Update on STI vaccines and implications for HIV

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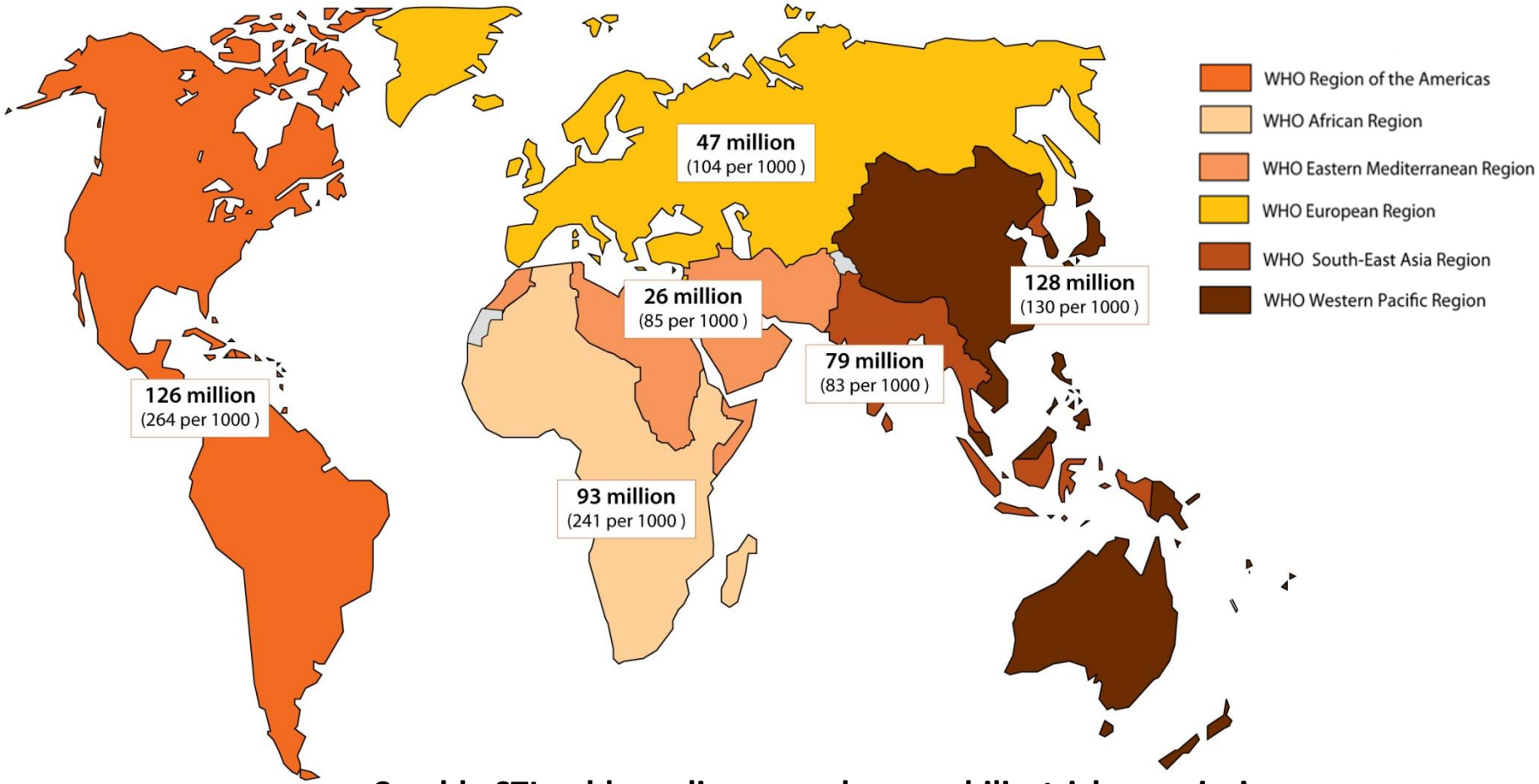
SA HIV Clinicians Society Conference 2014

Overview

- The need for STI vaccines
- Current vaccines and applications in the context of HIV
  - E.g. HPV
- Future vaccines

The case for STI vaccines

WHO estimates 499 million new cases of curable STIs in 2008



Curable STIs: chlamydia, gonorrhea, syphilis, trichomoniasis

Source: WHO. Global incidence and prevalence of selected curable sexually transmitted infections - 2008.

Significant global burden of disease associated with curable STIs

- Individual curable STIs, 2008

106 million	Chlamydia
106 million	Gonorrhea
11 million	Syphilis
276 million	Trichomoniasis

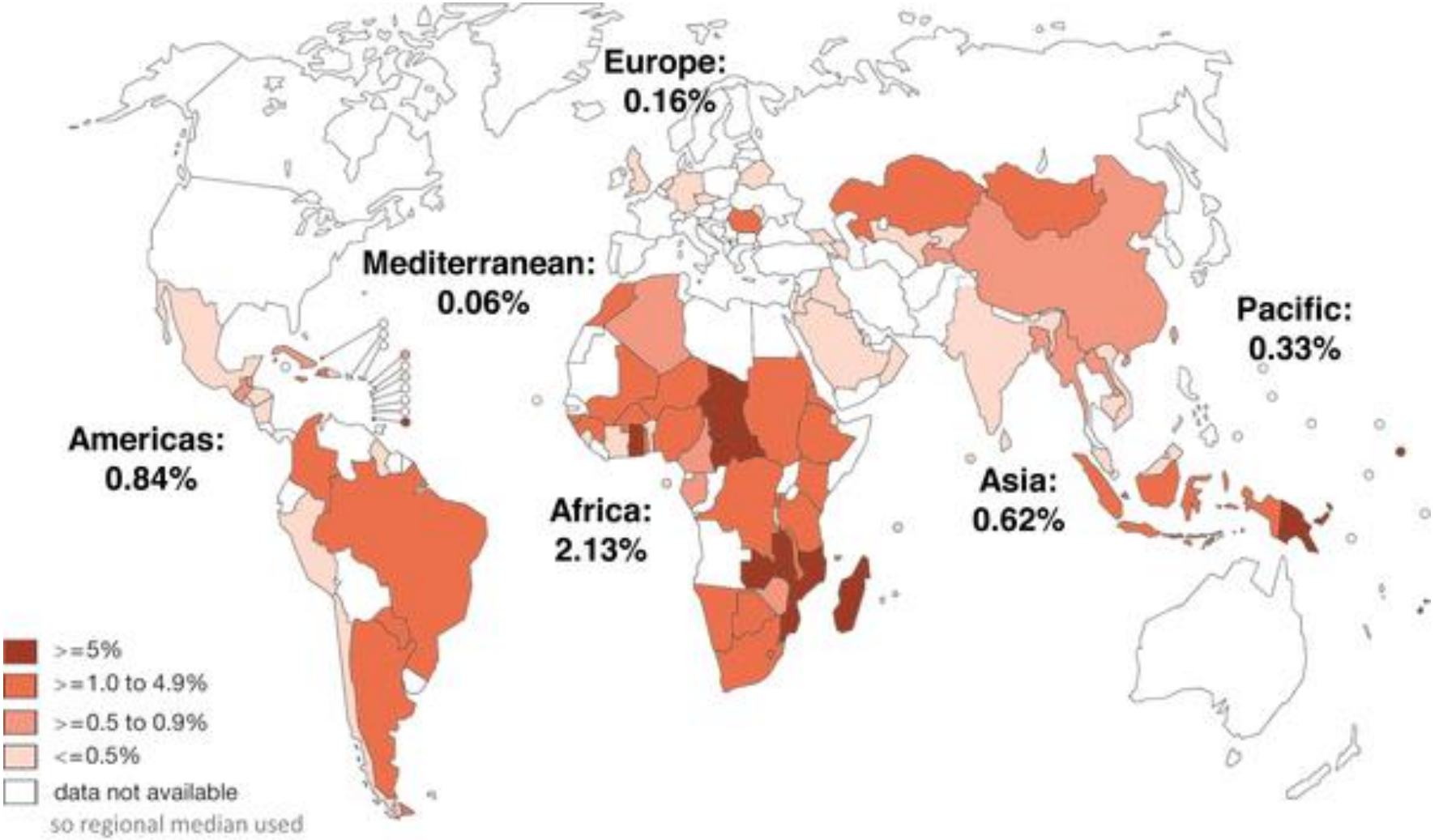
- Overall, numbers not decreasing compared with 2005 estimate of 448 million

- In all cases, highest incidence in **sub-Saharan Africa region**

- **The majority of infections are asymptomatic**

Source: WHO. Global incidence and prevalence of selected curable sexually transmitted infections - 2008.

Syphilis RPR Positivity - Antenatal Attendees by WHO Region (2008-09)



Source: Newman *et al*., (2013) PLoS Med 2013;**10**(2): e1001396. doi:10.1371/journal.pmed.1001396

Viral STIs: large proportion of prevalent STIs

- HSV-2 infection affects an estimated 536 million people globally
- An estimated 291 million women have HPV infection at any point in time
  - Numbers of men likely similar
- Approximately 360 million people suffer chronic HBV infections
  - Most acquired perinatally
- **Significant burden in populations with HIV**

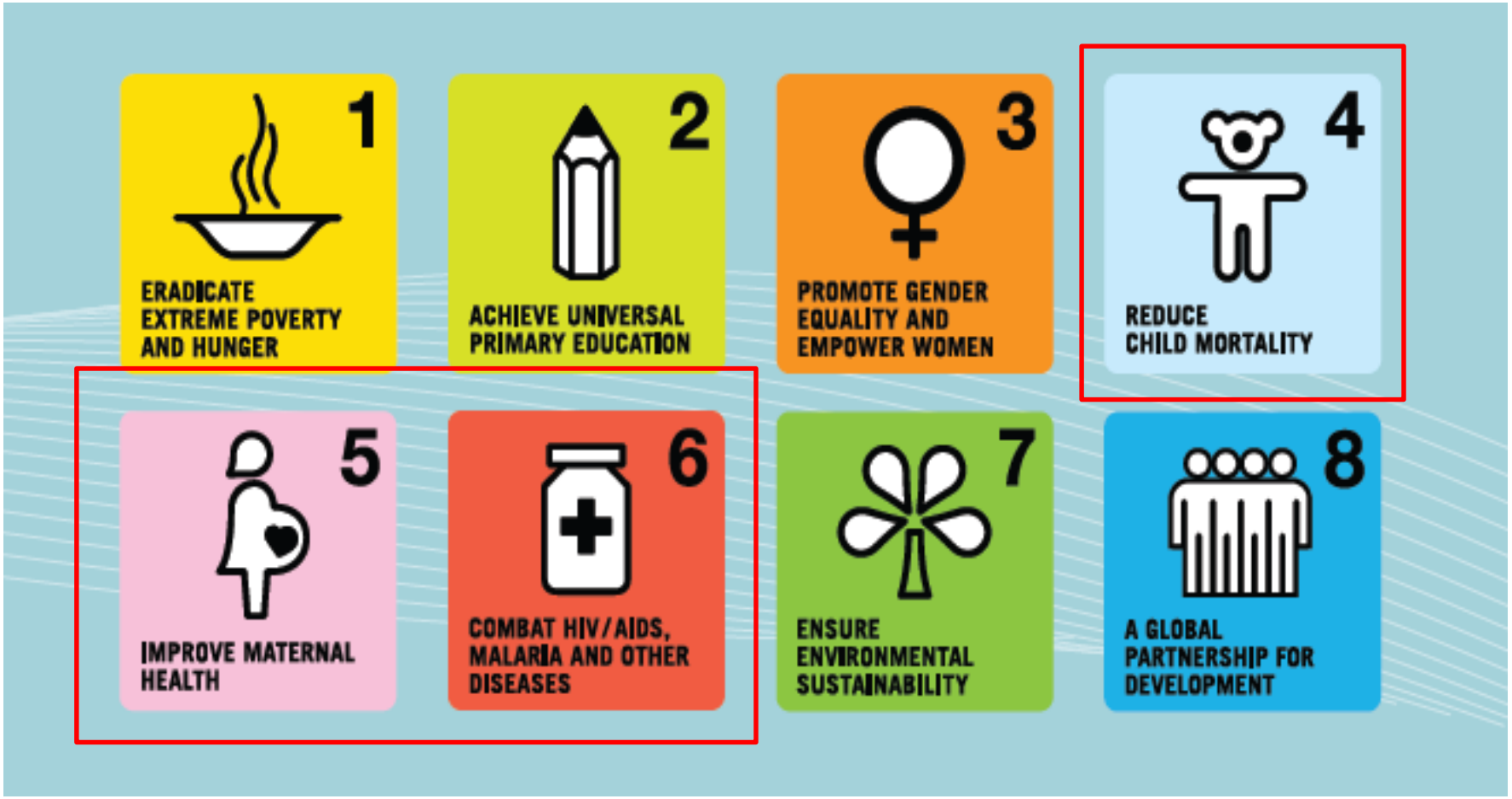
Neglected STIs are a significant cost to already constrained health systems

- **HPV** cause 3·3 million disability adjusted life years (DALYs)
  - included in estimates of mortality and morbidity due to cancer rather than STIs
- **Syphilis** is responsible for 4·2 million DALYs.
  - Effective screening programmes infant mortality at a cost per DALY that is lower than prevention of a case of perinatal HIV infection.

- **Chlamydia and gonorrhoea** cause 7 million DALYs as a result of cause tubal infertility and, potentially fatal, ectopic pregnancy.
- **Vaginal discharge** prompts women to seek frequent care, which is expensive, often ineffective, and sometimes harmful.
  - Candida and bacterial are not included in the burden of disease calculations.

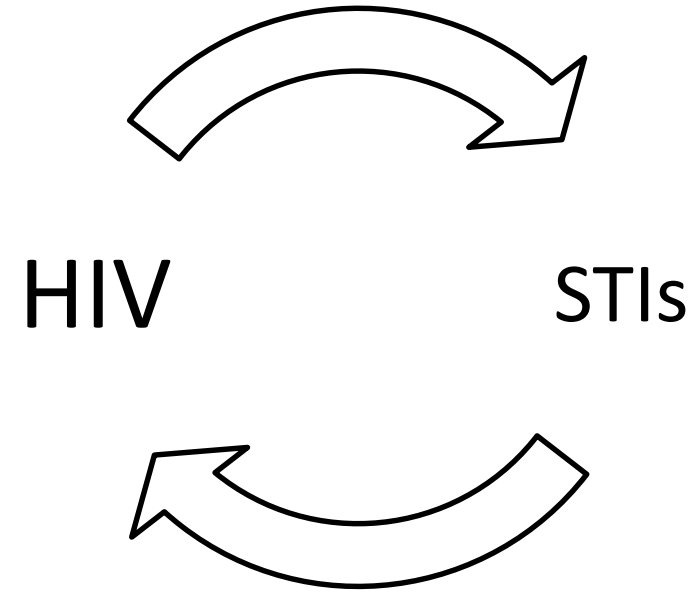
Source: Low, Lancet 2006

Untreated STIS impact on achieving the Millennium development goals



Epidemiological synergy – STIs increase HIV transmission

- HSV-2
  - 3-fold increase HIV risk
  - Increased shedding in HIV positives
- Urethritis/cervicitis
  - 2-3 fold increased risk
  - More prevalent
- Treatment of curable STIs of limited value for population level reductions in incidence
  - Beneficial for individuals



Currently available vaccines

HPV vaccines are highly effective

- Efficacy=prevention of new infection and/or disease caused by vaccine-associated types (fully vaccinated women aged 16-26)

Study	Vaccine	No of subjects		Endpoints	Vaccine efficacy % (95% CI)
		Vaccine	Control		
Munoz, 2010	6/11/16/18	4616 4689	4680 4735	CIN 2/3, (AIS), VIN 2/3, VAIN 2/3, GW	100 (90-100) 95 (70-100)
Lehtinen, 2011	16/18	5824	5820	CIN3+, (AIS)	100 (85-100

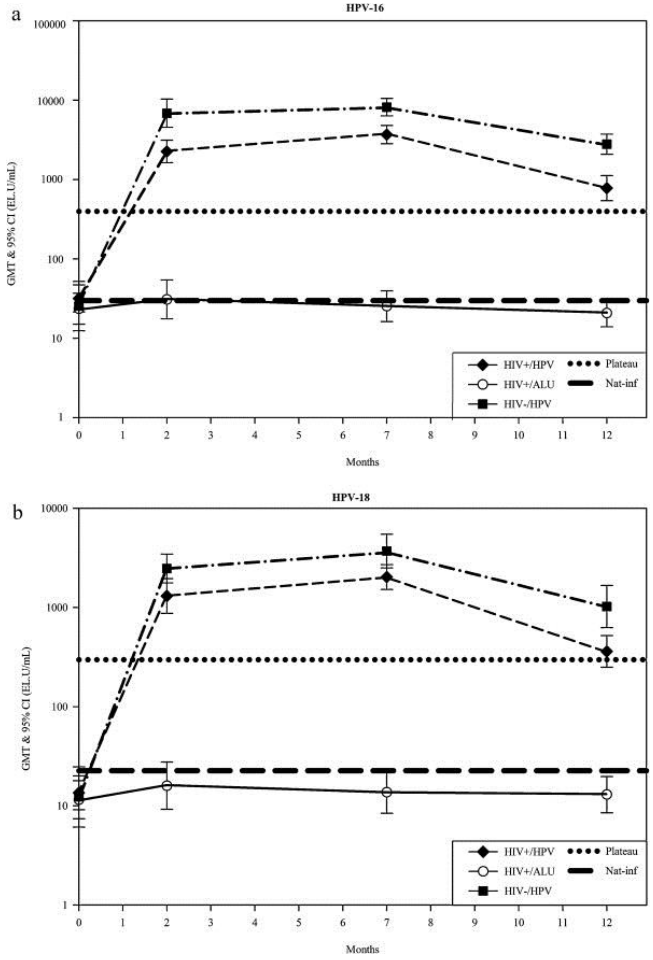
Vaccine efficacy against non-vaccine types more limited: Bivalent>quadrivalent

Since these initial trials with 3 doses, vaccines have been licensed for two doses

HPV vaccines are safe

- Trials (Lu, 2011)
  - Systematic review and analysis of 44, 142 females
  - Safe with no evidence of difference in risk
    - SAE RR: 1.00 (0.91-1.09); vaccine-related SAE RR: 1.82; 0.79-4.20
- Post-licensure (Gee,2011)
  - Assessment of 600, 558 doses of quadrivalent vaccine from 7 managed care organisations
  - No vaccine related risk associated with prespecified outcomes including Guillian-Barre Syndrome, thrombo-embolic disease, appendicitis and allergic reactions
- WHO Global Advisory Committee on Safety continues to monitor (statement March 2014)

HPV vaccines can be used safely in HIV positive populations



Women aged 18-25 years

- Vaccine safe and immunogenic in HIV positive women
- All HIV positive women seroconverted for HPV 16/18
- Antibody levels>natural immunity
- Sustained anti-HPV 16/18 CD4+ T-Cell responses inducted
- No association between immune response and CD4+ count or viral load
- Similar results in other studies of quadrivalent vaccine (Levin 2010, Wilkin 2010)

Denny, Vaccine 2013

Lessons learnt from HPV vaccine implementation – relevance for HIV vaccines

- South Africa 1st dose
  - 91% school coverage,
  - 87% learner coverage,
  - > 340 000 Grade 4 girls were vaccinated in over 15 000 schools in South Africa in the period March 10 - April 23 2014.
  - No major adverse events

Lessons learnt from HPV vaccine implementation – relevance for HIV vaccines

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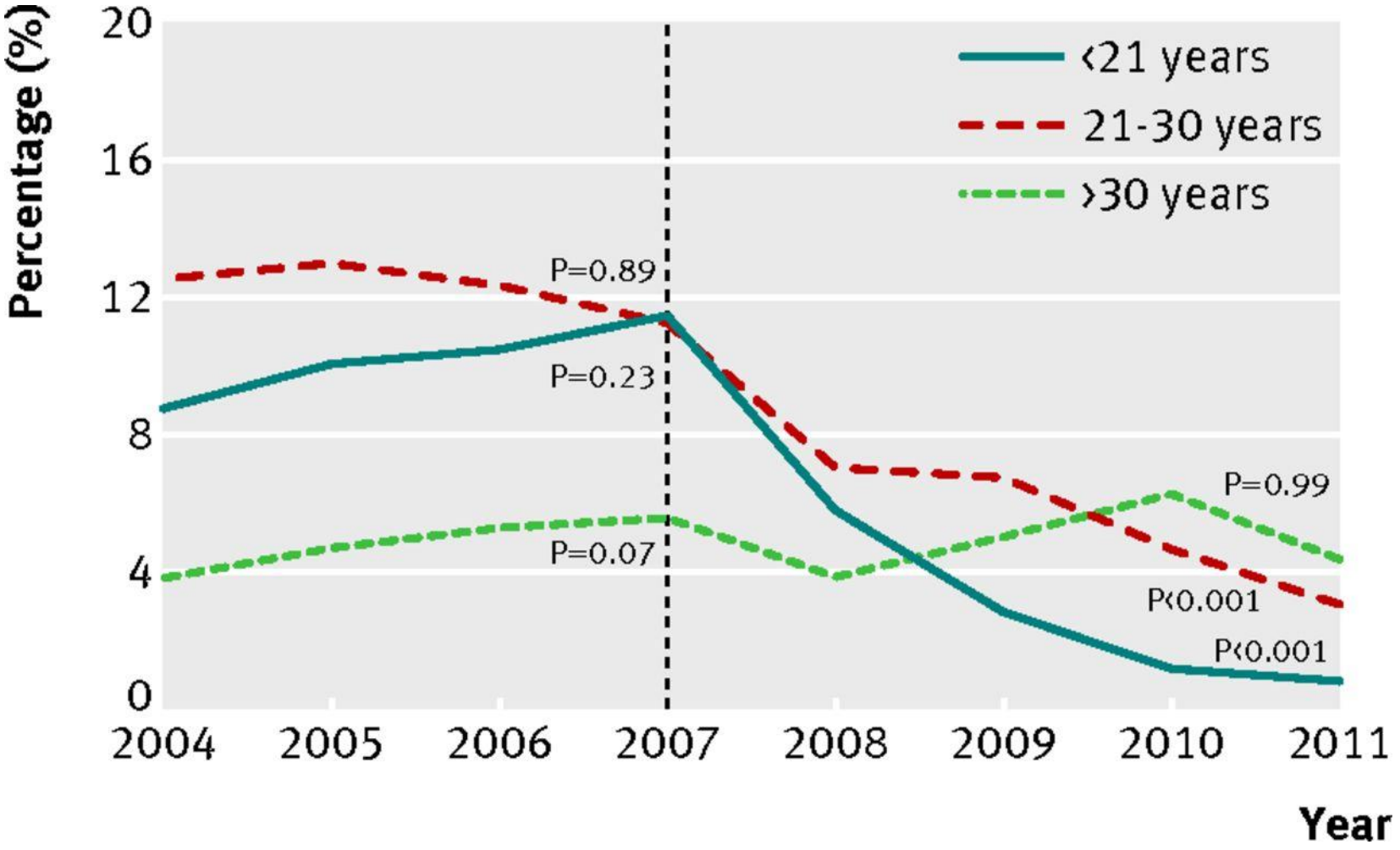
  - 91% school coverage,
  - 87% learner coverage,

Should we vaccinate boys? Who else might benefit?

March 10 - April 23 2014.

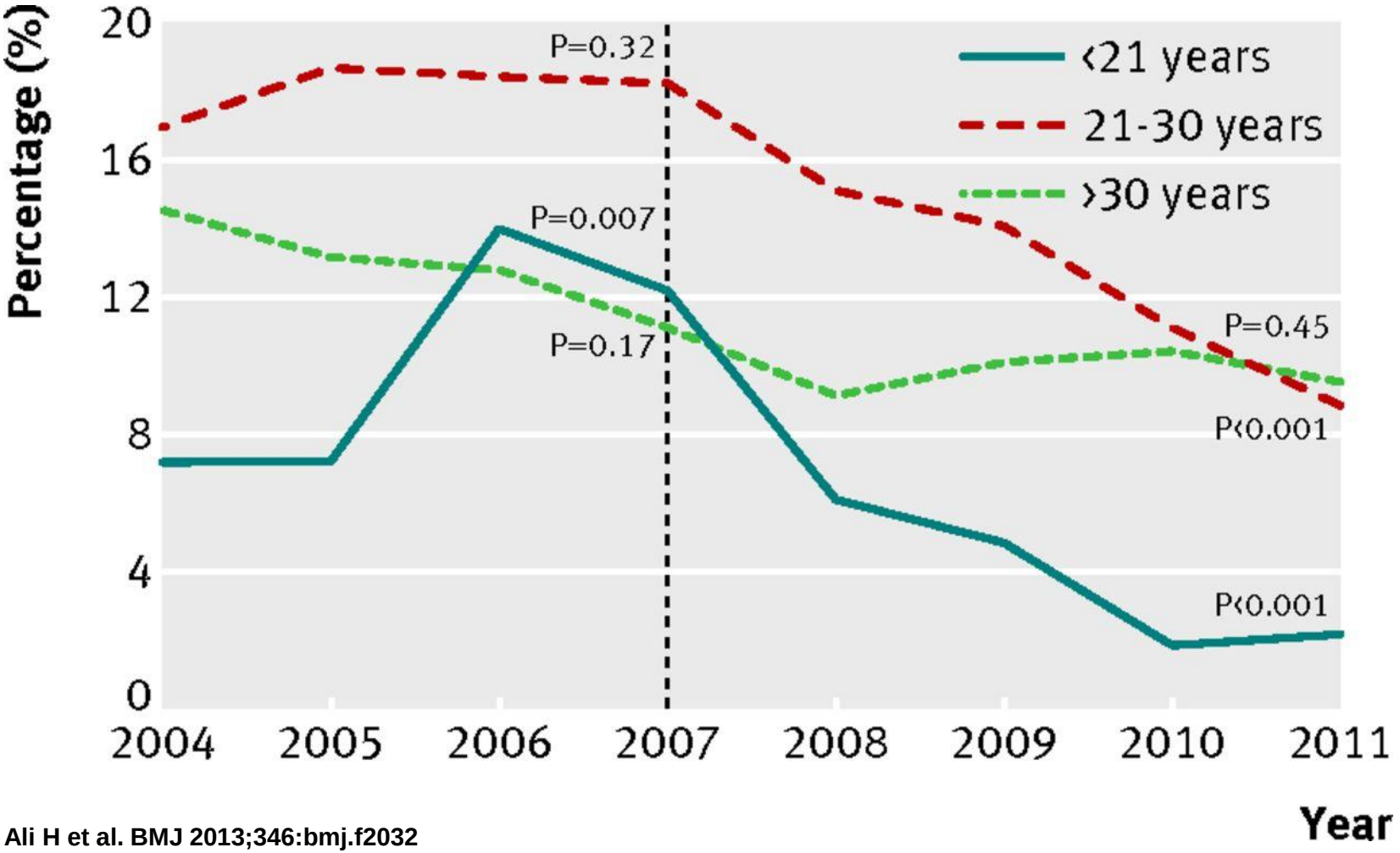
  - No major adverse events

Age-dependent decrease in GW in Australian women after vaccine introduction in 2007



Ali H et al. BMJ 2013;346:bmj.f2032

Herd immunity: declines in incidence GW in heterosexual men after 2007



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No benefits for herd immunity from MSM

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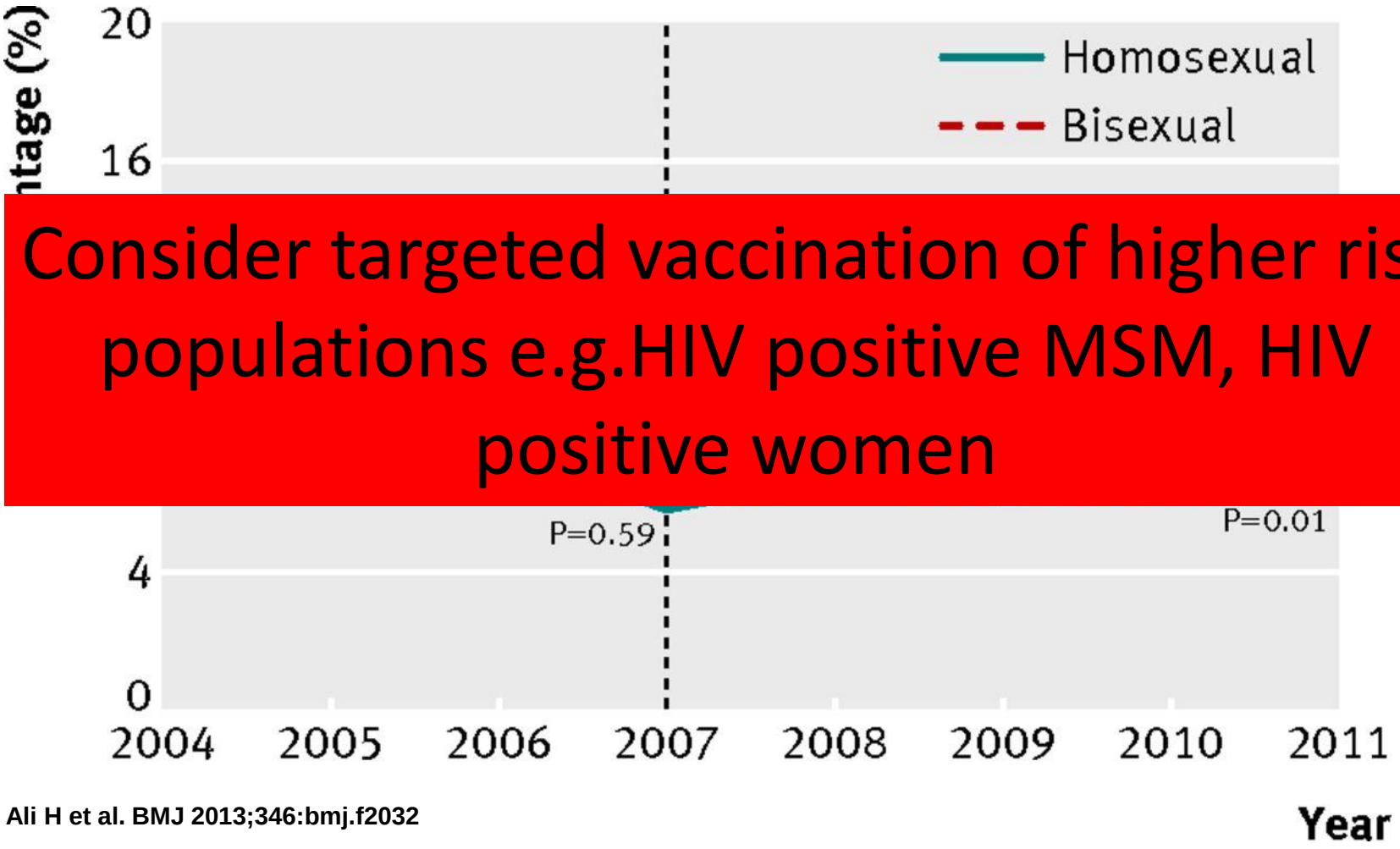
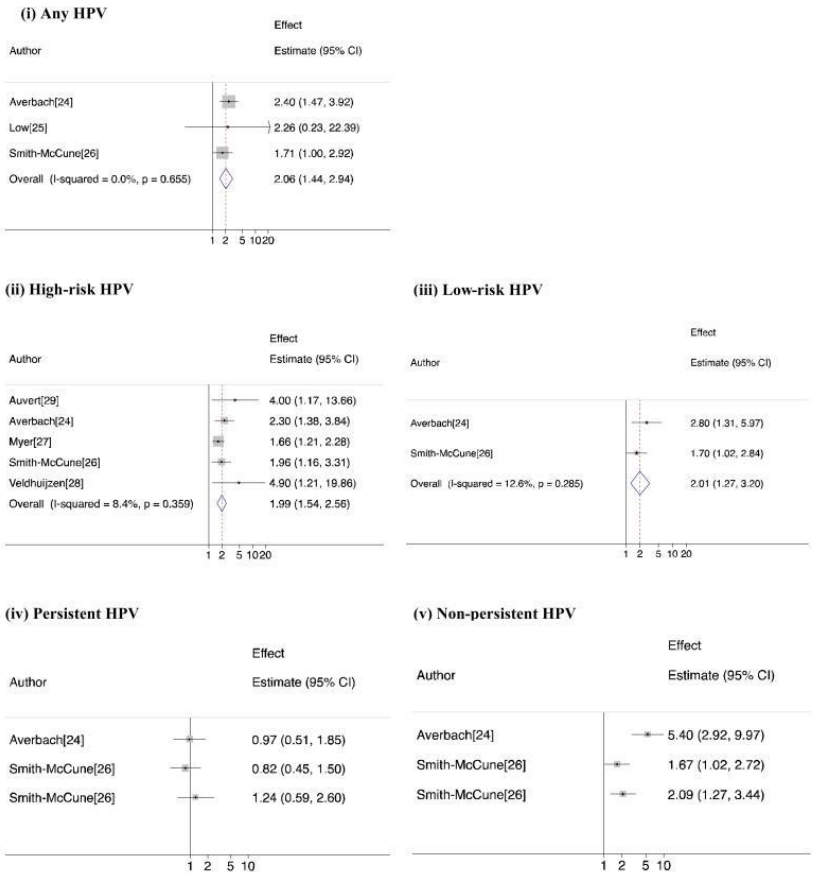


Consider targeted vaccination of higher risk populations e.g.HIV positive MSM, HIV positive women

Ali H et al. BMJ 2013;346:bmj.f2032

Longer term - potential value of vaccination for HIV prevention?



- 8 studies
  - RR Women 2.06
  - Association also in M
  - Similar for HR and LR
  - PAF 21-37%

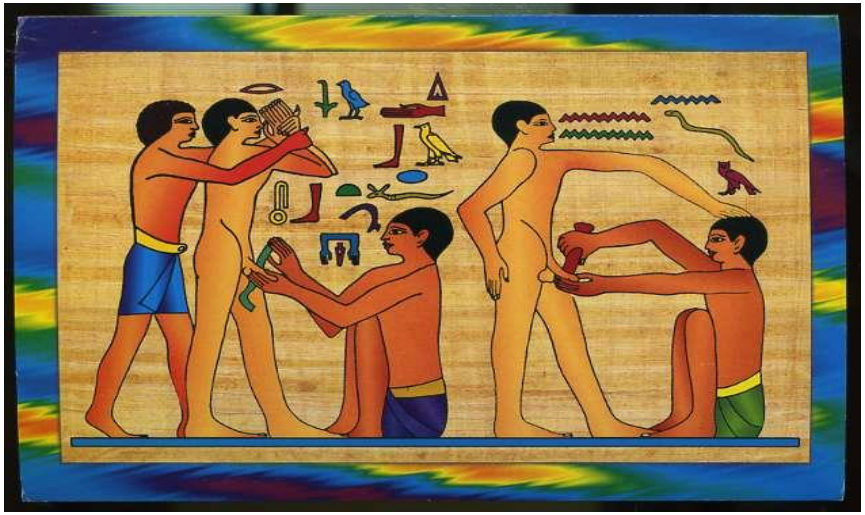
Houlihan, 2012

Progress on future vaccines

HSV-2 vaccines – the need

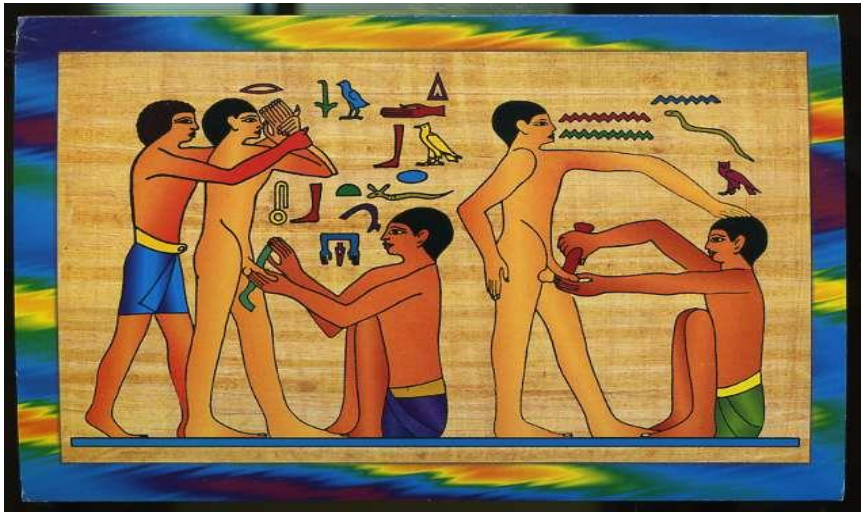
- Significant morbidity
- Risk of vertical transmission
- Risk of HIV acquisition, transmission and disease progression

Limited prevention options with public health impact



Limited prevention options with public health impact

No benefit of HSV-2 treatment on HIV acquisition and transmission



The immune response to HSV-2

- Animal models limited
  - No good models for recurrences or severity

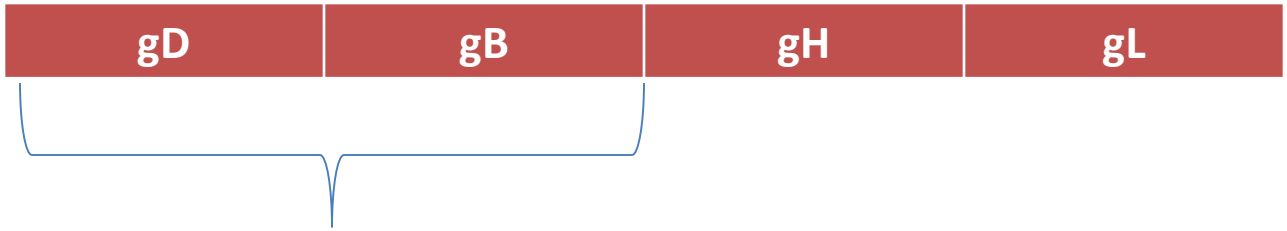
- Human host/virus interactions poorly understood

  ? Control of viral reactivation

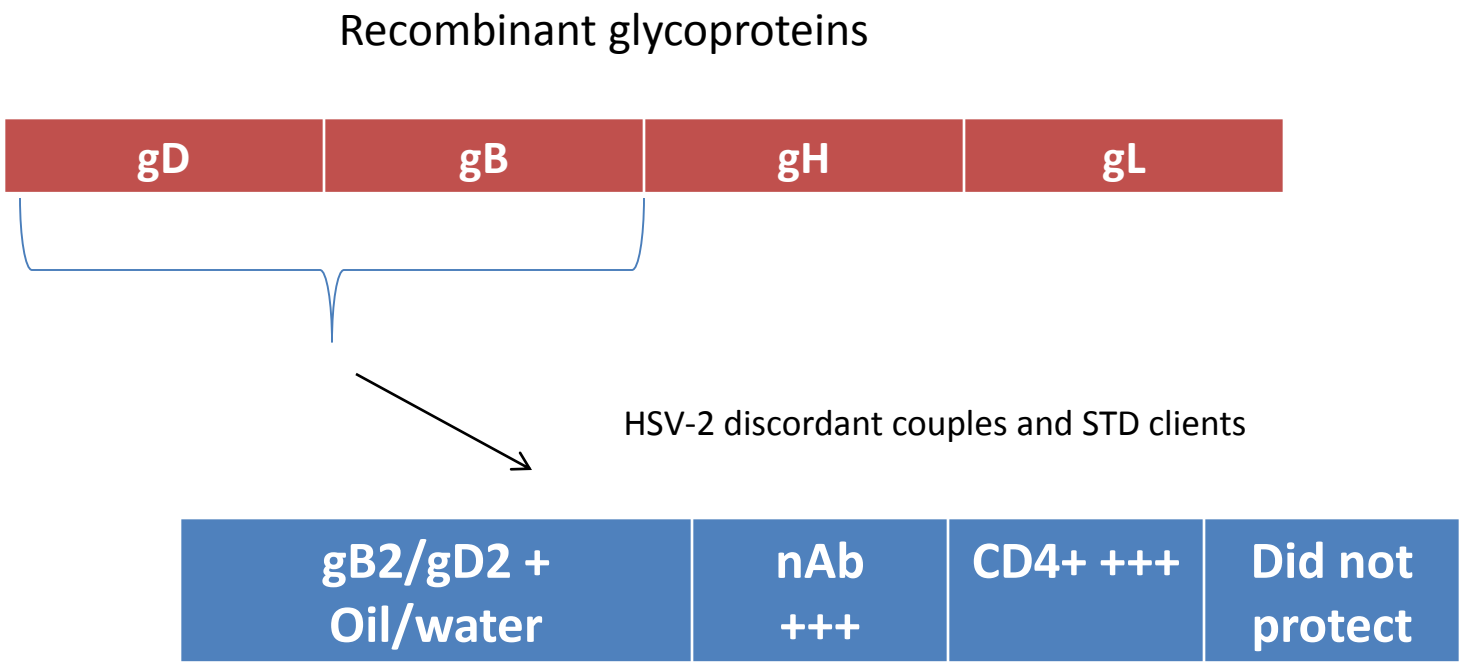
  ? Promotes viral clearance

Early prophylactic vaccine trials

Recombinant glycoproteins

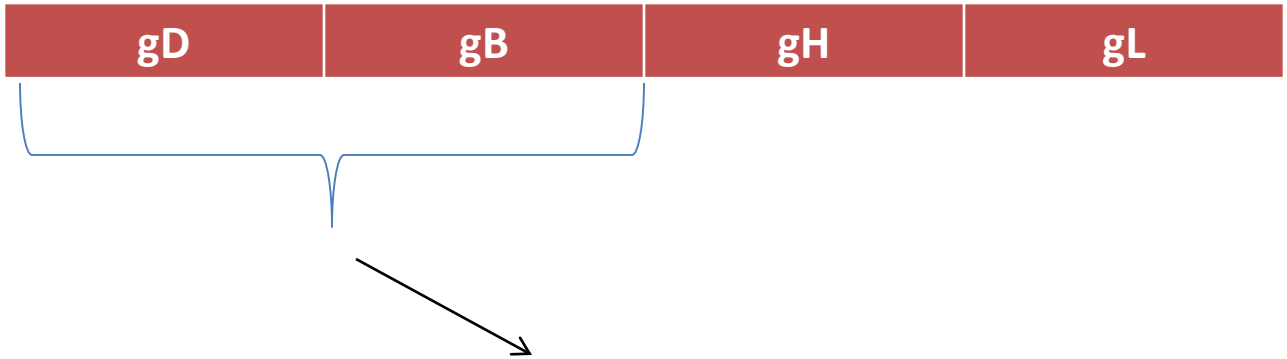


Early prophylactic vaccine trials



Early prophylactic vaccine trials

Recombinant glycoproteins



gB2/gD2 + Oil/water	nAb +++	CD4+ +++	Did not protect
gD2/alum/MPL	nAb +++	CD4+ +++	Protection in sub-group of HSV-1 negative women

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy Results of a Trial of a Herpes Simplex Vaccine

Robert B. Belshe, M.D., Peter A. Leone, M.D., David I. Bernstein, M.D., Anna Wald, M.D., Myron J. Levin, M.D., Jack T. Stapleton, M.D., Iris Gorfinkel, M.D., Rhoda L. Ashley Morrow, Ph.D., Marian G. Ewell, Sc.D., Abbie Stokes-Riner, Ph.D., Gary Dubin, M.D., Thomas C. Heineman, M.D., Ph.D., Joann M. Schulte, D.O., and Carolyn D. Deal, Ph.D., for the Herpevac Trial for Women

- 8323 sexually active HSV-1/HSV-2 negative women
- 3 doses of gD2 vaccine or control

- No protection vs. HSV-2 infection or disease
  - *But significant decrease in HSV-1 infection and genital disease*
  - *Lower antibody titres associated with HSV-1 acquisition*
  - *Magnitude of CD4+ cell response not associated with prevention*
  - *CD8+ responses not detected*

HSV-2 vaccines: lots in the pipeline

Vaccine	Name	Construct	Stage of development
HSV-2 functionally mutated for ICP0 [95]	0ΔNLS	Replication-competent whole virus	Preclinical
HSV-1 functionally mutated for *UL43*, *UL49.5*, *UL55*, *UL56*, and *LAT* expression [96]	HF10	Replication-competent whole virus	Preclinical
HSV2 glycoprotein E deletion mutant [98]	HSV2 gE mutant	Replication-competent whole virus	Preclinical
HSV-2 functionally mutated for γ*34.5*, *UL43.5*, *UL55-56 US10*, *US11*, *US12* [99]	AD472	Replication-competent whole virus	Preclinical
HSV-2 functionally mutated for *UL5*/*UL29* [100–102]	ACAM-529/HSV529	Replication-incompetent whole virus	Phase I
HSV-2 glycoprotein D dominant negative, functionally mutated for ICP0/*UL9* [104]	CJ2-gD2	Replication-incompetent whole virus	Preclinical
HSV-2 functionally mutated for thymidine kinase (TK) [39]		Replication-competent whole virus, followed by topical vaginal application of CXCL9 and CXCL10	Preclinical
HSV-2 functionally mutated for ICP10 [86,113]	ICP10ΔPK	Replication-competent whole virus.	No active program, has been in phase I/II, therapeutic
HSV-2 functionally mutated for ICP47, vhs, γ*34.5*, *US5*, *UL43* [114]	ImmunoVEX^{HSV2}	Replication-competent whole virus	Phase I
Inactivated HSV-2 in MPL/alum [105,106]		Formalin-inactivatedvirus administered after DNA boost	Preclinical
HSV-1 glycoprotein B [107]		Lentiviral vector	Preclinical
Recombinant secreted HSV-1 glycoprotein B [109]		Intranasal immunization with immunogen in non-ionic surfactant vesicles	Preclinical
Recombinant HSV-2 gD [45]		Recombinant gD2 with IC31 adjuvant	Preclinical
Recombinant HSV-2 gD [110]		gD2 DNA prime followed by intranasal protein boost (liposomal encapsulation)	Preclinical
gD2/*UL46*/*UL47* DNA [108]	gD2-Vaxfectin	Plasmid gD2/*UL46*/*UL47*polyvalent DNA with cationic lipid adjuvant	Phase I therapeutic announced
Modified gD2 DNA [115]		Plasmid gD2 fused to ubiquitin mixed with codon-optimized non-linked gD2	Phase I
32 unique 35-mer HSV-2 peptides [112]	HerpV	Synthetic peptides, multivalent with heat shock protein adjuvant	Phase II, therapeutic
gD2 and ICP4 [66]	GEN-003/MM2	Recombinant bivalent proteins with Iscomatrix adjuvant	Phase 1b/II, therapeutic

An HSV-2 vaccine has the potential to prevent HIV infection

- Potential to reduce HIV infection, especially in young women
  - Incidence in young women
- Future vaccine trials likely to be conducted in settings like South Africa
  - High prevalence and incidence
  - Need populations that are HSV-1 positive/negative
  - Need to assess potential of different strain effects
- Future trials will focus on demonstrating effects by gender, on seroconversion and shedding
  - Even low prevention effect but high control of reactivation may have benefits for transmission and impact on HIV

BBC NEWS

MAGAZINE

24 April 2013 Last updated at 23:45 GMT

Koala chlamydia: The STD threatening an Australian icon

- Significant technical difficulties with the development of vaccines for CT, NG, TV and TP
- Some progress with animal studies

Development of vaccines against STIs – importance for HIV

- Decade of vaccines
  - WHO global commitment to fund the development of vaccines for neglected STIs
- Significant benefits for maternal, child and reproductive health
- Existing vaccines already demonstrate benefits for HIV positive populations
- Lessons learned from delivery are critical for the eventual development of an HIV vaccine
- Future vaccines may be an important components of a package for HIV prevention