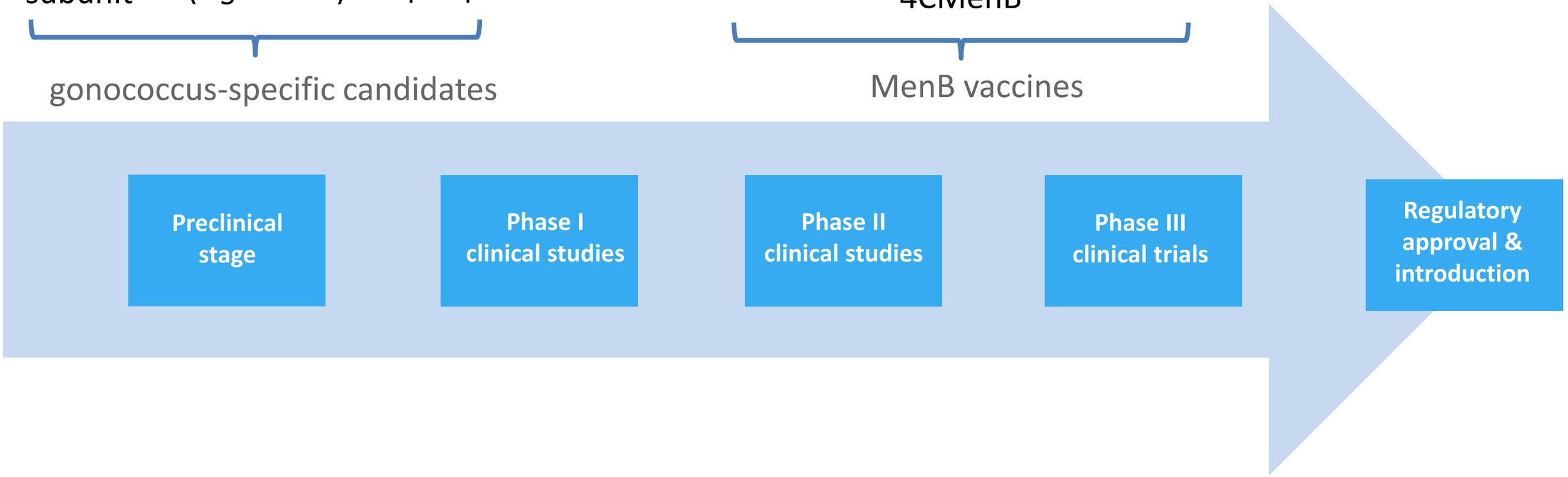
OMV-based (*Ng* or *Nm*)

LOS epitope

gonococcus-specific candidates

*Nm* OMV vaccine*:* 4CMenB

MenB vaccines



# Randomized controlled trials of 4CMenB vaccination to prevent gonococcal infection

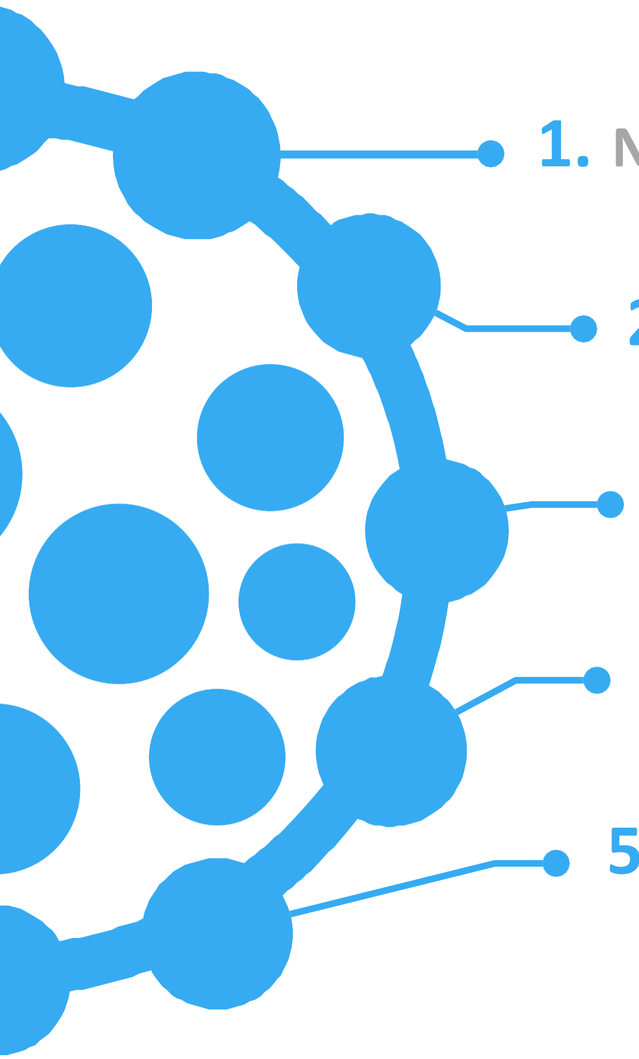


| Country | Phase | Population | n | Primary Outcome | Timing | Sponsor | Identifier |
|---|---|---|---|---|---|---|---|
| Australia | III | MSM | 130 | Time to infection (oropharyngeal, urogenital, anorectal) | Started 2020 | Gold Coast University Hospital | ACTRN12619001478101 |
| Australia | III |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

First results may be available as soon as 2023

# Outline





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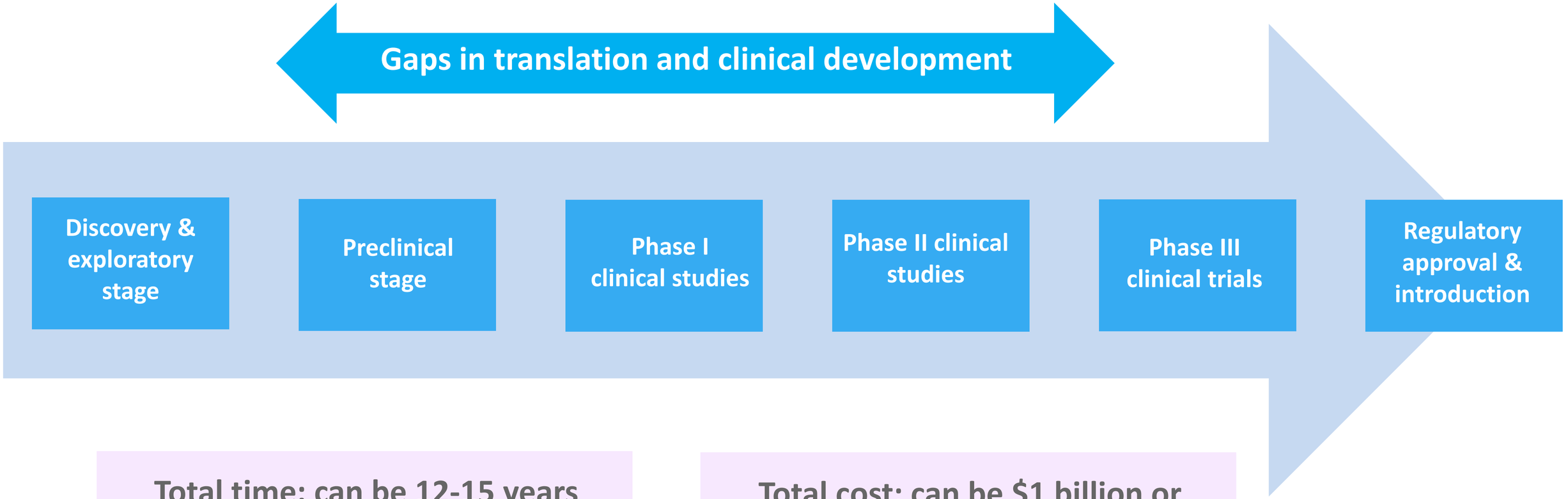
# Pathway of vaccine development to initial licensure



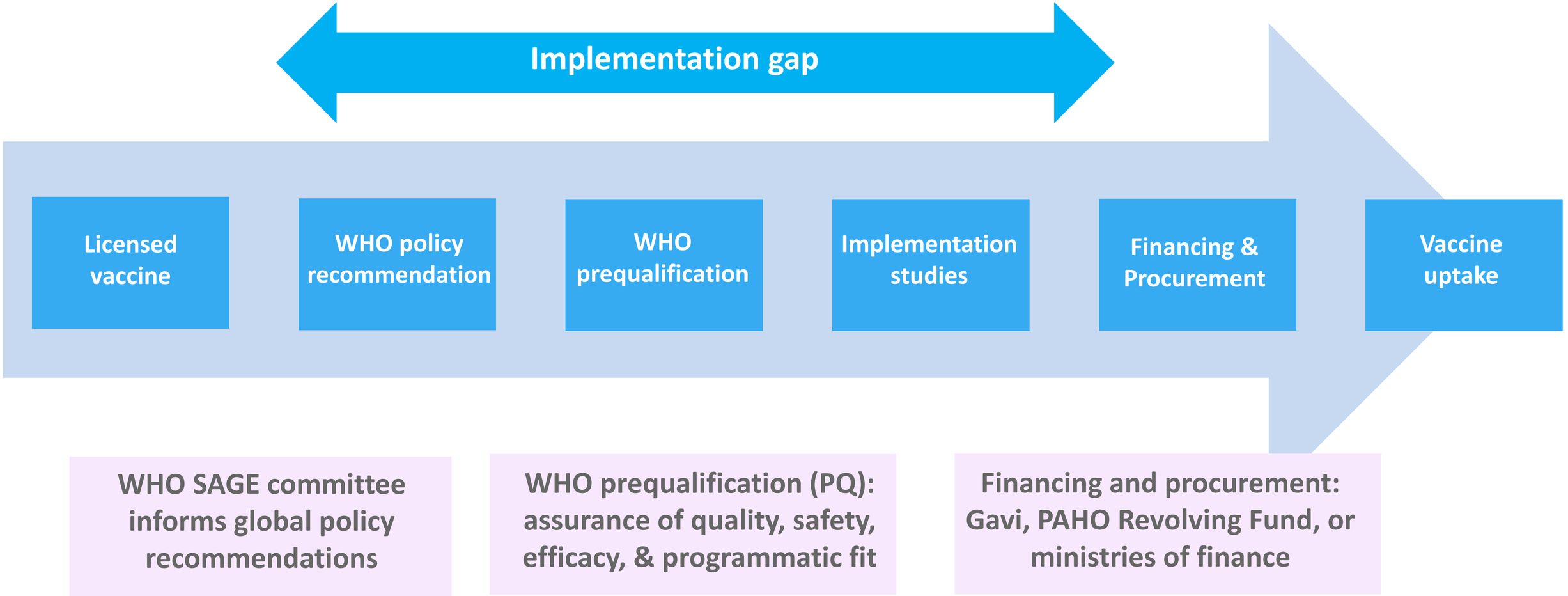



**Total time: can be 12-15 years or more**

**Total cost: can be $1 billion or more per product**

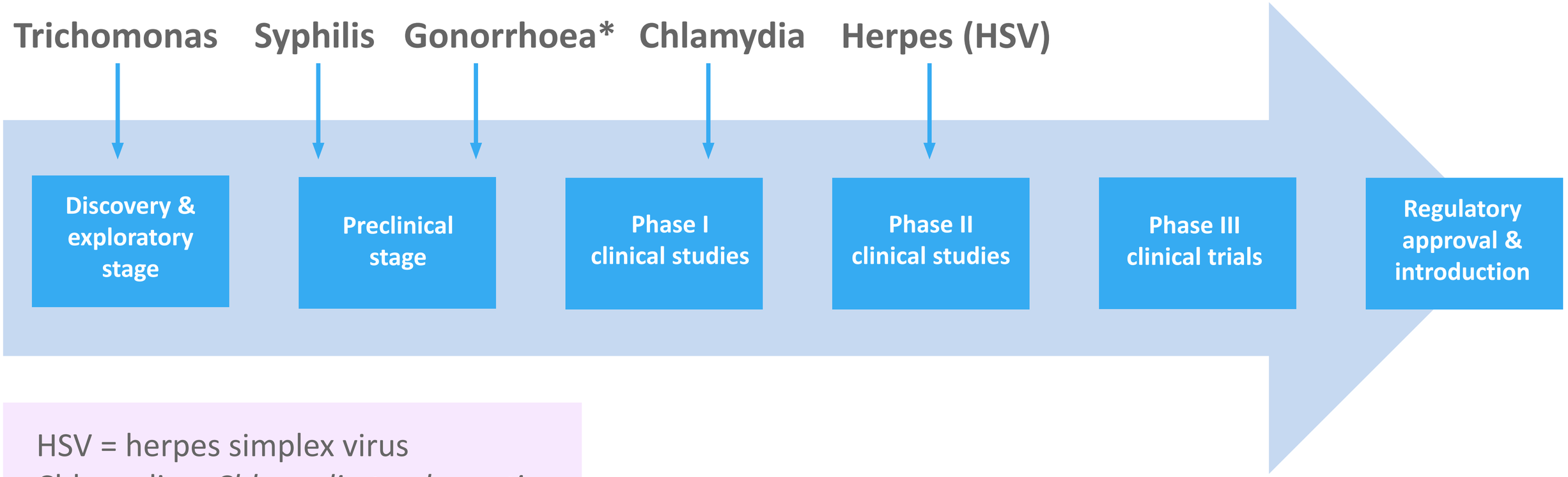
# Additional steps for implementation in low- and middle-income countries (LMICs)





# Current status of the development pathway of STI vaccines





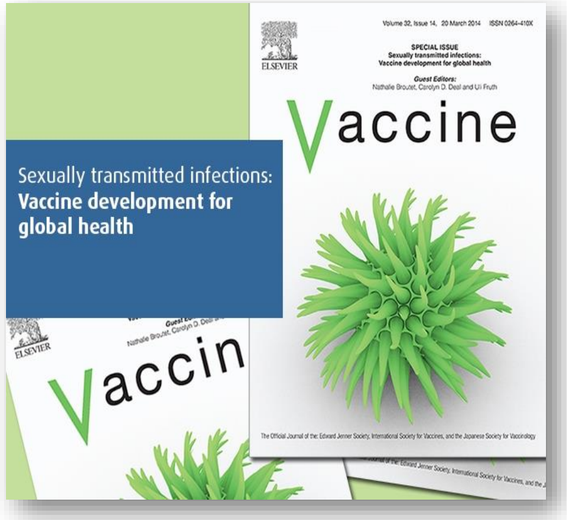

HSV = herpes simplex virus
Chlamydia = *Chlamydia trachomatis*
Gonorrhoea = *Neisseria gonorrhoeae*
Syphilis = *Treponema pallidum*
Trichomonas = *Trichomonas vaginalis*

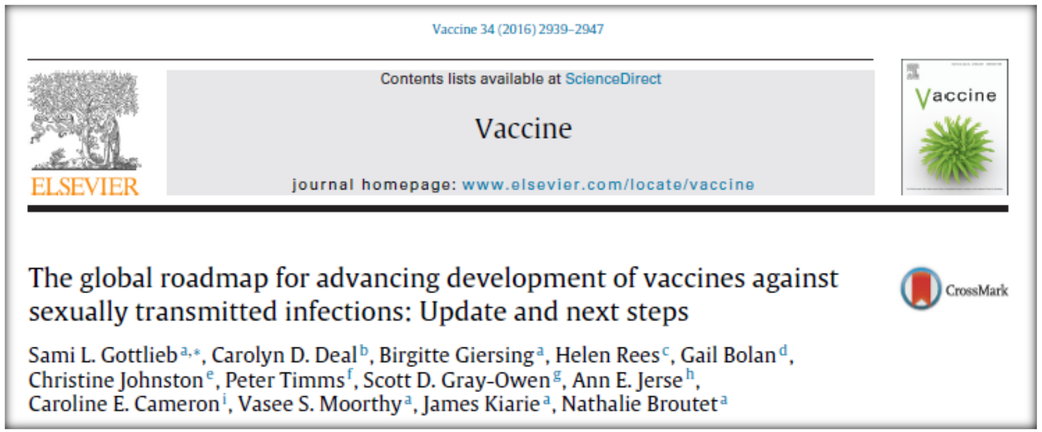
*Licensed *N meningitidis* B vaccine may also have some activity against *N gonorrhoeae*

# Global STI Vaccine Roadmap



- Joint technical consultation by WHO and NIH on STI vaccines
- Global roadmap to advance STI vaccine development
- Important steps: pre-vaccine development → vaccine introduction



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

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The global roadmap for advancing development of vaccines against sexually transmitted infections: Update and next steps

Sami L. Gottlieb[a,*], Carolyn D. Deal[b], Birgitte Giersing[a], Helen Rees[c], Gail Bolan[d], Christine Johnston[e], Peter Timms[f], Scott D. Gray-Owen[g], Ann E. Jerse[h], Caroline E. Cameron[i], Vasee S. Moorthy[a], James Kiarie[a], Nathalie Broutet[a]

# STI vaccine roadmap: key workstreams



## Public health value assessment

- What is the public health need the vaccine would address?
- How valuable would the vaccine be?

## Research and development pathways

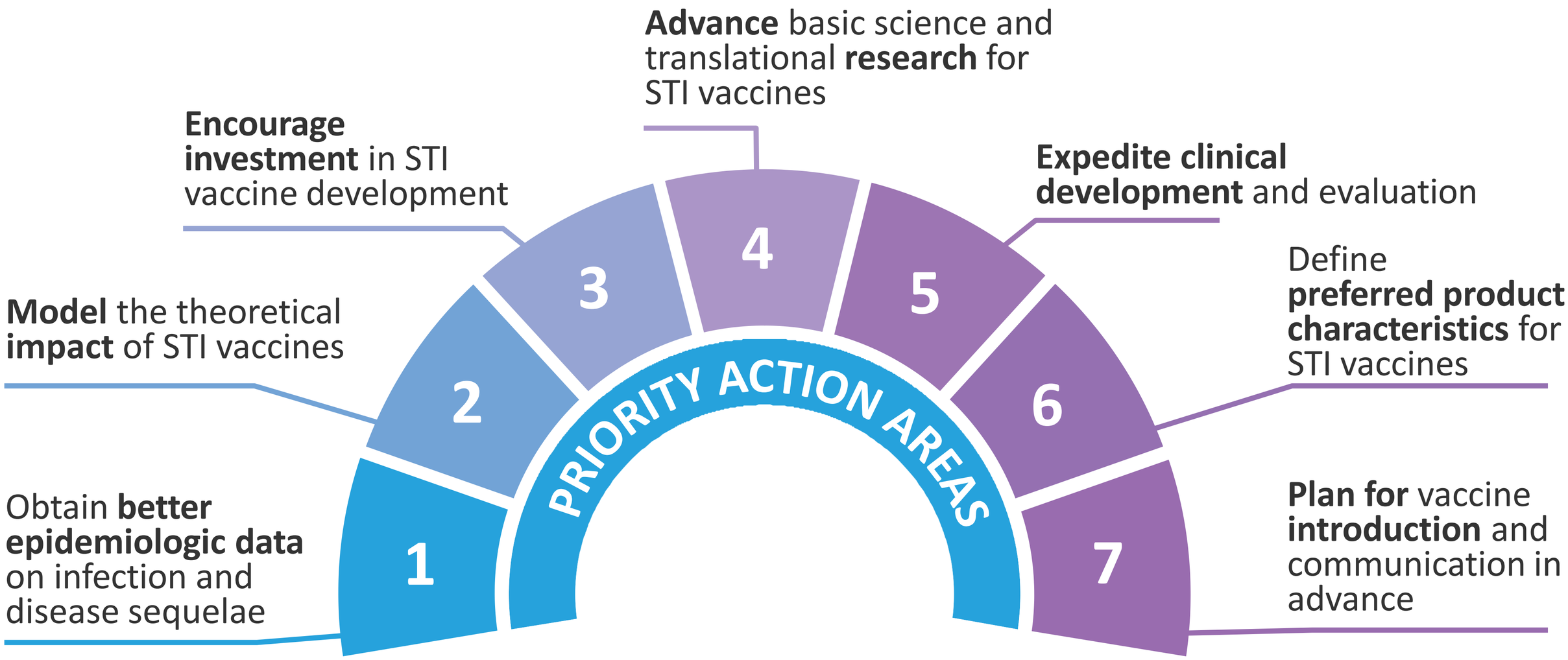
- What will it take to develop an effective vaccine?
- How can we facilitate the research and development?

## Preferred product characteristics

- What should the vaccine look like to maximize its benefits?
- Who will get it and how will it be used?

# STI Vaccine Roadmap: Priority Action Areas





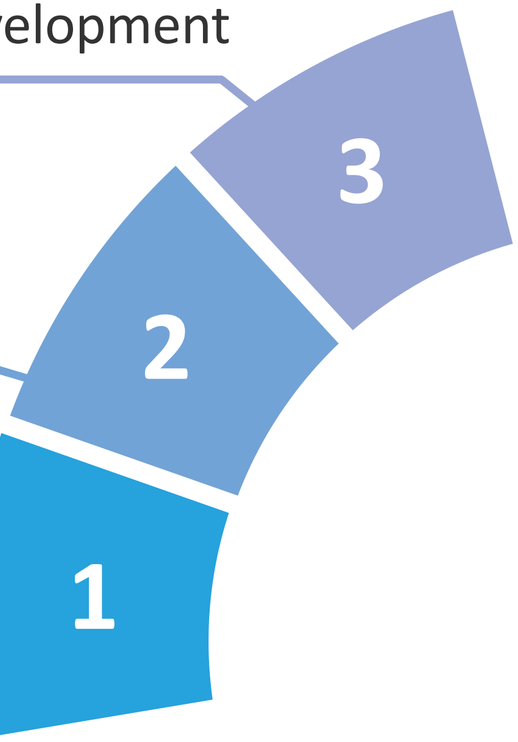
# STI Vaccine Roadmap: Priority Action Areas



**Encourage investment** in STI vaccine development

**Model** the theoretical **impact** of STI vaccines

Obtain **better epidemiologic data** on infection, disease sequelae, costs




## Public health value assessment

- What is the public health need the vaccine would address?
- How valuable would the vaccine be?

# STI Vaccine Roadmap: Priority Action Areas

## Research and development pathways

- What will it take to develop an effective vaccine?
- How can we facilitate the research and development?

**Advance** basic science and translational **research** for STI vaccines

4

5

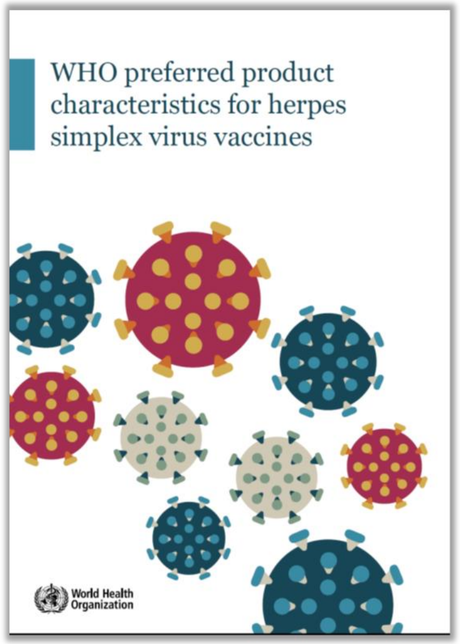
**Expedite clinical development** and evaluation

# STI Vaccine Roadmap: Priority Action Areas



## Preferred product characteristics

- What should the vaccine look like to maximize its benefits?
- Who will get it and how will it be used?

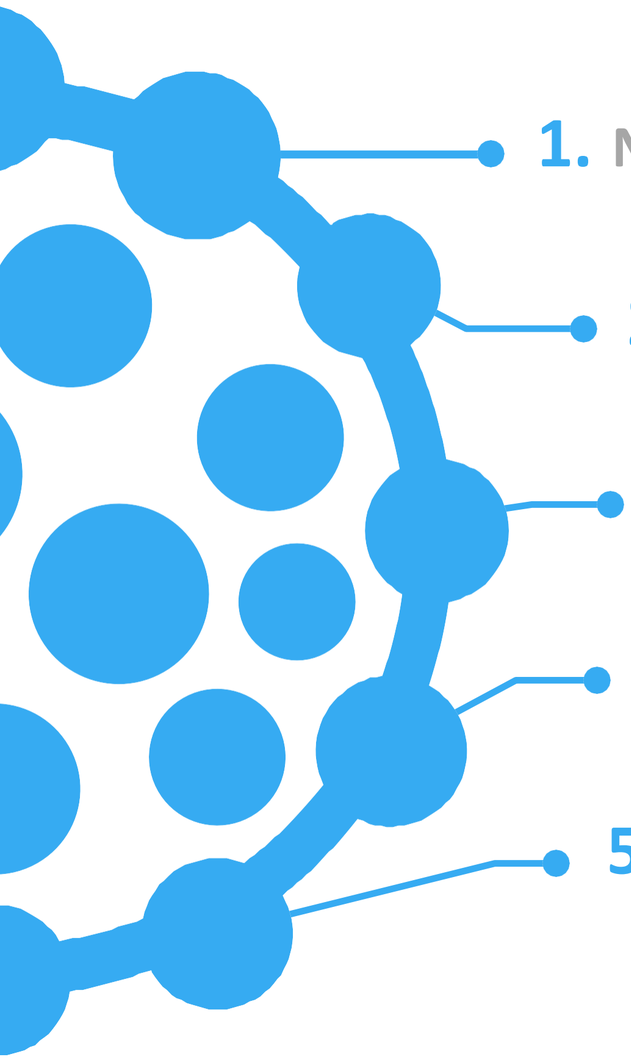



6 Define **preferred product characteristics** for STI vaccines

7 **Plan for** vaccine **introduction** and communication in advance

# Outline





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# Some countries have relatively high gonococcal infection prevalence in general populations



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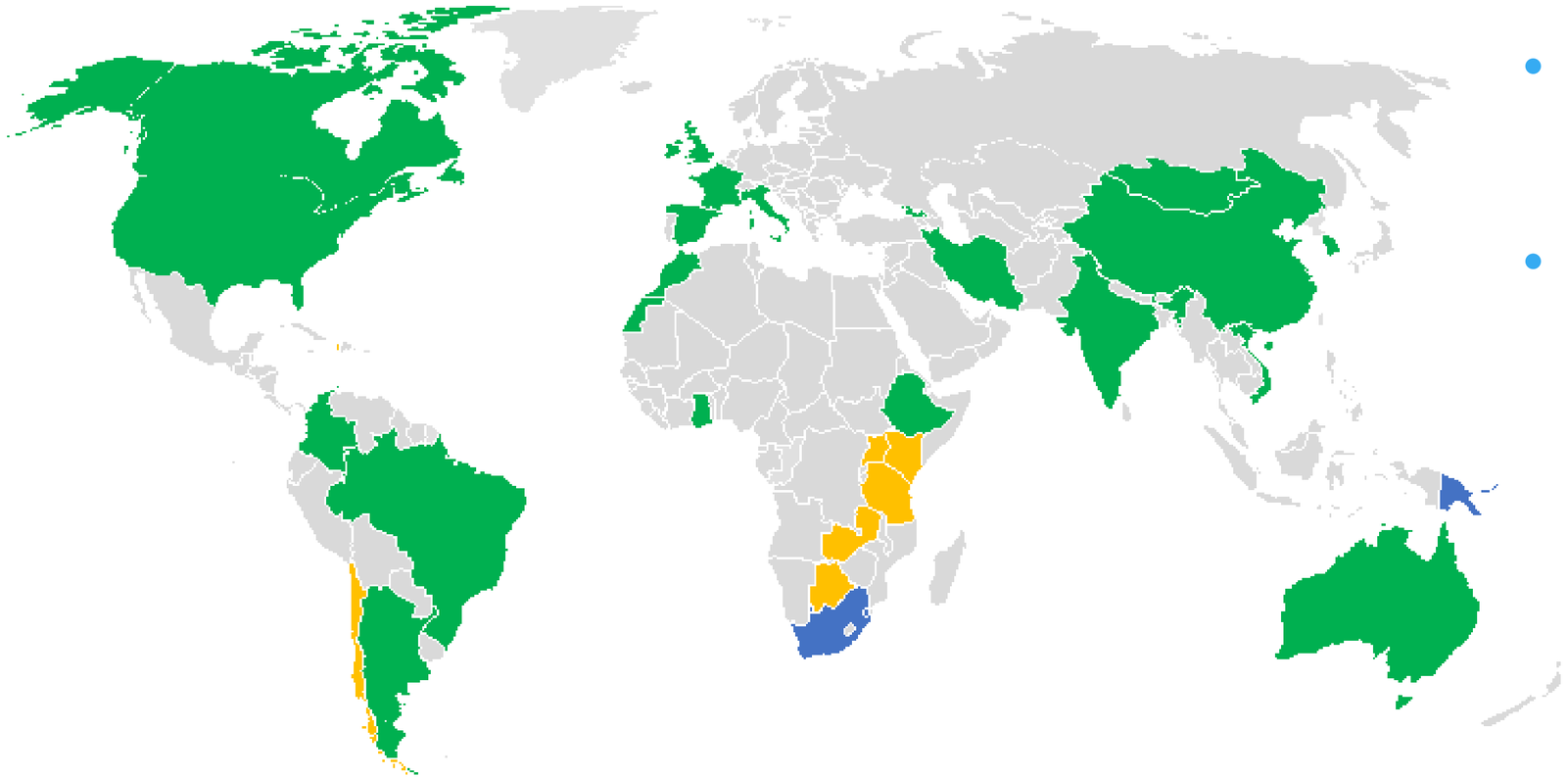


Gonorrhoea prevalence in women age 15-49.

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

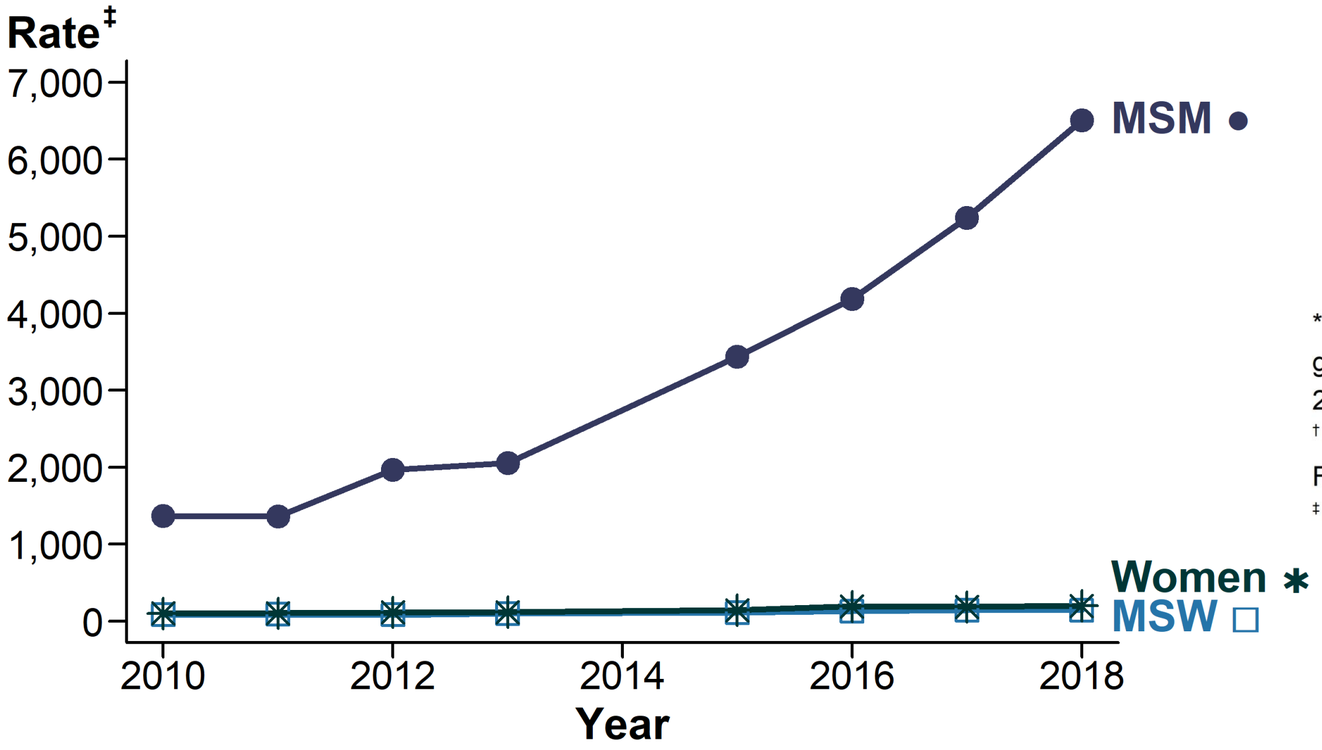
Rowley et al, manuscript in preparation.

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

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



**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

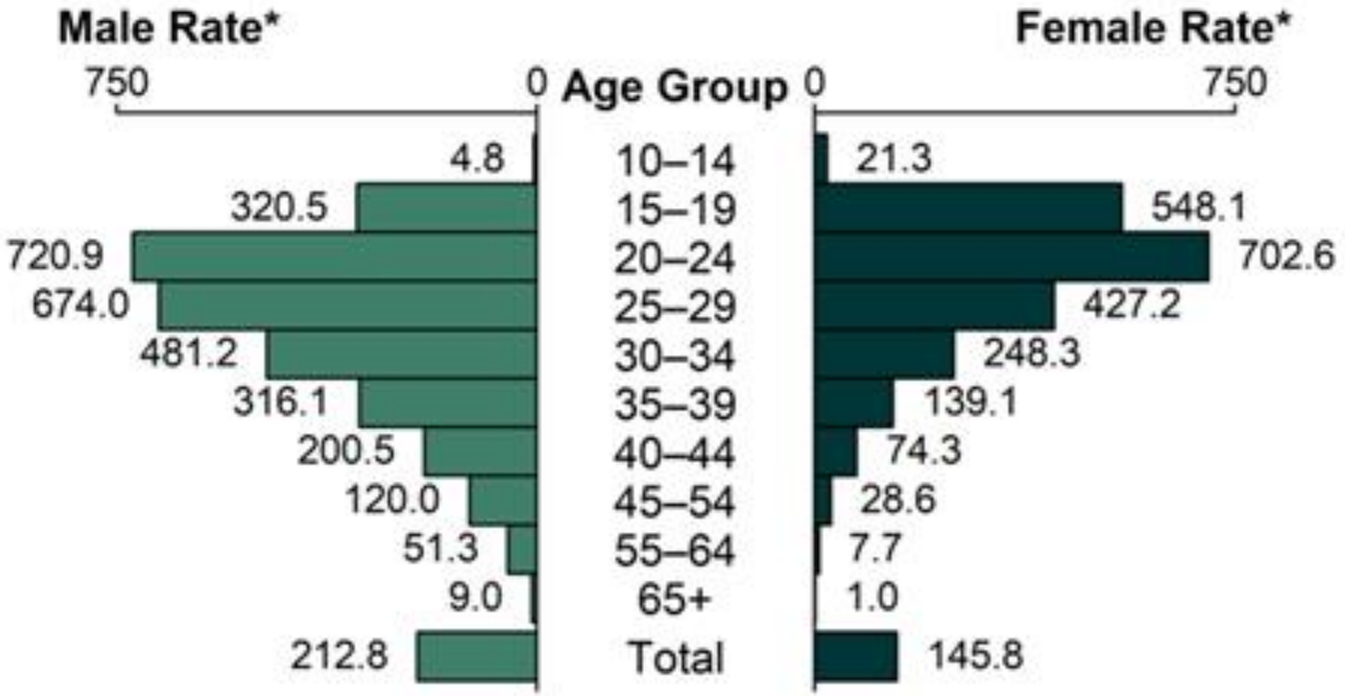
Source: https://www.cdc.gov/std/stats18/default.htm

* 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



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



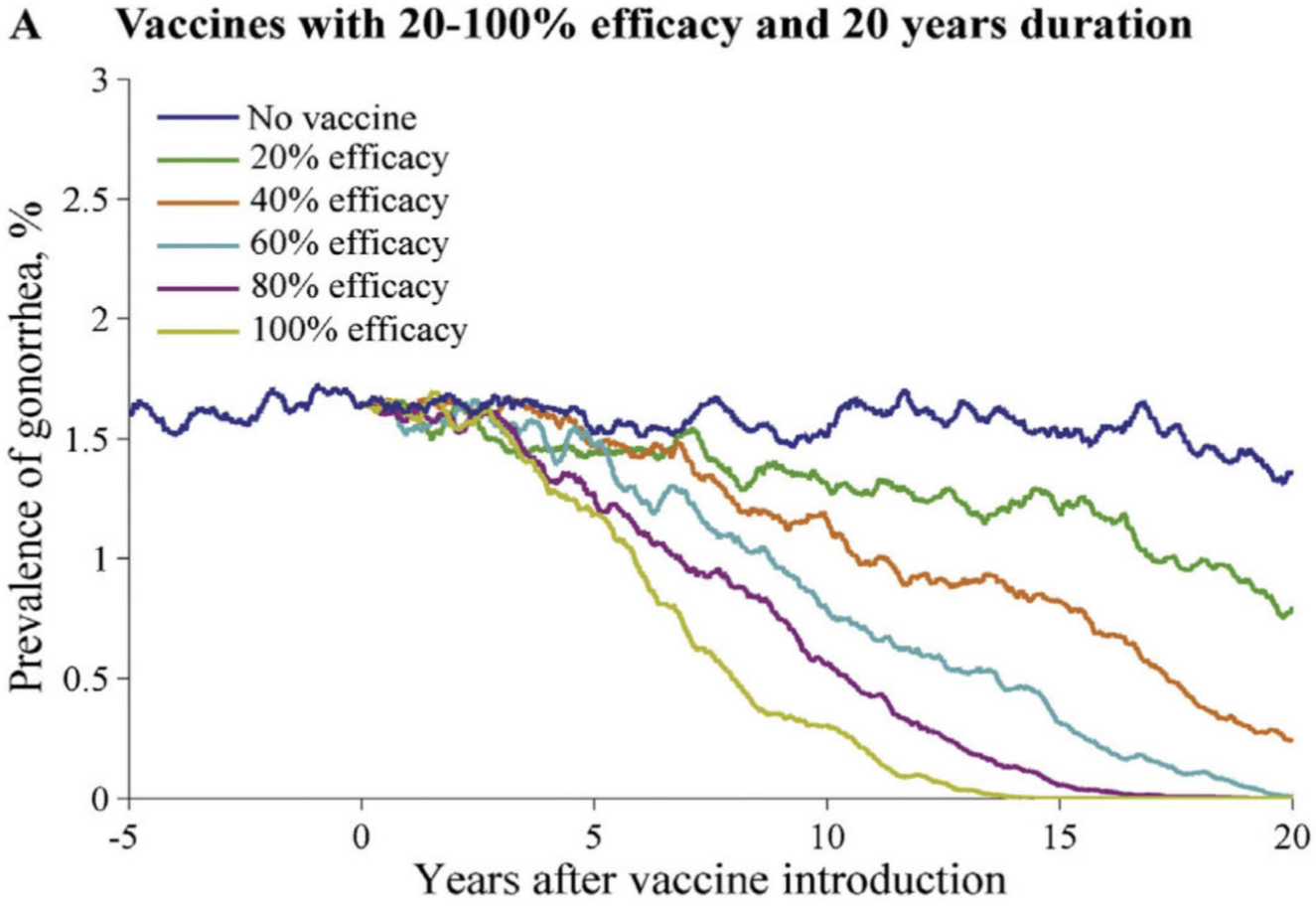

* Per 100,000.

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

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



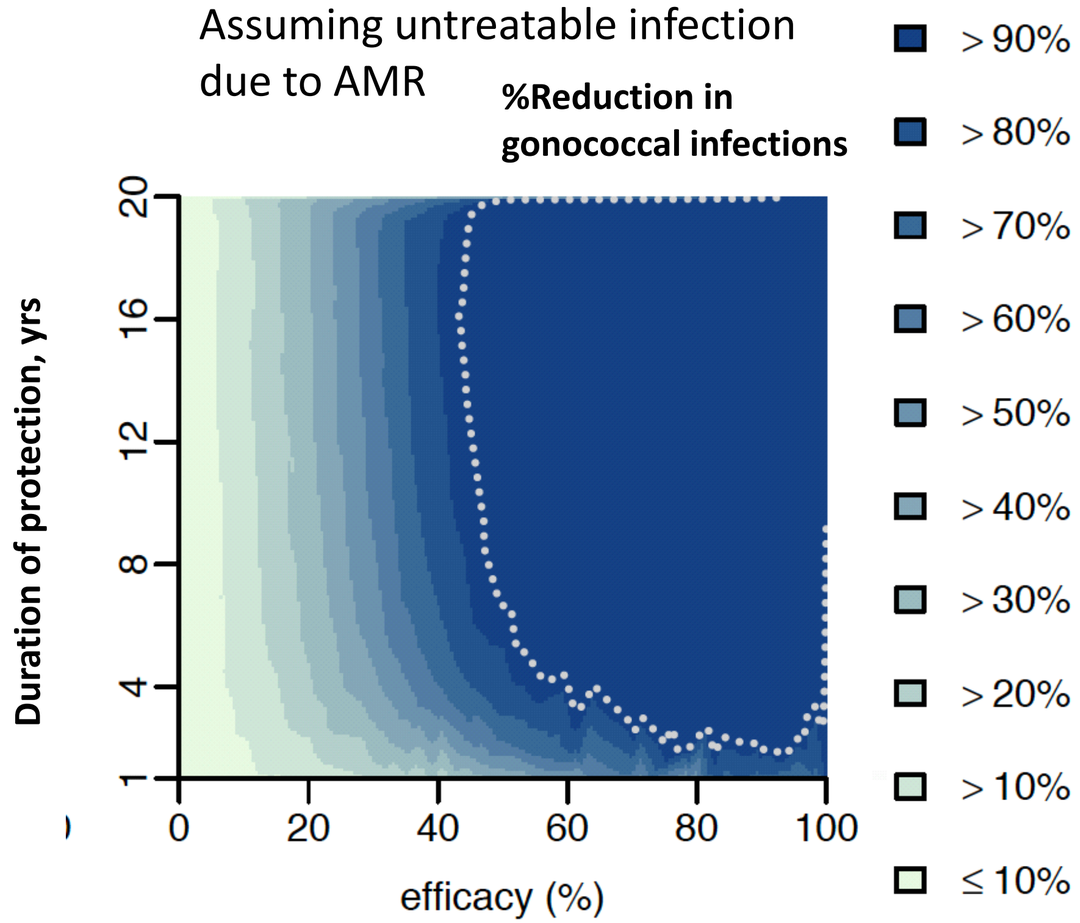



- Even partially effective vaccine could have substantial impact
- Depends on duration of protection: with shorter duration, need higher efficacy

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.

# Preferred target populations for gonococcal vaccines: young people AND/OR populations at higher risk



- Young people = adolescents (ages 10-19 years) and young adults (ages 20-24 years)
- Specific populations at higher risk for gonococcal infection – may vary by setting
- Key rationale for having either or both as options:
  - Varying epidemiologic and programmatic scenarios: best to align with existing vaccine delivery programmes
  - May also depend on vaccine characteristics: duration of protection will not be known at licensure

# Considerations for use of MenB vaccines for gonococcal infections: Overlap in infections



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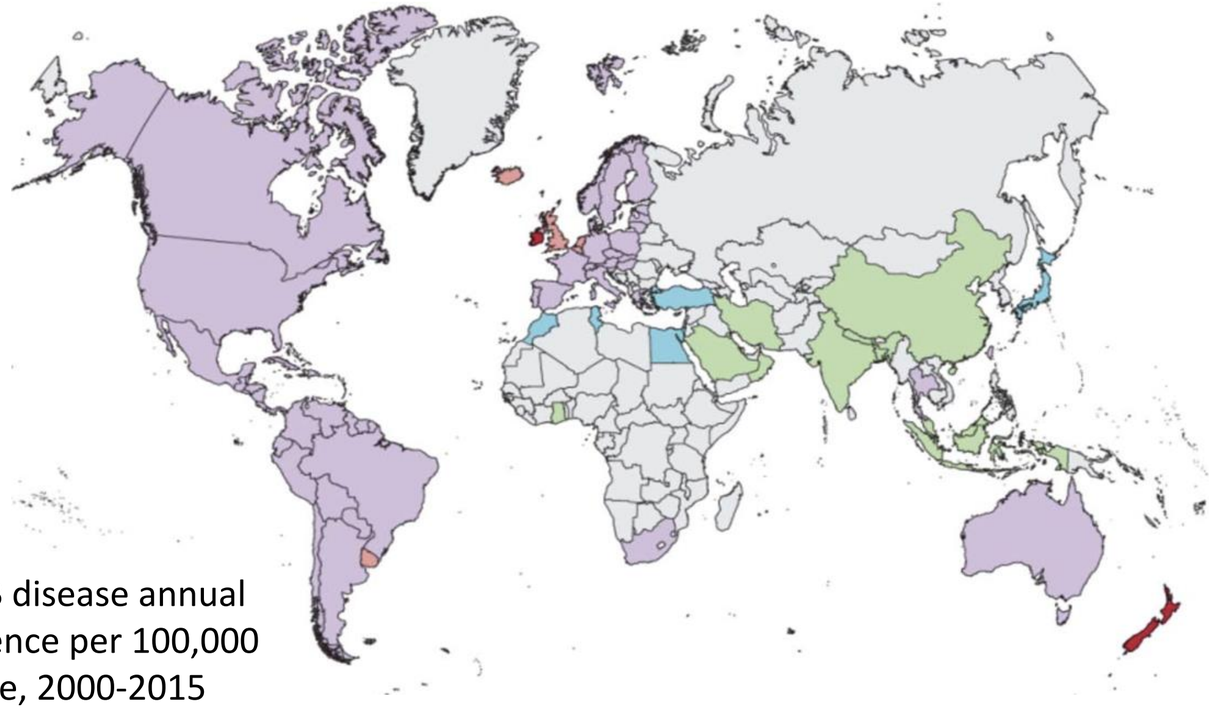
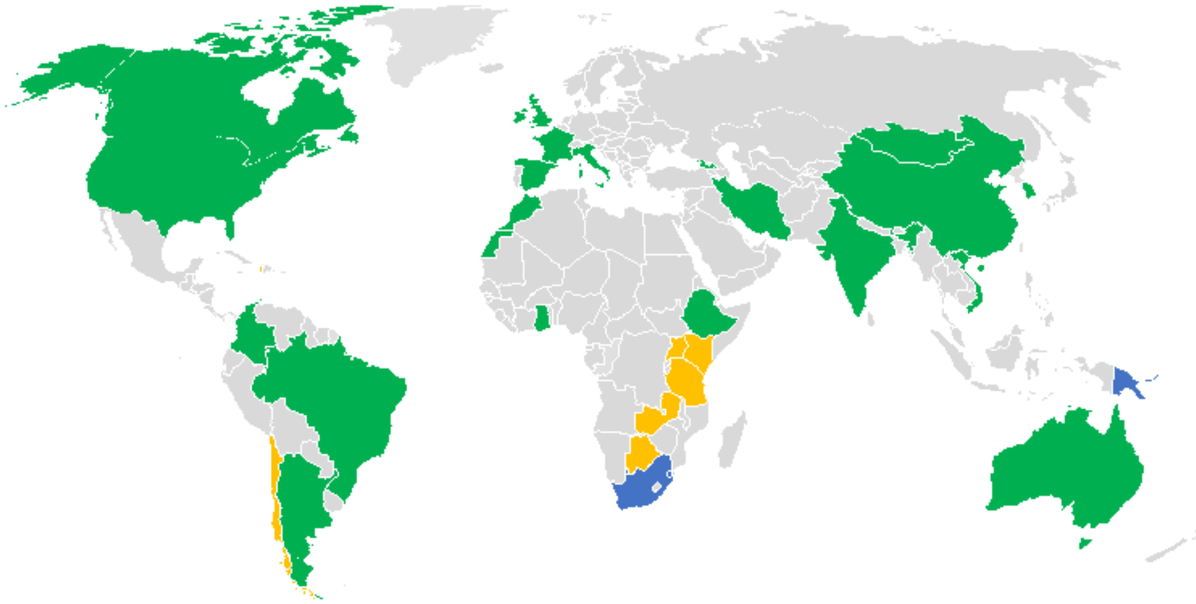


MenB disease annual incidence per 100,000 people, 2000-2015

- >2
- 1·0–2·0
- 0·01–0·99
- Countries where incidence is not reported but serogroup B forms >20% of IMD isolates
- At least one NmB isolated during study period but no incidence data or proportion of IMD isolates due to serogroup B <20%
- No NmB isolated during the study period or no NmB data identified



Gonorrhoea prevalence in women age 15-49.

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

- Variability by location and over time; some unpredictable outbreaks
- Highest incidence in infants, smaller peak in adolescence; occurs at all ages

Source: Sridhar et al, Lancet ID, 2015; Rowley et al, manuscript in preparation.

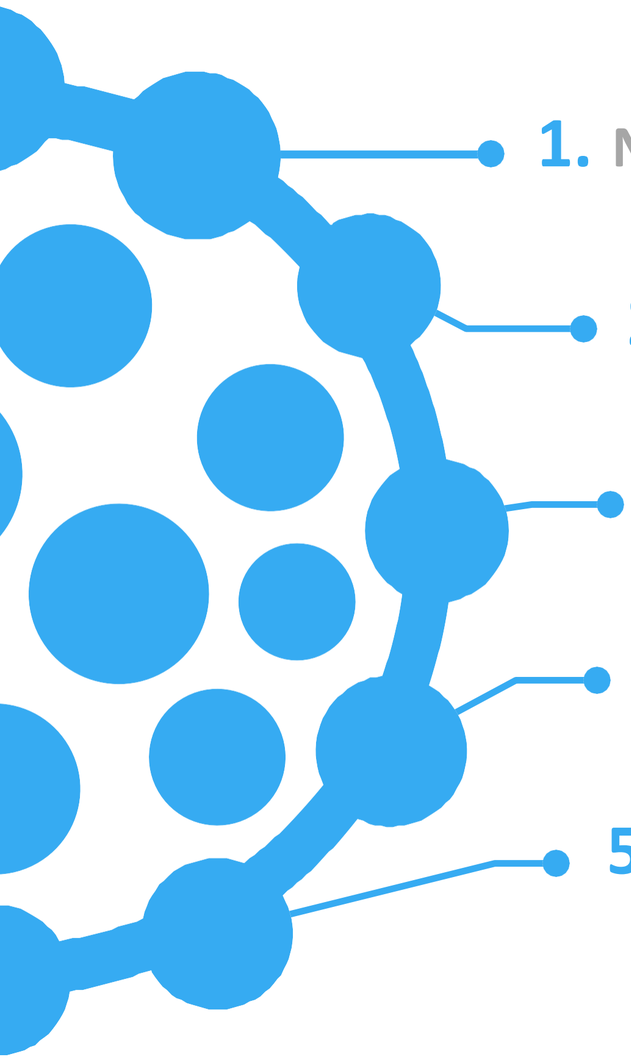
# MenB vaccines and gonorrhoea



- Ongoing trials of MenB vaccines to prevent gonococcal infection will help define path forward for use of these vaccines for both infections
- Delineating public health value essential
  - Collecting better data on both conditions
  - Understanding community wishes and needs early on
- Advancing gonococcal vaccine development crucial as part of package of efforts to fight AMR

# Outline



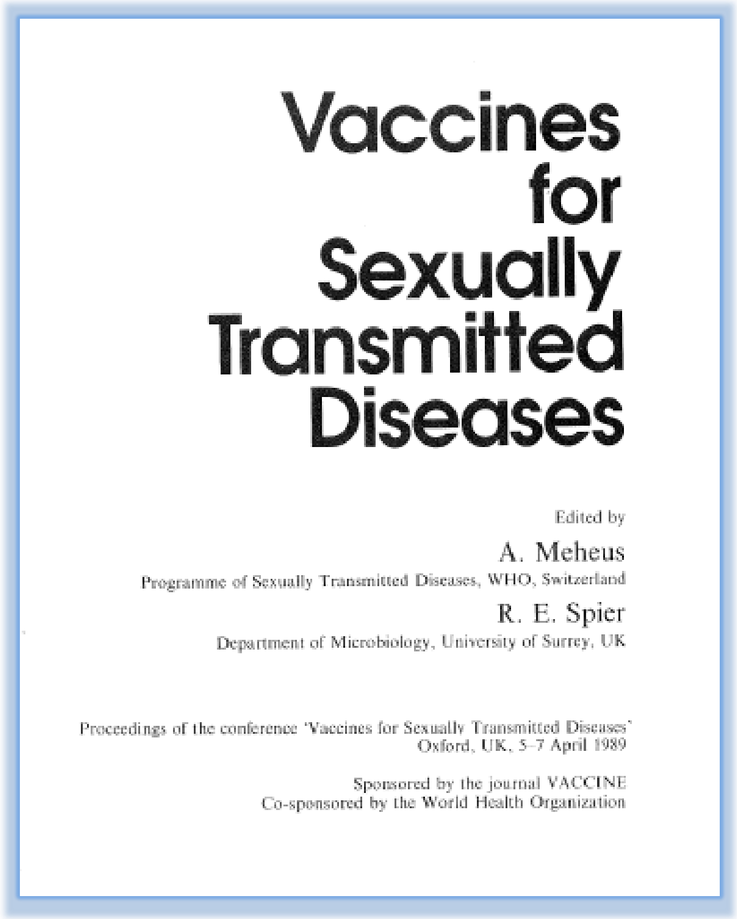


1. Need for vaccines against gonococcal infection
2. Can gonococcal vaccines be developed?
3. Global Roadmap to Advance STI Vaccine Development
4. Epidemiology and the use case for gonococcal vaccines
5. **Looking to the future**

# First WHO meeting on STI vaccines: 1989



- Predicted development of HPV vaccine unlikely, with too many barriers, and perhaps should not be pursued



Vaccines for Sexually Transmitted Diseases

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Proceedings of the conference 'Vaccines for Sexually Transmitted Diseases' Oxford, UK, 5–7 April 1989

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## Concluding remarks, HPV vaccine (D. McCance)

There are nevertheless a number of questions which need to be answered before we embark on a vaccine production campaign.

Firstly, should we produce such a vaccine;

I think not.

Secondly, how could we test the vaccine bearing in mind that once a subject has been vaccinated at say 11-16 years old the success of the vaccine would not have been evident until some 20-30 years later; a period which a commercial manufacturer would find intolerable?

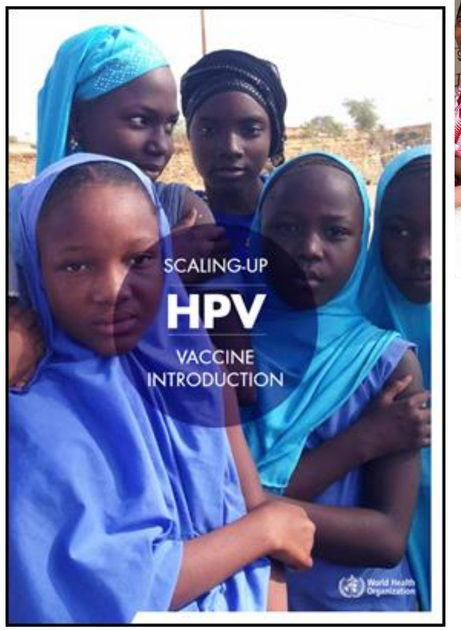
Thirdly, will people actively wish to be vaccinated? Imagine you are a parent with a 12 year old child, would you take this child to the clinic and ask for him/her to be vaccinated against a disease which, according to the press, can only be acquired through promiscuous sexual activity?

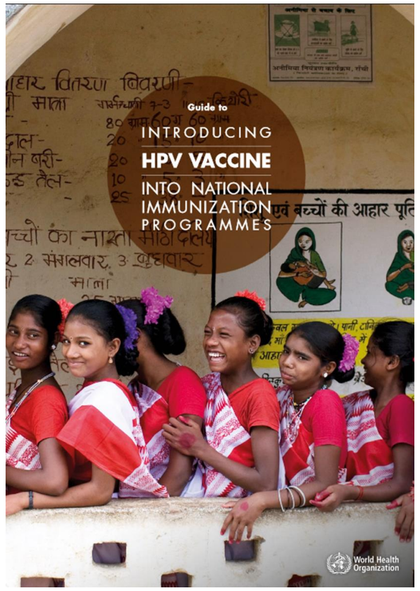
I am not sure, therefore, that even if a safe and effective vaccine were available, people would wish to avail themselves of its utility.

# Less than 20 years later…



- HPV vaccines were licensed: safe and highly efficacious
  - 2-valent (HPV 16, 18)
  - 4-valent (HPV 6, 11, 16, 18)
  - 9-valent (HPV 6, 11, 16, 18, 31, 33, 45, 52, 58)
- WHO global recommendations for girls age 9-14 years
  - Several countries also recommend HPV vaccine for boys

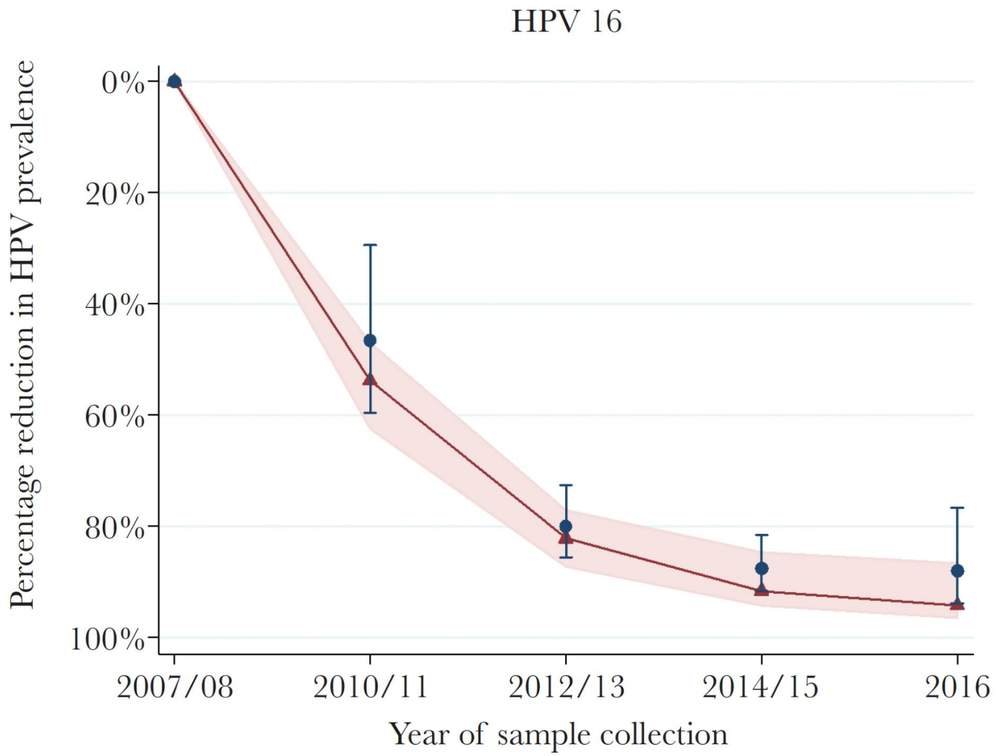


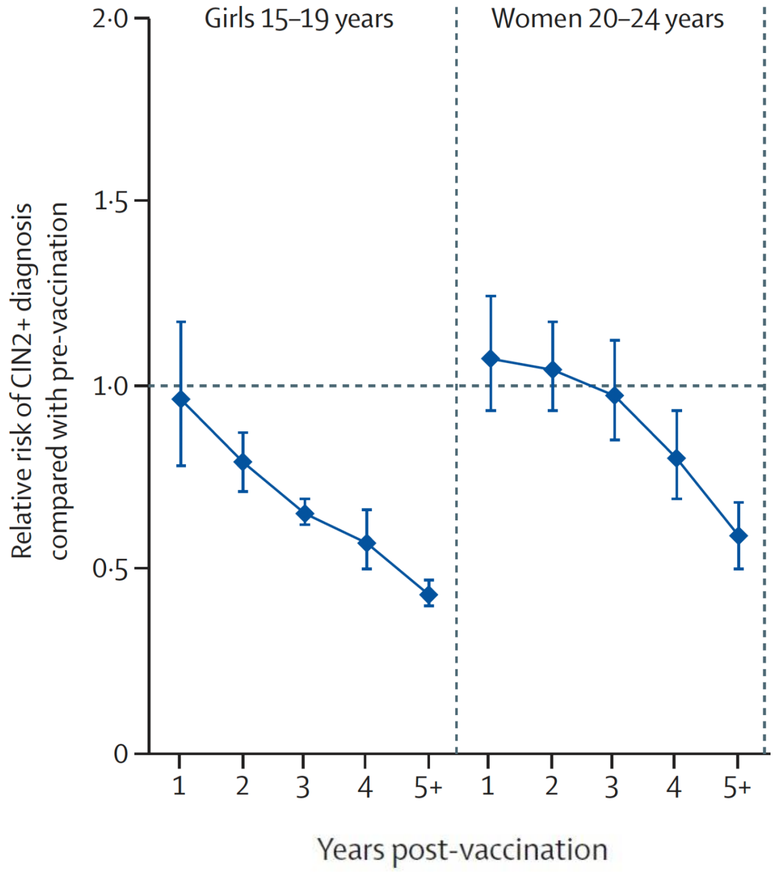
# Dramatic declines in HPV, genital warts, and cervical pre-cancers



**Change in HPV 16 prevalence among 16-18 year-olds from 2007/08 (pre-vaccination) during the first 8 years after HPV vaccine introduction in England**




**Change in CIN2+ among screened women, first 7 yrs after HPV vaccine introduction: Australia, Canada, Denmark, Scotland, USA**




Sources: Mesher et al, JID 2018; Drolet et al, Lancet 2019

# May 2018: WHO Director General's Call to Action to Eliminate Cervical Cancer



# Advancing the global STI vaccine roadmap



- STI epidemiologic, biologic, clinical, economic, and modelling data can all inform key STI vaccine roadmap activities
- Early engagement can allow us to build a path toward STI vaccines while improving and scaling up existing interventions
- Challenges but also opportunities to advance STI vaccine development

# Thank you!



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**https://www.who.int/teams/sexual-and-reproductive-health-and-research**