The Global Roadmap for STI Vaccine Development

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Disclaimer

- Dr E. David McIntosh is an employee of MSD and an Honorary Clinical Senior Lecturer at Imperial College, London
- The views expressed herein are his own and do not necessarily reflect those of Merck MSD or Imperial College

Abstract

- With the success of vaccination against hepatitis B virus and human papillomavirus, and the possibility that vaccination against *Neisseria meningitidis* serogroup B may offer a degree of protection against *Neisseria gonorrhoeae*, the door opens on future possibilities
- Zika virus candidates are under intense study
- And there are other possibilities which will be explored, for example, syphilis, chlamydia, herpes simplex virus (HSV) and HIV
- See: https://www.who.int/news-room/fact-sheets/detail/sexually-transmitted-infections-(stis)

WHO Key Facts
Sexually Transmitted Infections (STIs)

- In 2016, it was estimated that more than 1 million sexually transmitted infections (STIs) are acquired every day worldwide
- Each year, there are an estimated 357 million new infections with 1 of four STIs: chlamydia, gonorrhoea, syphilis and trichomoniasis
- More than 500 million people are estimated to have genital infection with herpes simplex virus (HSV)
- More than 290 million women have a human papillomavirus (HPV) infection
- The majority of STIs have no symptoms or only mild symptoms that may not be recognized as an STI
- STIs such as HSV type 2 and syphilis can increase the risk of HIV acquisition
- Over 900 000 pregnant women were infected with syphilis resulting in approximately 350 000 adverse birth outcomes including stillbirth in 2012
- In some cases, STIs can have serious reproductive health consequences beyond the immediate impact of the infection itself (e.g., infertility or mother-to-child transmission)
- Drug resistance, especially for gonorrhoea, is a major threat to reducing the impact of STIs worldwide

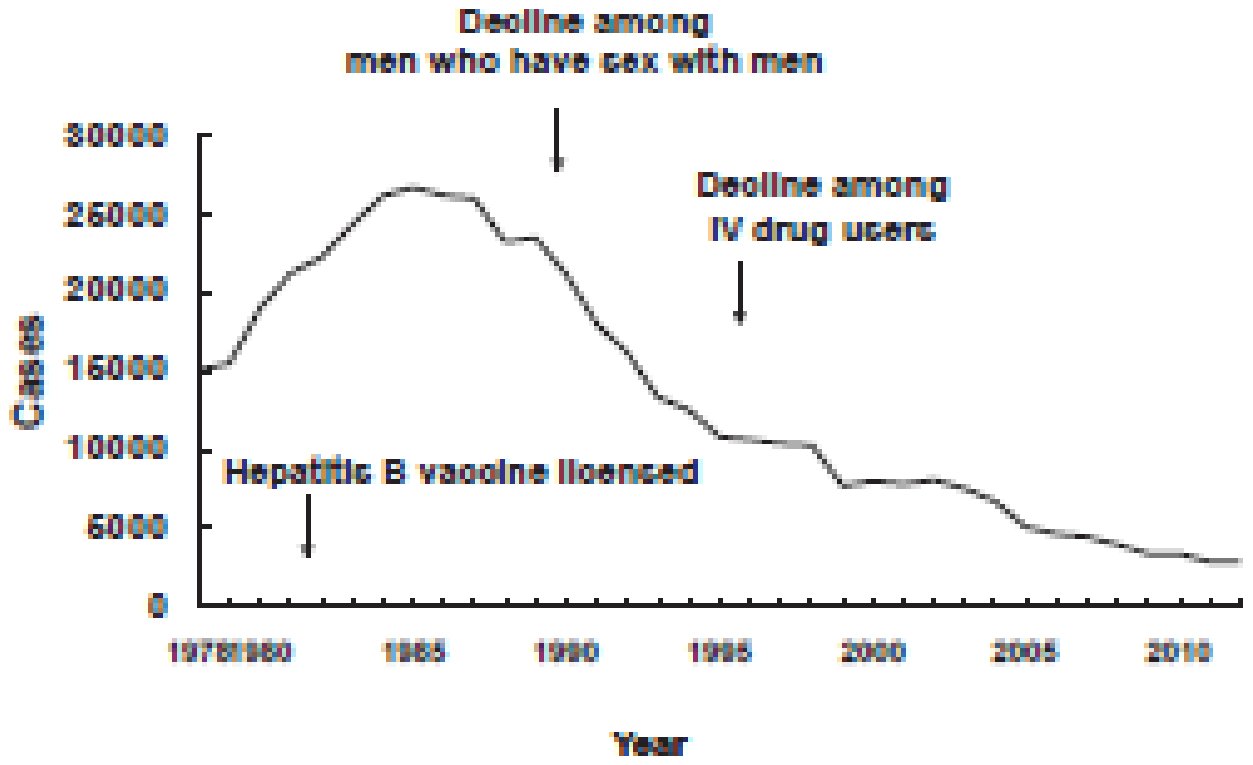
https://www.who.int/news-room/fact-sheets/detail/sexually-transmitted-infections-(stis)

WHO statement on vaccines for sexually transmitted infections

- Safe and highly effective vaccines are available for 2 STIs: hepatitis B and HPV. These vaccines have represented major advances in STI prevention. The vaccine against hepatitis B is included in infant immunisation programmes in 93% of countries and has already prevented an estimated 1.3 million deaths from chronic liver disease and cancer.
- HPV vaccine is available as part of routine immunization programmes in 65 countries, most of them high- and middle-income. HPV vaccination could prevent the deaths of more than 4 million women over the next decade in low- and middle-income countries, where most cases of cervical cancer occur, if 70% vaccination coverage can be achieved.
- Research to develop vaccines against herpes and HIV is advanced, with several vaccine candidates in early clinical development. Research into vaccines for chlamydia, gonorrhoea, syphilis and trichomoniasis is in earlier stages of development

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

Hepatitis B: USA 1978 to 2012



https://www.cdc.gov/vaccines/pubs/pinkbook/hepb.html

Global Human Papillomavirus Vaccination

- Human papillomavirus (HPV) infections continue to be one of the most common sexually transmitted infections worldwide
- The oncogenic potential of this virus was well established in anogenital malignancies and oropharyngeal cancers
- Even though a fall in cervical cancer rates has been reported worldwide, the subsequent rise in HPV-associated head and neck cancers among men and women has been reported from developed countries, necessitating the vaccination of adolescent boys as well

https://www.ncbi.nlm.nih.gov/pubmed/29517117

Global Human Papillomavirus Vaccination

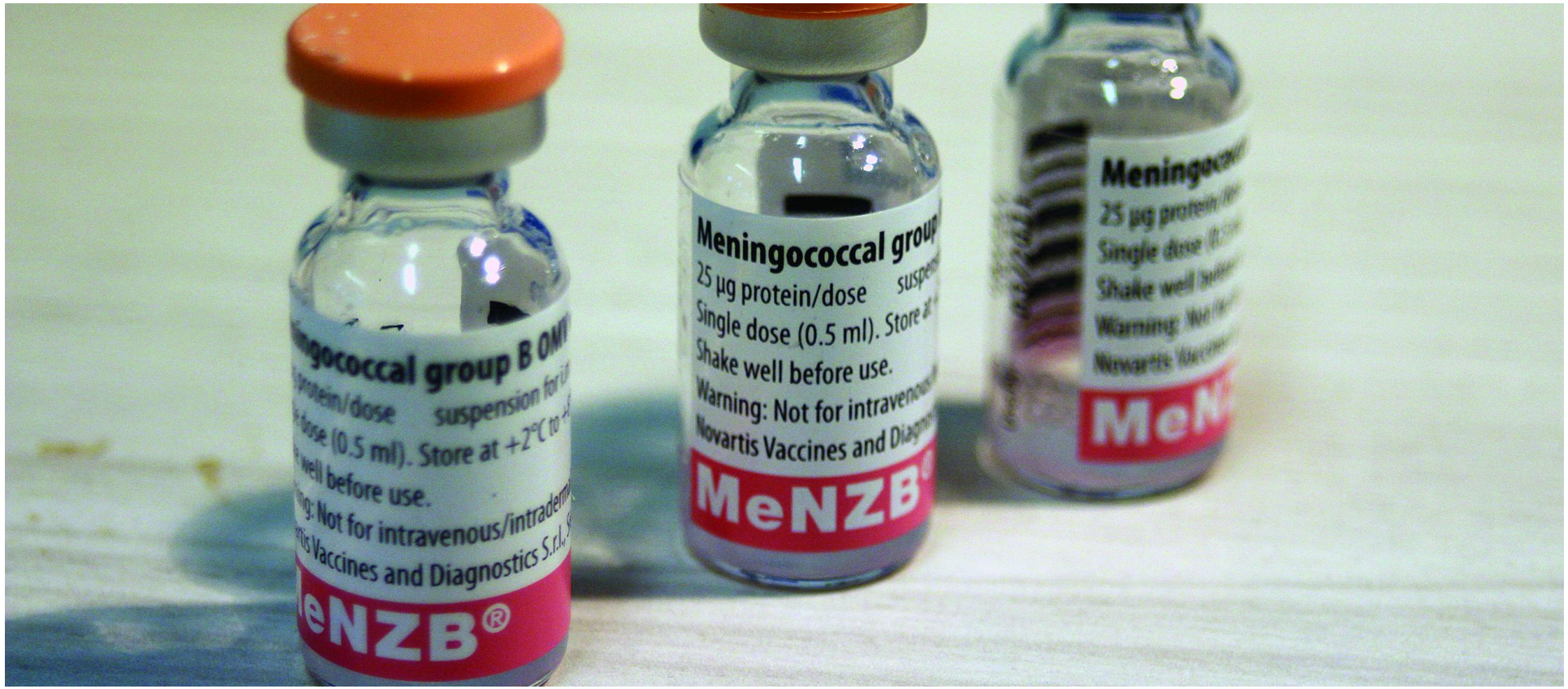
- An electronic search of databases was carried out by Sabeena *et al*. 2018 to retrieve information concerning HPV vaccine implementation between July 2006 and 2017, with special emphasis on current viewpoints, controversies and ethical issues
- Globally, 74 countries have implemented the HPV vaccine in the national immunisation schedule, and this vaccine is listed as an essential medicine by WHO
- About 60% of the low- and lower-middle-income countries studied have implemented the vaccine with financial assistance from Gavi and WHO
- “HPV vaccine is a safe vaccine with no serious adverse effects as per the data available from developed nations as well as low/lower middle/upper middle-income countries”
- Long-term follow-up is essential to substantiate the impact of the vaccination programs in cancer prevention

https://www.ncbi.nlm.nih.gov/pubmed/29517117

Ten Years of Human Papillomavirus Vaccination in the United States (Markovitz *et al*. 2018)

Outcome	Population	Comparison Years	Main Findings
HPV prevalence	Females	2007/10 with 2003/06	56% decrease in prevalence of 4vHPV types in cervical-vaginal samples among 14 to 19 yr olds
		2009/12 with 2003/06	64% decrease in above and 34% decrease in 20 to 24 yr olds
		2011/14 with 2003/06	71% decrease in above and 61% decrease in 20 to 24 yr olds
Genital warts	Females and males	2007/2010 with pre-vaccine era	Decrease in anogenital wart prevalence in females 15 to 19 yr olds from 2.9/100,000 person-yrs in 2006 to 1.8 in 2010
		2013 with 2004	Decrease in rate of genital warts in 16 to 26 yr olds from 3.5% to 1.5% among females; from 3.6% to 2.9% in males
Cervical cancer precursors 2007 to 2014			Substantial decreases

https://www.academicpedsjnl.net/article/S1876-2859(17)30494-1/pdf


Meningococcal group
25 µg protein/dose
Single dose (0.5 ml). Store
Shake well before use.
Warning: Not for intravenous
Novartis Vaccines and Diagn
MeNZB
MeNZB®

The serogroup B meningococcal vaccine 4CMenB (Bexsero) elicits antibodies to *Neisseria gonorrhoeae*

- Bioinformatic analysis was performed to assess the similarity of MeNZB OMV and Bexsero antigens to gonococcal proteins. Rabbits were immunised with the OMV component or the three recombinant antigens of Bexsero, and Western blot and ELISA were used to assess generation of antibodies recognising *N.gonorrhoeae.* Serum from humans immunised with Bexsero was investigated assess the nature of the anti-gonococcal response
- There is a high level of sequence identity between MeNZB OMV and Bexsero OMV antigens, and gonococcal proteins. NHBA is the only Bexsero recombinant antigen that is conserved and surfaced exposed in *N.gonorrhoeae*. Bexsero induces antibodies in humans that recognise gonococcal proteins
- The anti-gonococcal antibodies induced by MeNZB-like OMV proteins could explain the previously seen decrease in gonococcal cases following MeNZB vaccination. The high level of anti-gonococcal-NHBA antibodies generated by Bexsero vaccination in humans may result in additional cross-protection against gonorrhoea

https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciy1061/5247042

See also: https://www.tandfonline.com/doi/full/10.1080/21645515.2017.1381810

Potential impact of vaccination against *Neisseria meningitidis* on *Neisseria gonorrhoeae* in the United States: results from a decision-analysis model

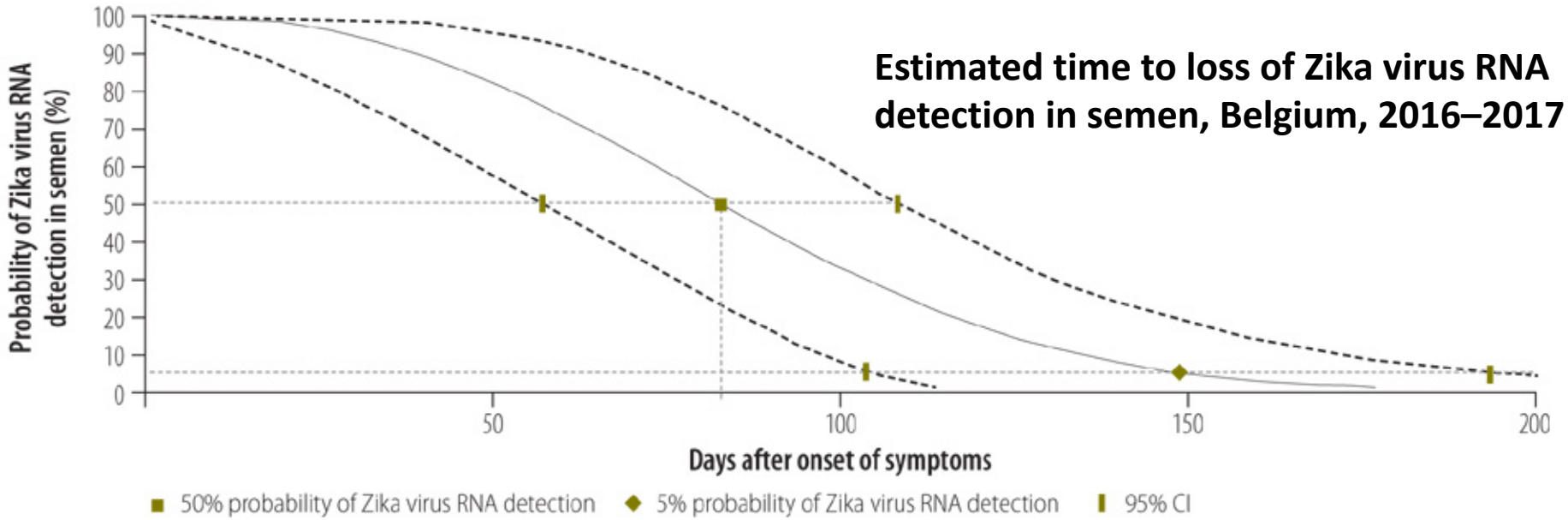
- Components in 4CMenB vaccine against *Neisseria meningitidis* serogroup B have shown to potentially cross-react with *Neisseria gonorrhoeae*
- The authors modeled the theoretical impact of a US 4CMenB vaccination program on gonorrhoea outcomes
- A decision-analysis model was populated using published healthcare utilisation and cost data
- A two-dose adolescent vaccination campaign was assumed, with protective immunity starting at age 15 years and a base-case efficacy against gonorrhoea of 20% (assumed)
- Key outcome measures were reductions in gonorrhoea and HIV infections, reduction in quality-adjusted life-years (QALYs) lost, and the economically justifiable price assuming a willingness-to-pay threshold of $75,000 per QALY gained.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4514066/

Potential impact of vaccination against *Neisseria meningitidis* on *Neisseria gonorrhoeae* in the United States: results from a decision-analysis model

- Adolescent vaccination with 4CMenB would prevent 83,167 (95% credible interval [CrI], 44,600-134,600) gonorrhoea infections and decrease the number of HIV infections by 55 (95% CrI, 2-129) per vaccinated birth cohort in the USA
- Excluding vaccination costs, direct medical costs for gonorrhoea would reduce by $28.7 million (95% CrI, $6.8-$70.0 million), and income and productivity losses would reduce by $40.0 million (95% CrI, $8.2-$91.7 million)
- Approximately 83% of the reduction in lost productivity is generated by avoiding HIV infections
- At a price of US$26.10, the net cost per infection averted would be $1,677 (95% CrI, $404-$2,564)
- Even if the cross-immunity of 4CMenB vaccine and gonorrhoea is only 20%, the reduction in gonorrhoea infections and associated costs would be substantial

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4514066/



Estimated time to loss of Zika virus RNA detection in semen, Belgium, 2016–2017

https://www.who.int/bulletin/volumes/95/12/17-181370/en/

WHO Zika Vaccine Tracker

Candidate	Platform	Immunogen	Adjuvant
GLS-5700	DNA	prME (pre-membrane and envelope)	None
AGS-v	Peptide	Mosquito salivary proteins	ISA-51
MV-Zika	Recomb. Viral vector	prME	None
mRNA-1325	mRNA	prME	None
VRC-ZKADNA085-00-VP and 090-00-VP	DNA	prME	None
ZIKV PIV	Inactivated whole target organism	Whole virus	Alum
PIZV or TAK-426	“	“	“

https://docs.google.com/spreadsheets/d/19otvINcayJURCMg76xWO4KvuyedYbMZDcXqbyJGdcZM/pubhtml#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A syphilis vaccine development strategy

- Because syphilis transmission occurs by contact with the infectious primary chancre or secondary lesions, prevention or attenuation of these lesions would be a necessary requirement of a syphilis vaccine, because it would serve to eliminate or reduce person-to-person syphilis transmission
- A second critical requirement of a syphilis vaccine is to target dissemination of *T. pallidum* within the infected host
- Such a dual pronged approach, combined with the selection of vaccine antigens that are conserved in sequence to ensure broad protection against circulating *T. pallidum* strains and reinfection, would provide a comprehensive vaccine strategy to protect against syphilis infection at both a public health and an individual level

https://journals.lww.com/stdjournal/Fulltext/2018/09001/Syphilis_Vaccine_Development___Requirements,.5.aspx

Key considerations for syphilis vaccine design

- Four intriguing aspects of *T. pallidum* infection that would need to be targeted in a successful syphilis vaccine:
  - Highly infectious chancre that develops at the site of infection
  - Extremely invasive nature of the pathogen
  - Capacity of the pathogen to cause repeat infections
  - Capacity to establish latency despite the development of a robust immune response
- The highly invasive nature of *T. pallidum*: early ability to cross the endothelial, placental and blood–brain barriers
- To eliminate disease symptoms within an infected individual and disease transmission at the population level, an effective syphilis vaccine would need to prevent:
  - Chancre development
  - Treponemal dissemination
  - Treponemal persistence
  - Reinfection

https://www.tandfonline.com/doi/full/10.1080/14760584.2016.1203262

Key issues to be assessed during the process of syphilis preclinical vaccine development

- Number of vaccine administrations required to achieve maximal immunity
- Duration of immunity that is induced following vaccine administration
- Cross-protection against diverse strains
- Appropriate multivalent vaccine preparation
- Adjuvant selection
- Optimisation to achieve the needed immune response for effective protection against *T. pallidum* infection

https://www.tandfonline.com/doi/full/10.1080/14760584.2016.1203262

Five-year view

- With an infusion of funding and regulatory support the field is poised to significantly advance over the next 5 years
- The application of modern research tools, including cutting-edge structural and proteomic methodologies, to the study of *T. pallidum* biology will increase the understanding of treponemal pathogenesis and will reveal novel vaccine candidates
- Cross-disciplinary studies that consider both sides of the host-pathogen interaction, including the host innate and adaptive immune responses to infection and the corresponding evasion mechanisms employed by *T. pallidum*, will confer an enhanced understanding of the correlates associated with protection from disease, especially in the context of human infection
- The existence of an excellent animal model that recapitulates the majority of disease stages and symptoms allows for pre-clinical studies that will be informative for ensuing Phase I clinical vaccine trials in humans
- The application of these research directions and methodologies to *T. pallidum* research will advance the field of syphilis vaccine development and it is anticipated a viable syphilis vaccine candidate will be realised within 10 years

https://www.tandfonline.com/doi/full/10.1080/14760584.2016.1203262


BBC NEWS

Development status of current chlamydia vaccine candidates

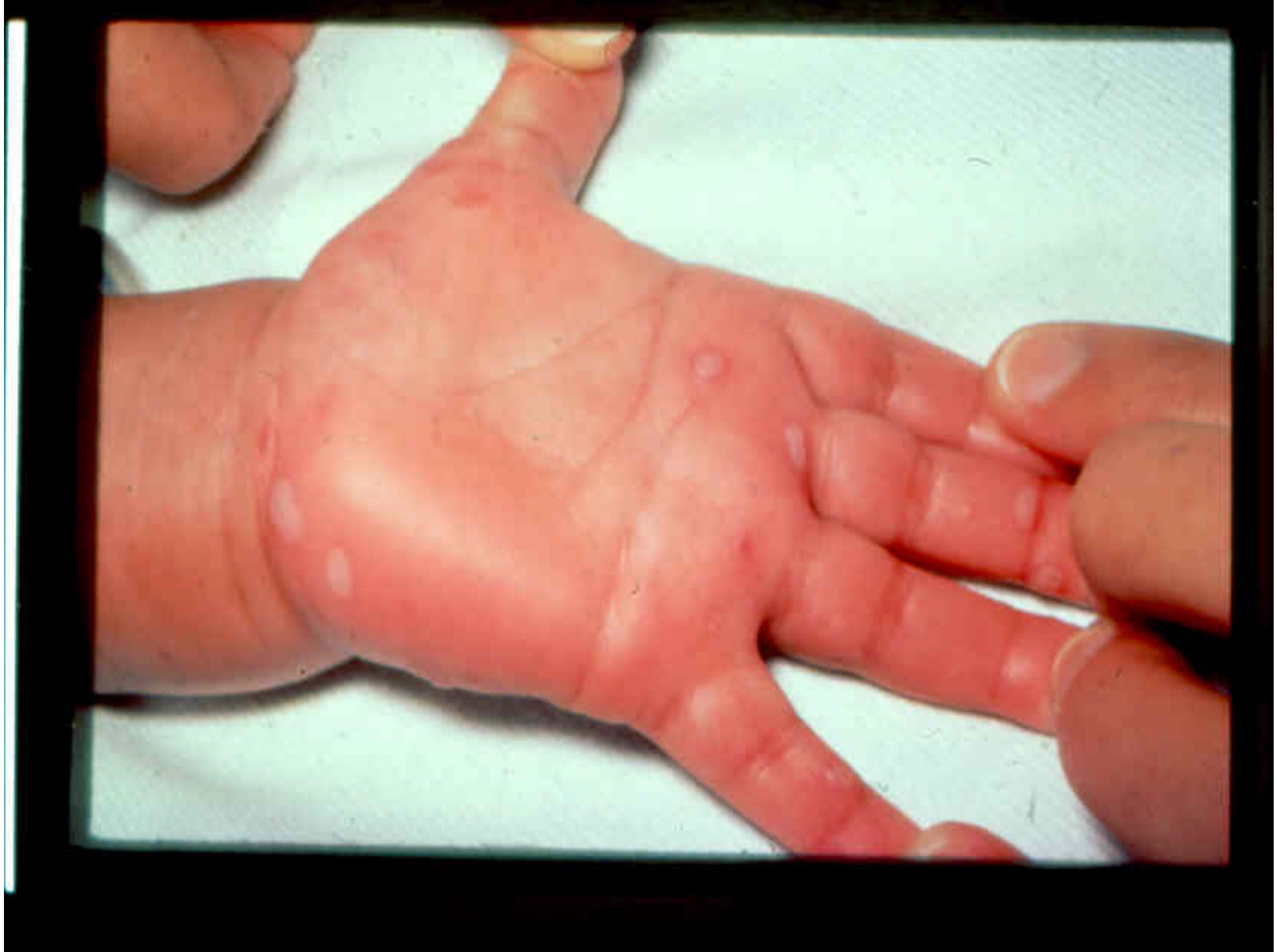
Candidate name/identifier	Pre-clin	Phase I	Ref.
MOMP (Major Outer Membrane Protein)-VD4 neutralising antibodies (Statens Serum Institut)		X	Olsen *et al*. J Infect Dis 2015; 212: 978-89; Boje *et al*. Immunol Cell Biol 2016; 94: 185-95
Intranasal MOMP nanoemulsion (NanoBio Corp)	X		Unpublished NanoBio
MOMP + Pmps (Polymorphic Membrane Proteins) (Pan-Provincial Vaccine Enterprise Inc. and British Columbia CDC)	X		Karunakaran *et al*. Vaccine 2015; 33: 2159-66
cSAP TLR7 agonist with UV-killed *Chlamydia* (Selecta Biosciences)	X		Stary *et al*. Science 2015; 348: aaa8205
Vaxonella platform (*Salmonella* vector) (Prokarium)	X		Gamory *et al*. Infect Immun 2005; 73: 2005-11
Live attenuated (plasmid-deficient) trachoma vaccine (NIH/NIAID)		X	Kari *et al*. J Exp Med 2011; 208: 2217-23

https://www.sciencedirect.com/science/article/pii/S0264410X17300427

Research priorities for an effective STI vaccine for *Chlamydia trachomatis*

Advancing basic science and translational research	Incorporate approaches to generate tissue-resistant memory T cells
	Evaluate antigens identified by reverse vaccinology, proteomics
	Test new adjuvant and antigen combinations
Defining preferred product characteristics	Outline infection versus disease indications
	Define target populations ie girls only vs girls and boys
	Consider efficacy needs: prevention at cervix vs ascension to upper genital tract
Facilitating clinical evaluation and vaccine introduction	Define clinical endpoints: infection vs PID
	Develop biomarkers, radiological tests, etc. for upper genital tract disease

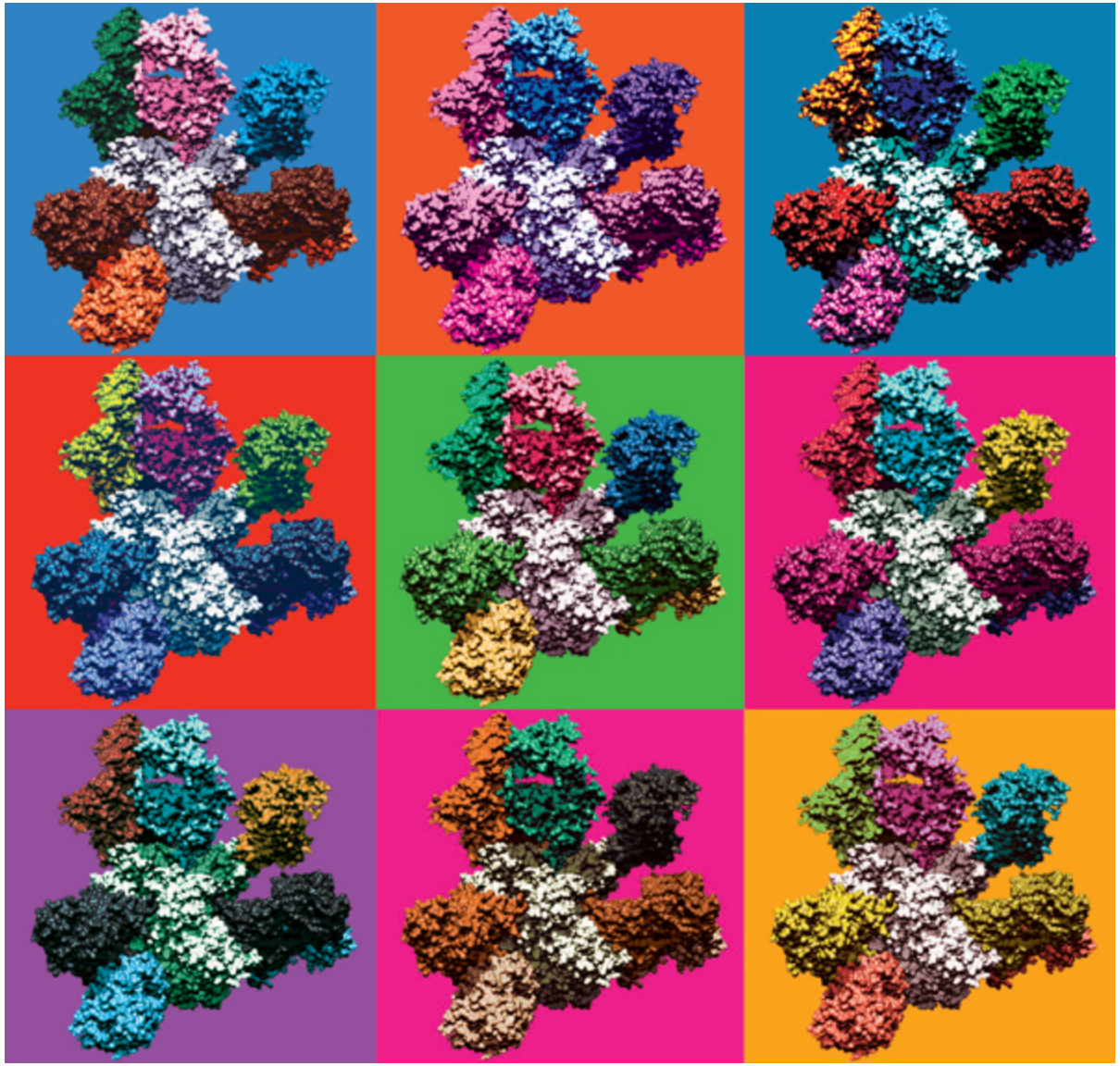
https://www.tandfonline.com/doi/full/10.1080/14760584.2018.1417044



HSV vaccine candidates in Phases I and II

Candidate name	Developer	Platform antigens	Phase I	Phase II
GEN-003	Genocea	Subunit vaccine gD2/ICP4 with Matrix M2 adjuvant		X
HerpV	Agenus	32 35-mer peptides, complexed with HSP, QS-21 adjuvant		X
Codon optimised polynucleotide	Admedus	DNA vaccine: gD2 codon		X
VCL-HB01/HM01	Vical	DNA vaccine gD2+/-UL46Vaxfectin		X
HSV529	Sanofi	Replication-defective HSV-2	X	

https://www.sciencedirect.com/science/article/pii/S0264410X16002978



https://www.iavireport.org/

HIV vaccine development

- There are now several vaccine candidates in clinical development designed to induce broadly neutralising antibody responses
- There are nearly a dozen broadly neutralising antibodies are in development for prophylaxis
- In addition, new methods of vaccine delivery including messenger RNA or mRNA are in development
- There are also two ongoing efficacy trials that are testing vaccine candidates that induce antibodies, which although not broadly neutralising may still be effective at blocking HIV infection

https://www.iavireport.org/

The STI vaccine roadmap

- Research to develop vaccines against herpes and HIV is advanced, with several vaccine candidates in early clinical development
- Research into vaccines for chlamydia, gonorrhoea, syphilis and trichomoniasis is in earlier stages of development
- *T. pallidum* research will advance the field of syphilis vaccine development and it is anticipated a viable syphilis vaccine candidate will be realised within 10 year
- Important questions remain about *policy* decisions and *implementation*