Gonorrhea: key immunological considerations for vaccine development & potential cross protection with 4CMenB

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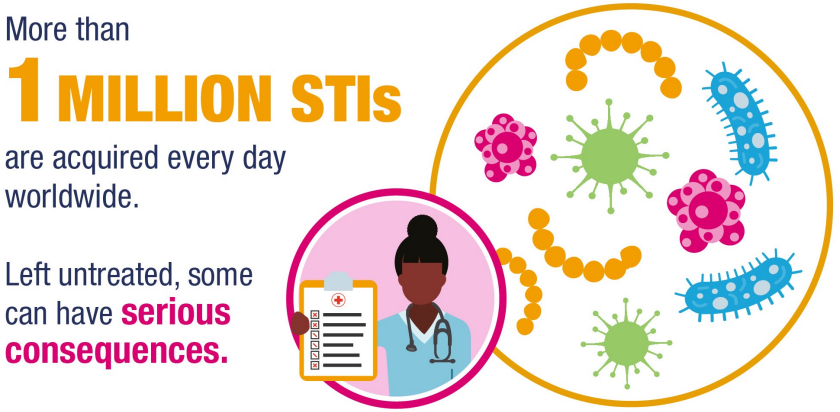
Key issues that highlight the need for a gonorrhoea vaccine

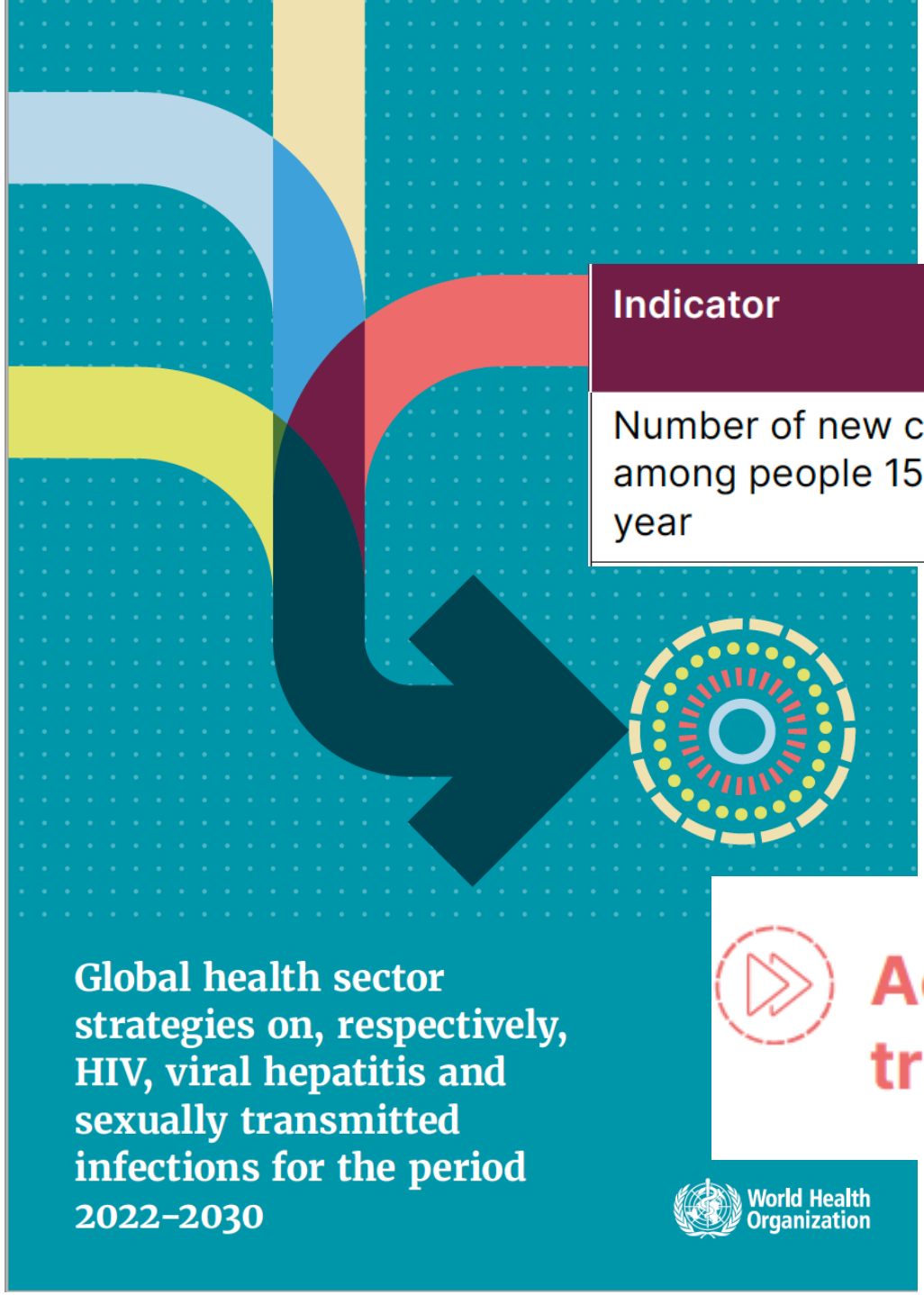
- **> 82 million** cases per year
- Majority of infections have **no/mild symptoms**
- Infection can have **significant, long term health consequences**
- No natural immunity after infection and **reinfection is common**
- May become untreatable due to **antibiotic resistance**
- Prevention by **vaccination is essential** for long term control of gonorrhoea



https://www.who.int/news-room/fact-sheets/detail/sexually-transmitted-infections-(stis)

Key Target

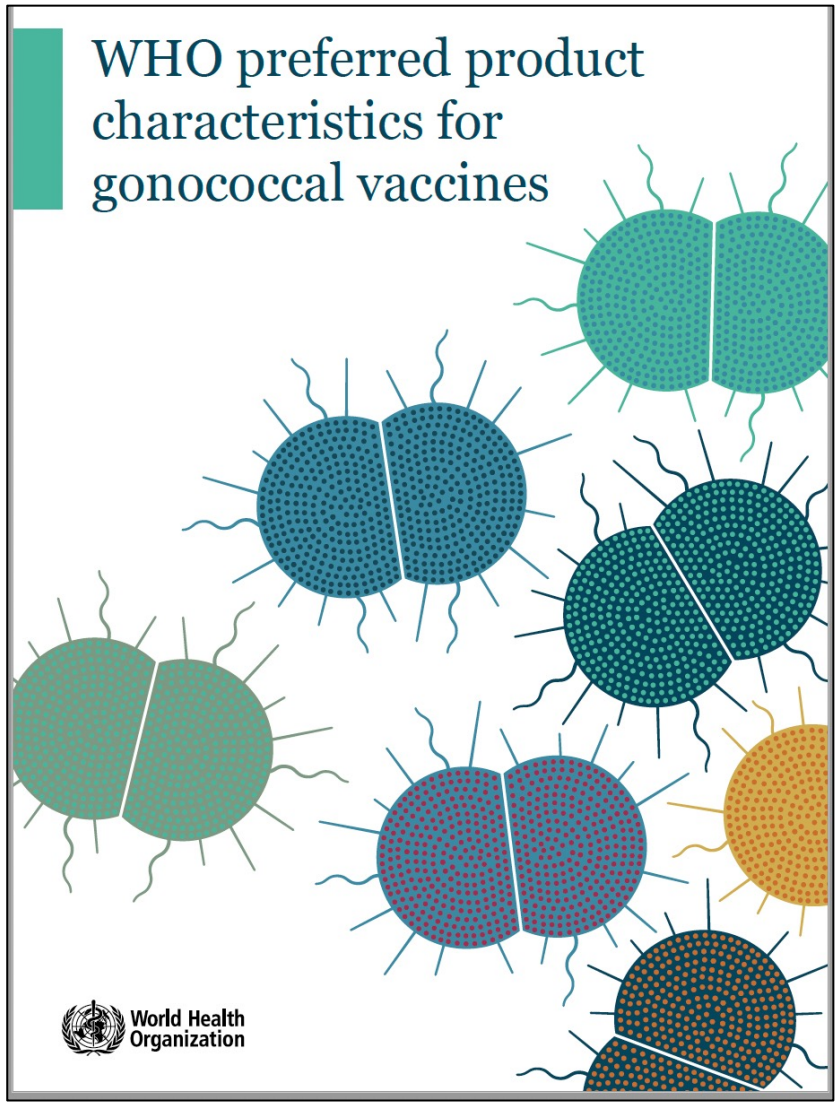
Indicator	Baseline – 2020[a]	Targets - 2025	Targets - 2030
Number of new cases of gonorrhea among people 15–49 years old per year	82.3 million	65.8 million	8.23 million



90% reduction in the number of new cases of gonorrhoea by 2030

Action 103: New vaccines for sexually transmitted infections.

Activities to facilitate vaccine development



- **Preferred product characteristics (PPC)**
  - Promote development of vaccines with optimal effectiveness and suitability, particularly in LMIC
  - Maximise global impact

- **Vaccine value profile (VVP)**
  - Provide a high-level assessment of current data to inform the potential public health, economic and societal value of a vaccine

https://www.who.int/publications/i/item/9789240039827

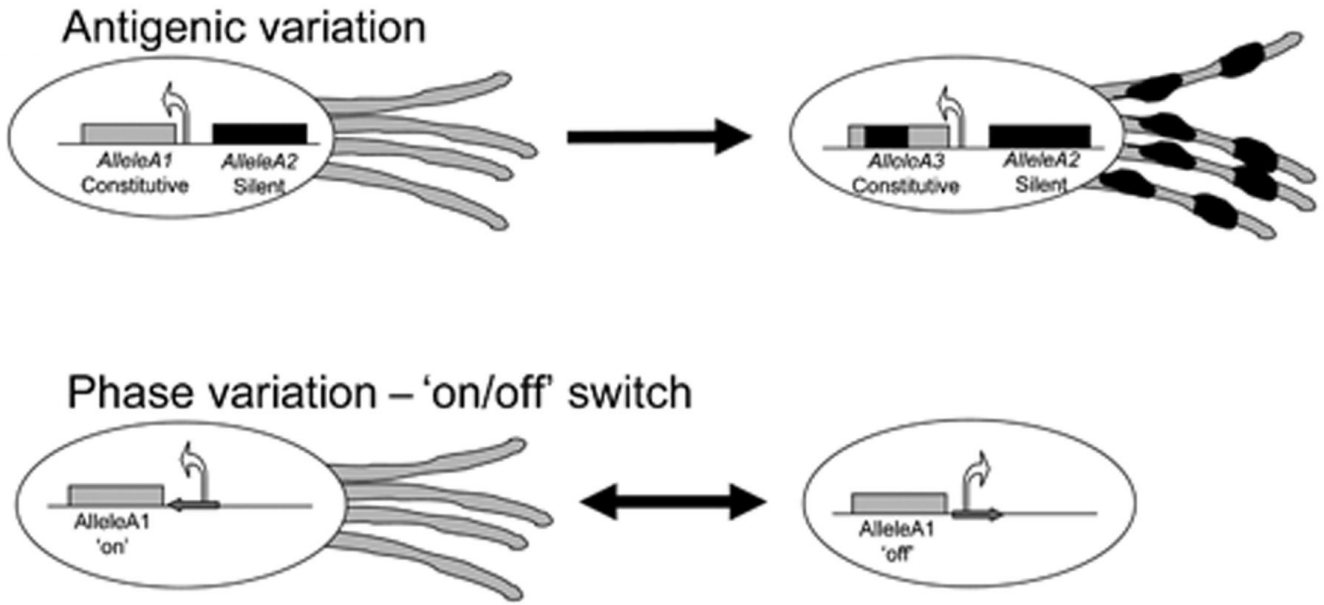
Obstacles to gonorrhoea vaccine development

- **Antigenically variable** bacteria
  - > Selection of broadly protective antigens is challenging
  - > Multicomponent vaccine needed
- **Humans are only natural host**
  - > Difficult to fully test vaccine candidates in animal models that lack human specific receptors and molecules
- **No / limited protective immunity** after infection
  - > Limited data on immune protection to guide vaccine development
  - > No correlate of protection

➢ **Gonorrhoea is highly adapted to evade / avoid immune system**

Evades / inhibits immune responses

- **Highly variable** surface structures both between strains and within strains over the course of infection



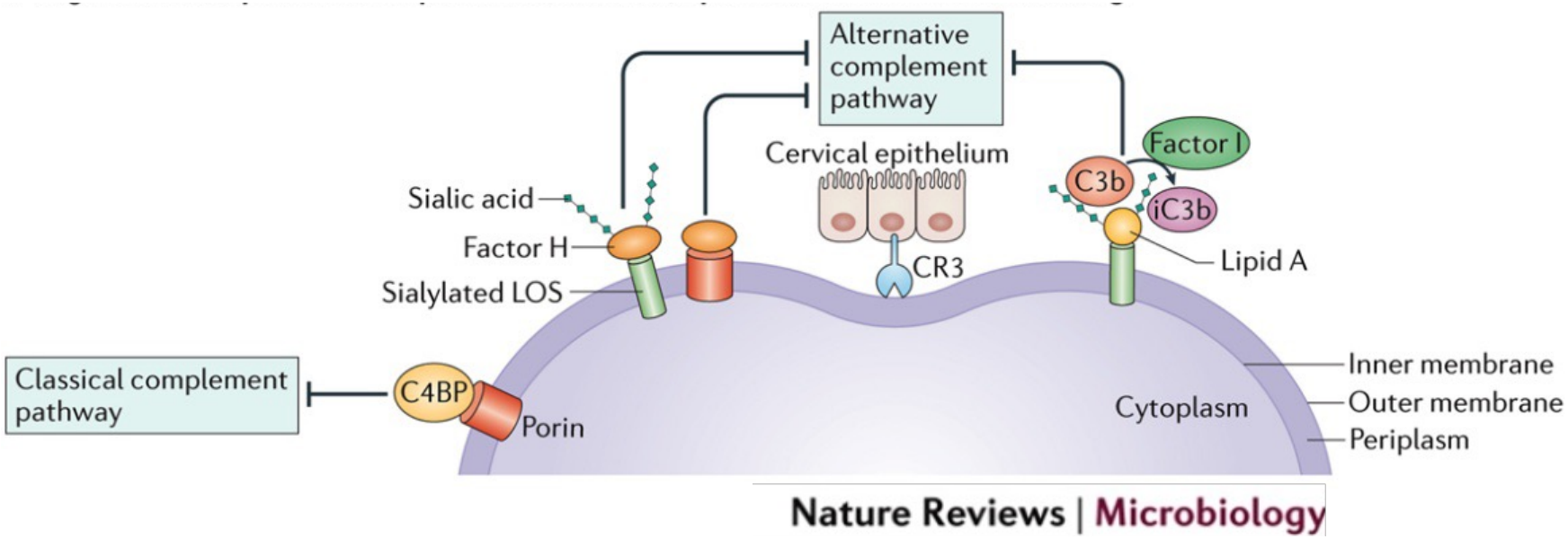
Sequence

Expression

Bayliss FEMS Microbiol Rev (2009)

Evades / inhibits immune responses

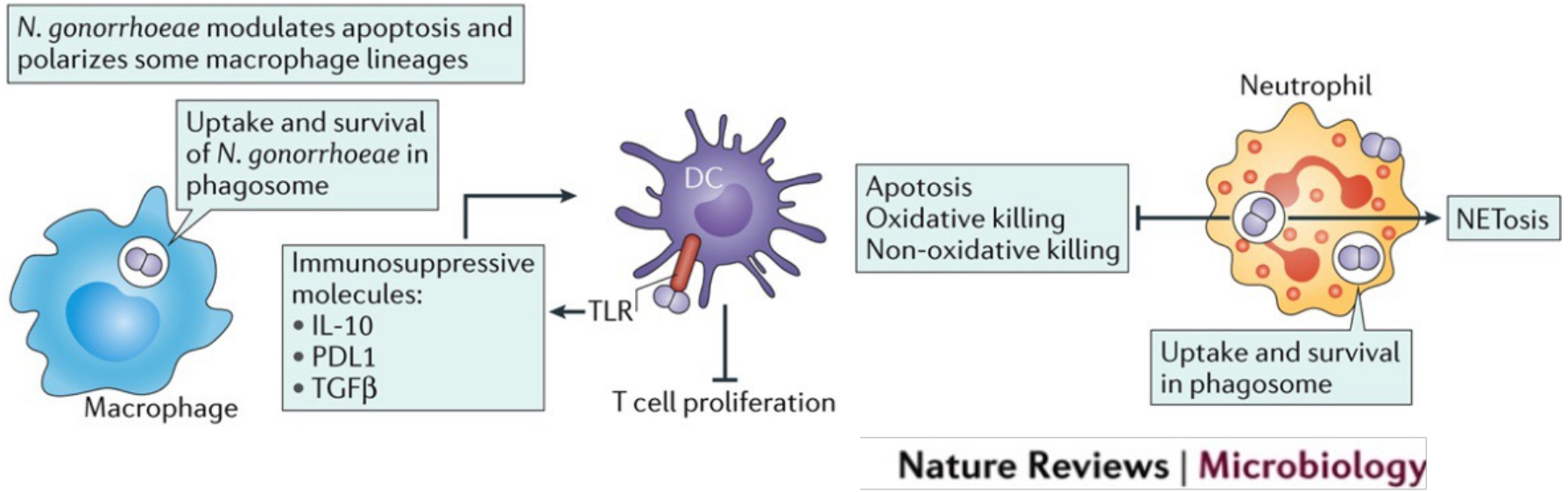
- **Mimics** host structures
  - Lipooligosaccharide (LOS) sialylation
- **Recruits complement inhibitors**
  - blocks alternative and classical complement pathways



Quillin & Seifert, Nat Rev Micro (2018); Jerse et al, Vaccine (2014); Lewis & Ram, FEBS Letters (2020); Rice et al, Annual Rev Micro (2017)

Evades / inhibits immune responses

- **Suppresses T cell proliferation** and activation of adaptive immune responses
- **Promotes survival** in macrophages and neutrophils
- Th1/Th2 responses are blunted - pro-inflammatory **Th17 responses dominate**



Quillin & Seifert, Nat Rev Micro (2018)

Modest immune responses following infection

- **Antibodies present** to gonorrhoea LOS/proteins in sera, seminal plasma, cervical secretions **following infection**
- **Pre-existing antibodies** to gonorrhoea LOS/proteins are common
  - Cross-reaction to nasal carriage of *N. meningitidis* or commensal *Neisseria*?
- **Some association** between antibodies to
  - LOS and resistance to infection in human re-challenge model
  - Opa and reduced relative risk of salpingitis in sex workers in Kenya
- **Cellular immune responses** poorly understood

> A vaccine needs to induce a non-native immune response

Lovett & Duncan, Front Immunol (2019)

Preclinical vaccine development

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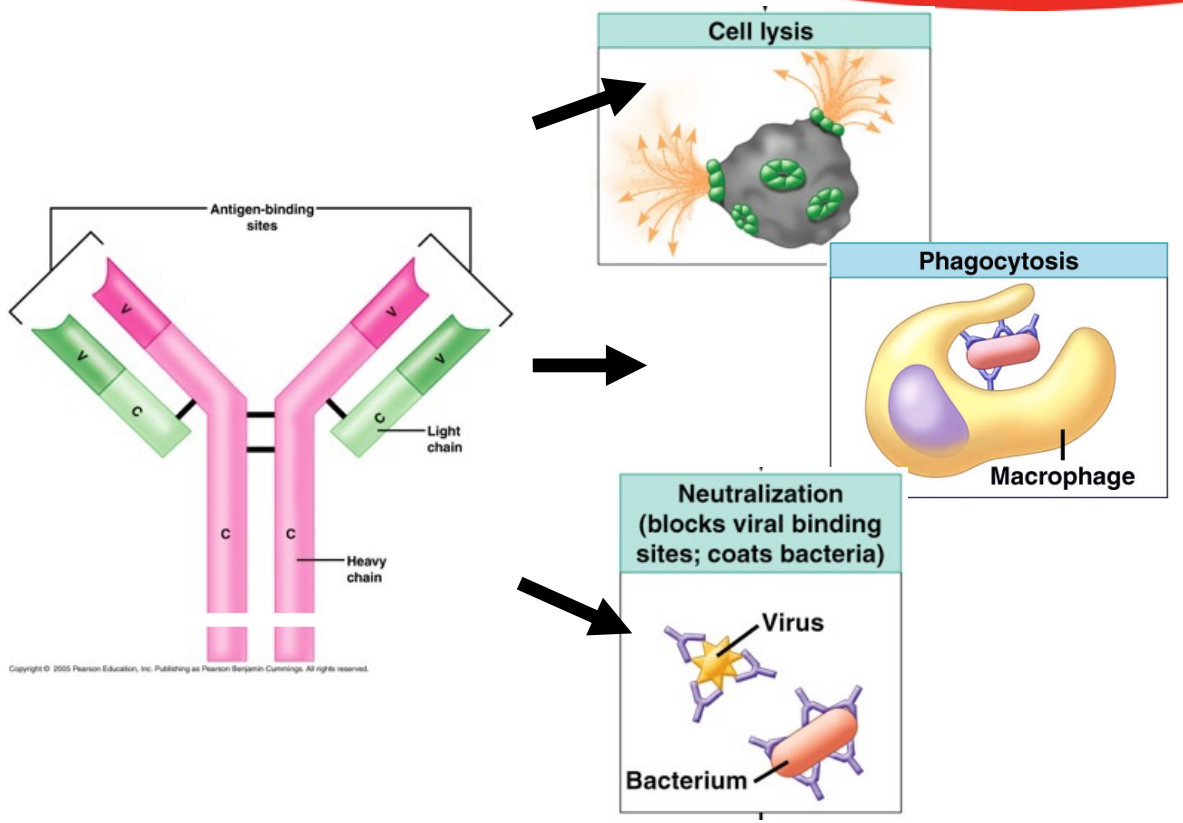
Subunit, protein
Lipooligosaccharide
Outer membrane vesicles (OMVs)

- Characterisation of promising gonococcal vaccine antigens

Edwards et al Crit Rev Microbiol (2016), Rice et al. Annu Rev Microbiol. (2017), Gottlieb et al Vaccine (2020)

Preclinical vaccine evaluation

- In vitro efficacy based on
  - Immunogenicity and surface-binding of antibodies (**ELISA** titres)
  - Bactericidal or opsonophagocytic activity (**SBA / OPA** titres)
  - **Inhibition/neutralisation** of target function



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Preclinical vaccine evaluation

- In vitro efficacy based on
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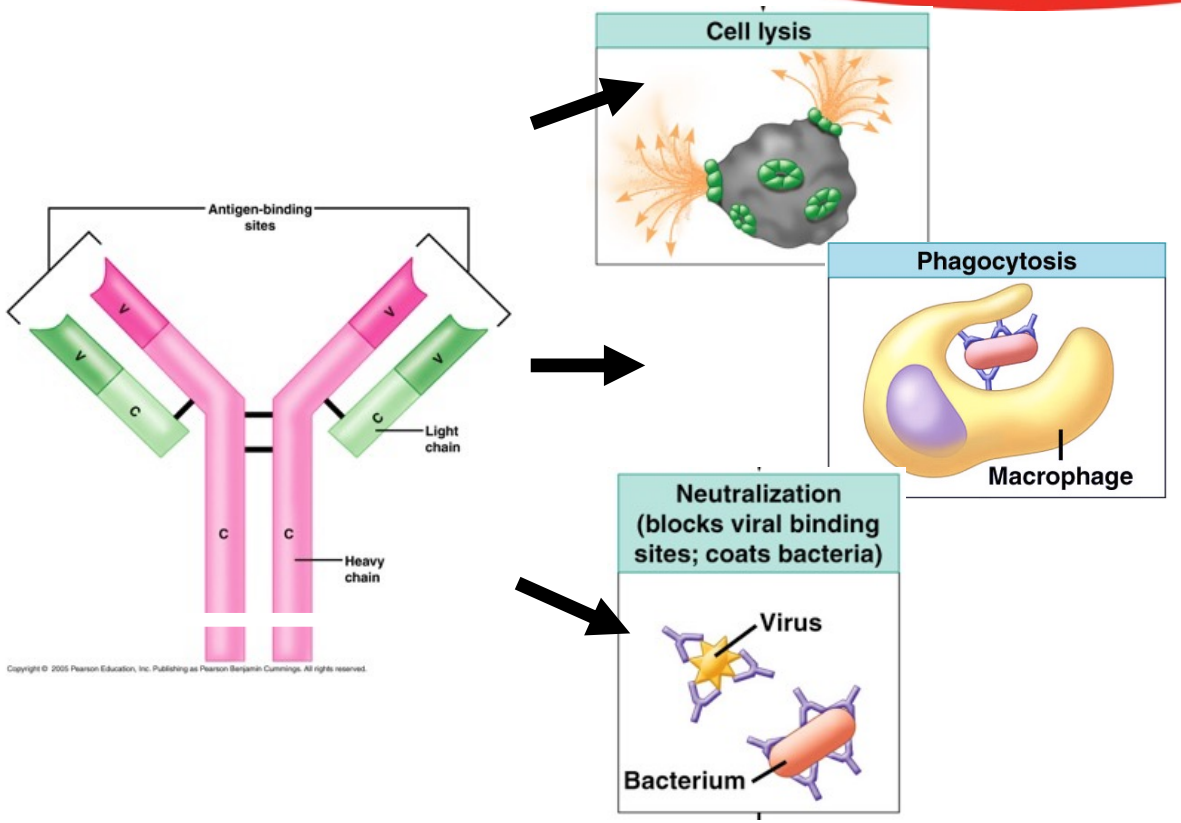
  - Bactericidal or opsonophagocytic activity (SBA / OPA titres)
  - Inhibition of target function

- In vivo efficacy
  - female **mouse genital tract infection model**
    - Does not replicate infection and transmission

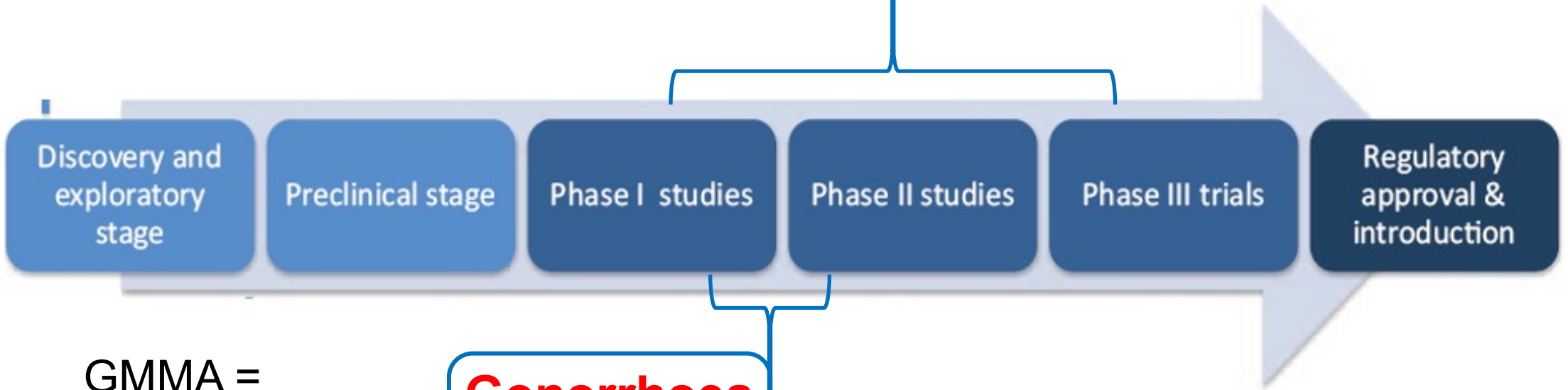


Edwards et al Crit Rev Microbiol (2016), Rice et al. Annu Rev Microbiol. (2017), Gottlieb et al Vaccine (2020)

Clinical vaccine evaluation

- Investigation of **cross-protection** by a meningococcal vaccine

Meningococcal 4CMenB vaccine

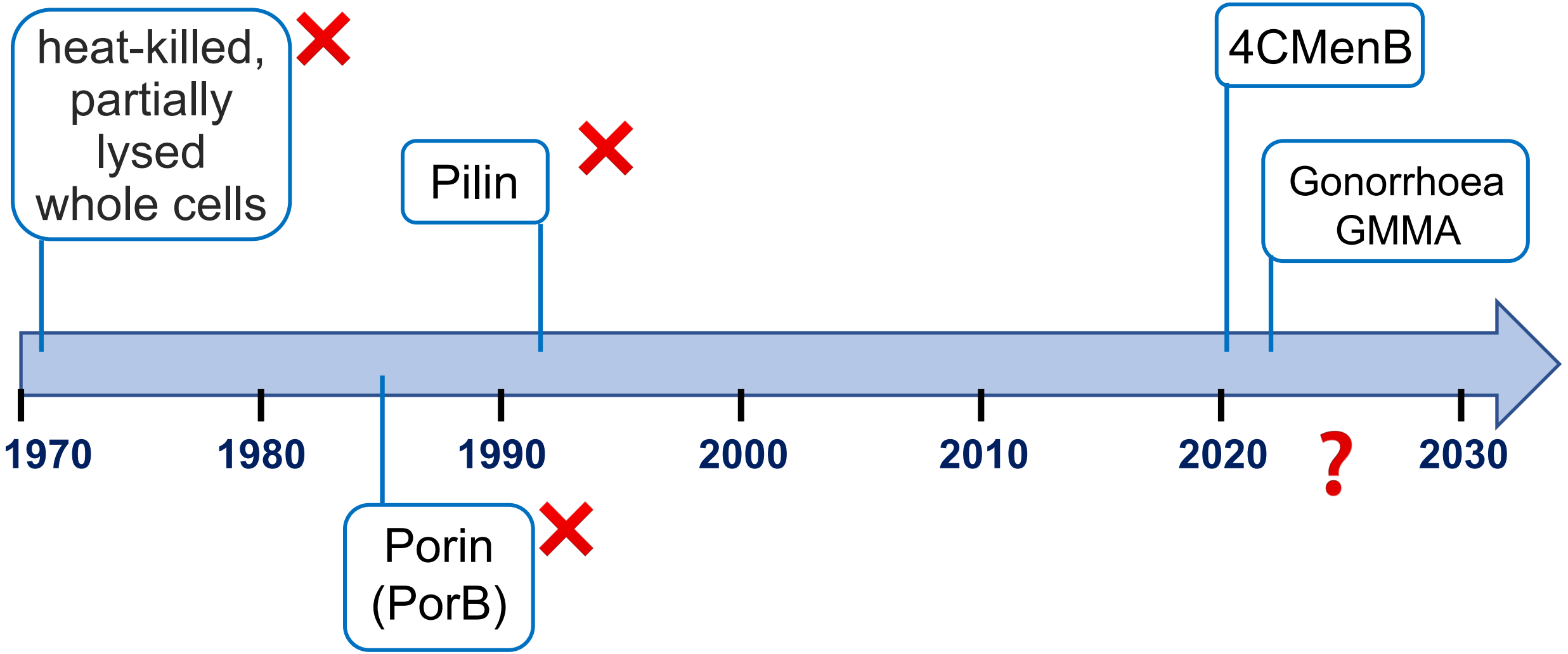


Gonorrhoea GMMA

GMMA = generalized modules for membrane antigens

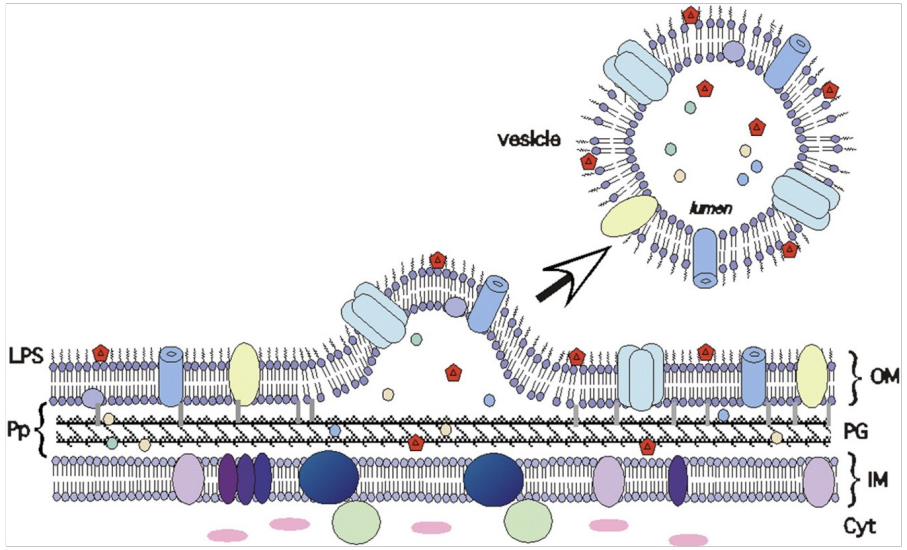
NCT05630859

Vaccine trials for gonorrhoea



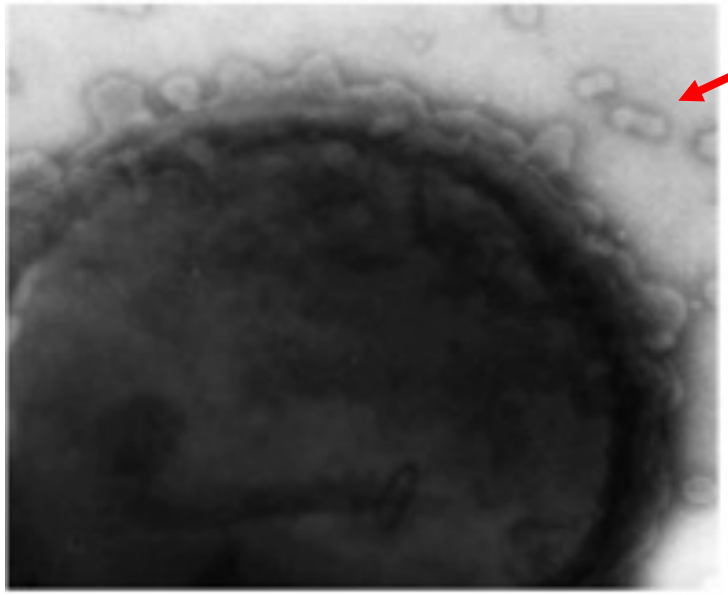
Evidence for MenB vaccine cross protection

- *Neisseria gonorrhoeae & Neisseria meningitidis*
  - closely related bacteria
  - share most genes/ virulence factors
- Have had distinct vaccine development pathways
  - Outer membrane vesicle (OMV) vaccines to serogroup B (MenB)



Meta J. Kuehn, and Nicole C. Kesty Genes Dev. 2005;19:2645-2655

Cold Spring Harbor Laboratory Press



OMVs

Evidence for MenB vaccine cross protection

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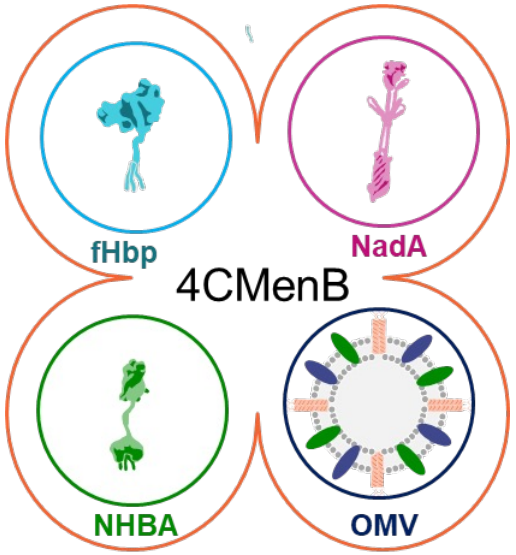
Study	Location	Vaccine	Outcome
Observational, case control, cohort	Cuba[1]	VA-MENGOC-BC	**30 - 50% effectiveness against gonorrhoea**
	Norway[2]	MenBvac	
	New Zealand[3]	MeNZB	
	Canada[4]	4CMenB	
	USA[5]		
	Australia[6]		
Randomised control trial	France[7]		

[1]Pérez et al., 2009, Ochoa Azze, 2019, Reyes Díaz et al., 2021. [2]Whelan et al., 2016. [3]Petousis-Harris et al., 2017. [4]Longtin et al., 2017. [5]Abara et al., 2022. [6]Wang et al., 2022. [7]Molina et al. 2023 NCT04597424.

Potential mechanism of action for MenB vaccines against *N. gonorrhoeae* (Ng)

- 4CMenB NHBA and OMV antigens have **homologues in Ng** [1-3]
- **Sera** from vaccinated humans **cross-reacts** with Ng [1]
- 4CMenB immunized **mice** [4]
  - **accelerated clearance and reduced Ng bacterial burden** in upper and lower reproductive tract
  - 4-fold increase in **serum bactericidal titers**
  - serum IgG and vaginal IgA & IgG **cross-reacts** with Ng
  - antibodies recognize Ng PilQ*, BamA, MtrE, NHBA*, PorB, and Opa (*also shown for human serum)



1. Semchenko et al 2019 doi: 10.1093/cid/ciy1061. 2. Marjuki et al 2019 doi: 10.1128/mBio.01668-19. 3. Hadad et al DOI: 10.1111/j.1600-0463.2012.02903.x.
4. Leduc 2020, doi: 10.1371/journal.ppat.1008602

Ongoing clinical trials with 4CMenB

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Trial number	Study type	Study name	Location, numbers
ACTRN12619001478101	RCT efficacy Immunogenicity	MenGO: Does the licensed meningococcal vaccine Bexsero® provide cross- protection against gonorrhoea?	Australia 130
NCT04415424	RCT efficacy Immunogenicity	GoGoVax: Efficacy study of 4CMenB Bexsero® to prevent gonorrhoea infection in gay and bisexual men	Australia 730
NCT04350138	RCT efficacy	Safety and efficacy study of meningococcal group B vaccine rMenB+OMV NZ Bexsero to prevent gonococcal infection	USA, Thailand 2,200
NCT05294588	RCT challenge	Efficacy of Immunization With 4C-MenB in Preventing Experimental Urethral Infection With Neisseria Gonorrhoeae	USA 140
NCT04722003	Immunogenicity	Mucosal immunity against *Neisseria gonorrhoeae* after 4CMenB vaccination	USA 50
NCT04094883	Immunogenicity	Study to assess gonorrhoeae immune responses induced by a *N. meningitidis* vaccine 4CMenB	USA 15
NCT04297436	Immunogenicity	Gonococcal vaccine study in key populations in Kenya BexKPK	Kenya 50
NCT04398849	Observational prospective cohort	Immunisation for adolescents against serious communicable diseases B Part of it NT	Australia 7,100

Source: https://clinicaltrials.gov https://www.anzctr.org.au/

Ongoing research towards establishing a correlate of protection

- Several 4CMenB clinical trials are investigating immune responses[1-5]
- **Humoral** immune responses
  - **Antibody levels** - Serum and mucosal IgG, IgA, IgM specific for recombinant protein antigens or OMVs
  - **Antibody function** - Serum bactericidal activity (SBA), opsonophagocytic killing (OPK), function neutralising
- **Cellular** immune responses
  - Peripheral blood mononuclear cells (PBMC) collected
  - Antigen-specific IFN secreting T cells and memory B cells investigated

1. NCT04722003; 2. NCT04297436; 3. NCT04415424; 4. ACTRN12619001478101; 5. NCT04094883

Ongoing research towards establishing a correlate of protection

- Controlled Human Infection Model (**CHIM**) [1]
  - Experimental urethral infection in 18-35 year old males - symptomatic urethritis seen in 80-90% of participants within 5 days
  - Participants will receive 2 doses of vaccine (4CMenB or comparator vaccine) then intraurethral challenge with Ng

1. NCT05294588

Summary

- Many obstacles to gonorrhoea vaccine development
- Several promising vaccine candidates in preclinical development
- 2 vaccines undergoing clinical evaluation
  - ➢ hopefully show protection
  - ➢ help identify correlates of protections
- Feasibility of mRNA gonorrhoea vaccine?