National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Informing HPV vaccination strategy about target groups: girls-only, gender-neutral, catch-up and selective adult vaccination

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Disclosure belangen spreker

(potentiële) belangenverstrengeling	**Geen**
Voor bijeenkomst mogelijk relevante relaties met bedrijven	**Niet van toepassing**
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	• • • •

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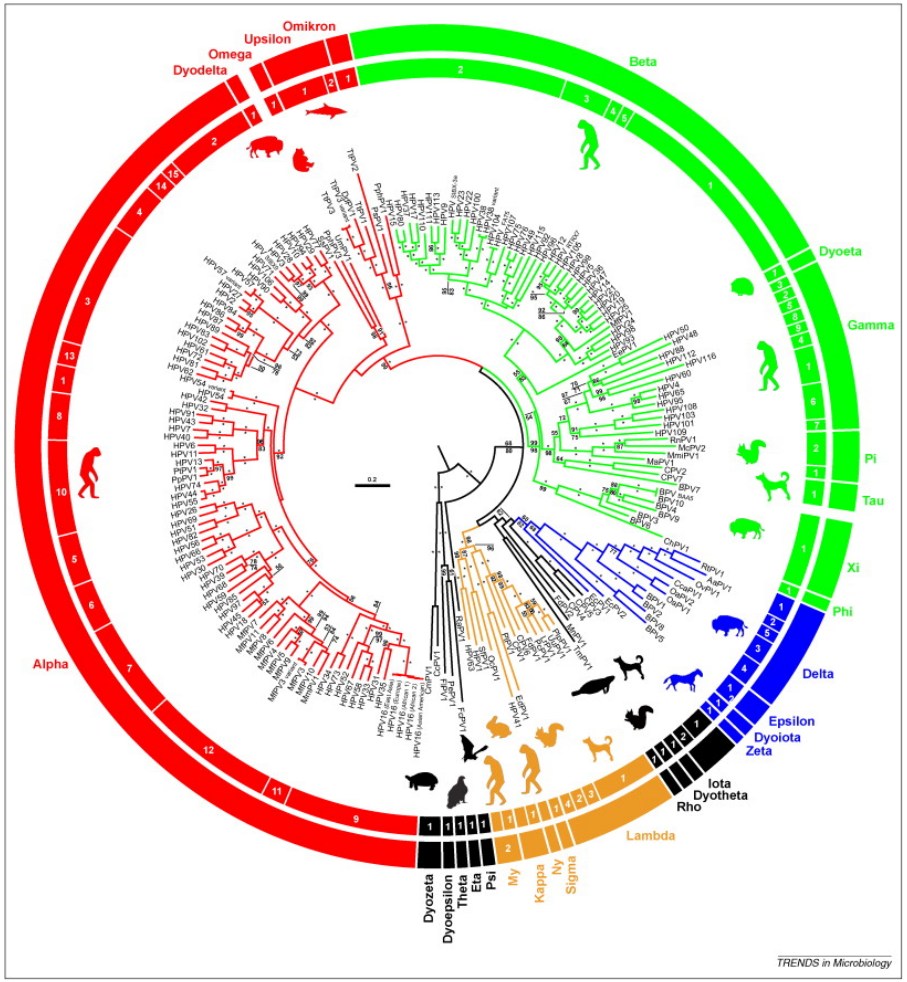
Outline

1. Some HPV background
2. Girls-only vaccination revisited
3. Improving HPV prevention?
4. Current outlook

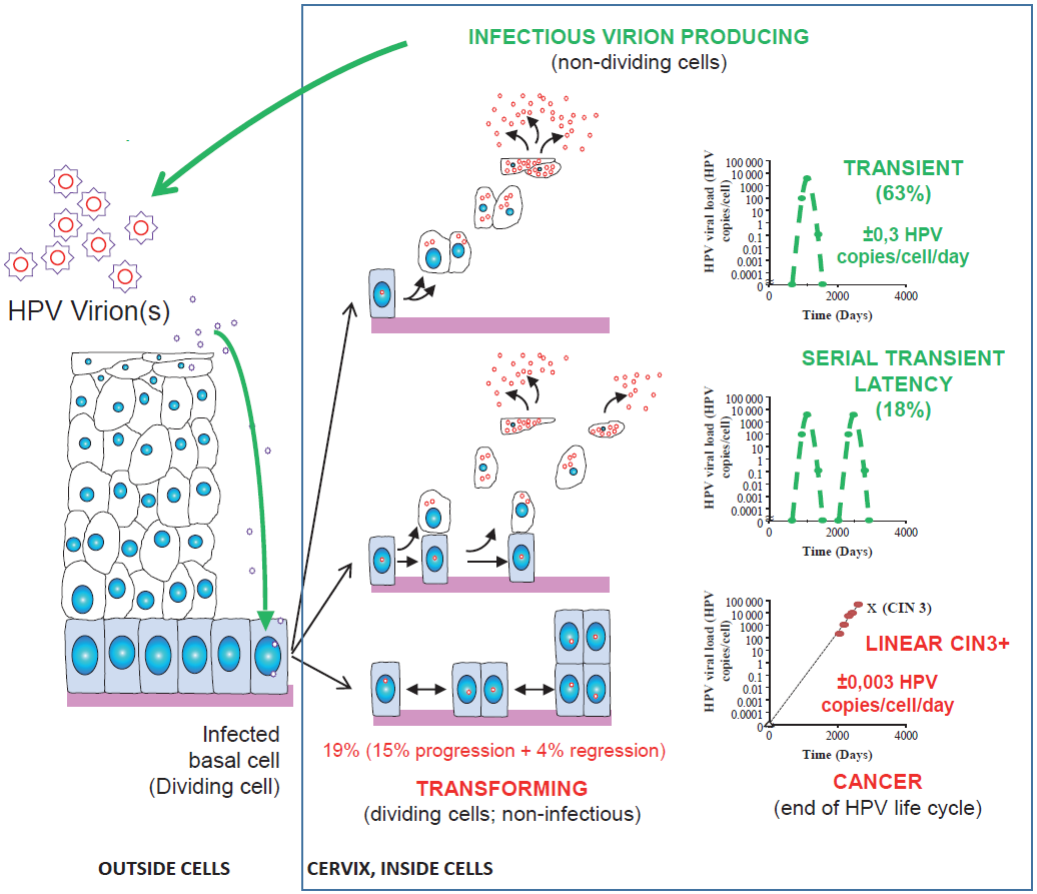
Human papillomavirus (HPV)

- Papillomaviridae: small skin viruses
  - ~8 kbp ds DNA circular genome
- Cutaneous vs mucosal tropism
  - Virus ≠ host-species phylogeny
- High diversity in mammalian hosts
  - >170 HPV types identified
- alpha-genus oncogenic in humans
  - 15 HPV types “high-risk”
  - Transmitted through sexual contact



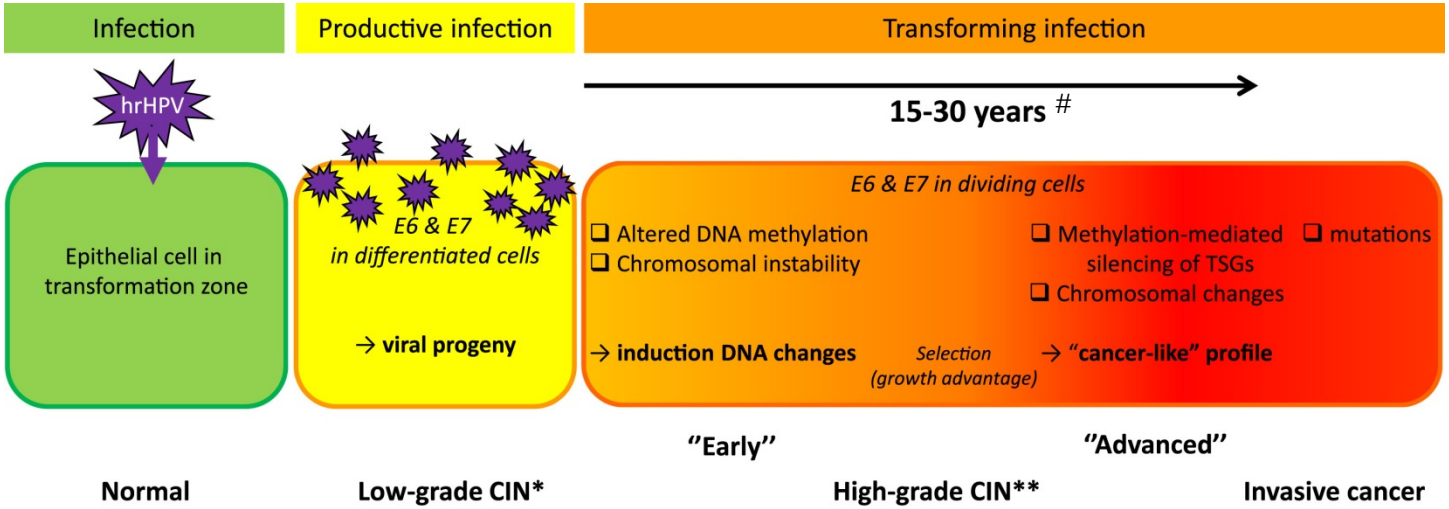
IG Bravo et al. (2010), *Trends in Microbiology*

HPV induced processes: infectious virion producing pathway in non-dividing cells and the clonal transforming pathway in dividing cells



Depuydt et al. (2016),
Facts Views Vis Obgyn

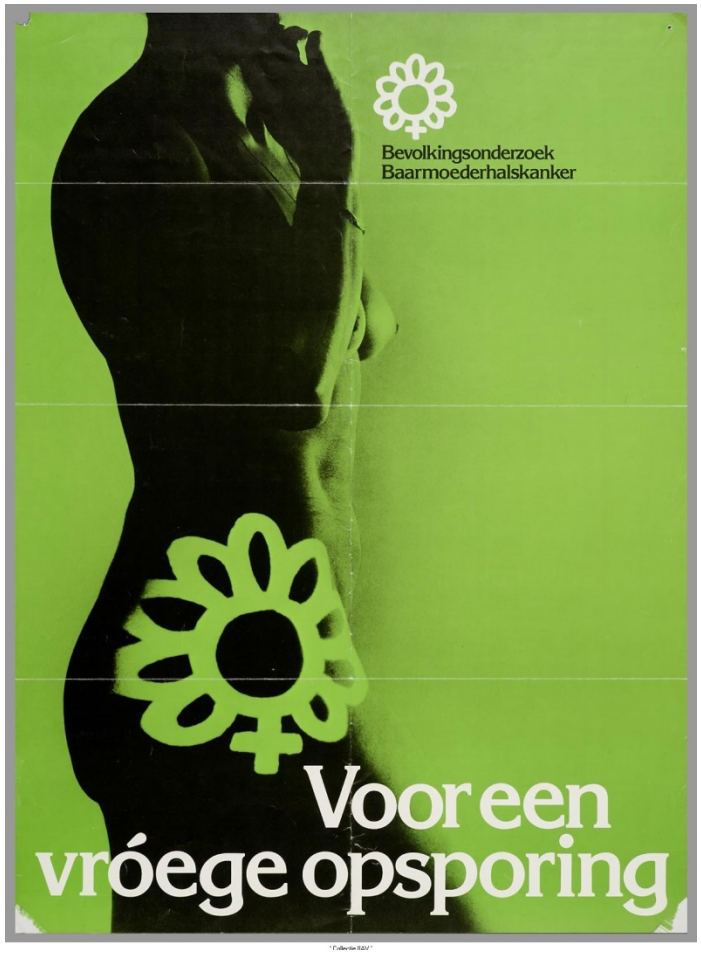
Molecular events leading to HPV-induced (high-grade) neoplasia, i.e. the abnormal proliferation of benign or malignant cells

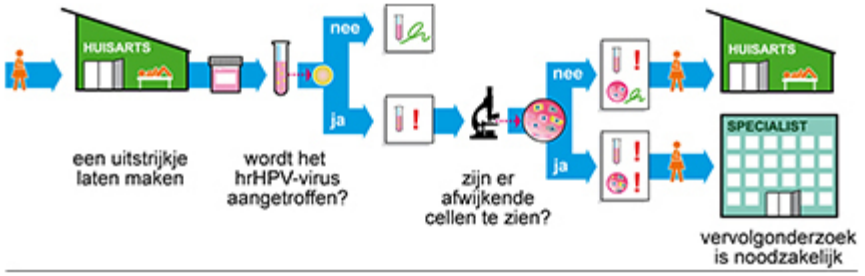


* CIN1 & subset CIN2: Productive CIN
** Subset CIN2 & CIN3: Transforming CIN

Wilting & Steenbergen (2016), *Papillomavirus Res*
Vink et al. (2013), *Am J Epidemiol*

Cervical screening relies on diagnosis and treatment of high-grade CIN

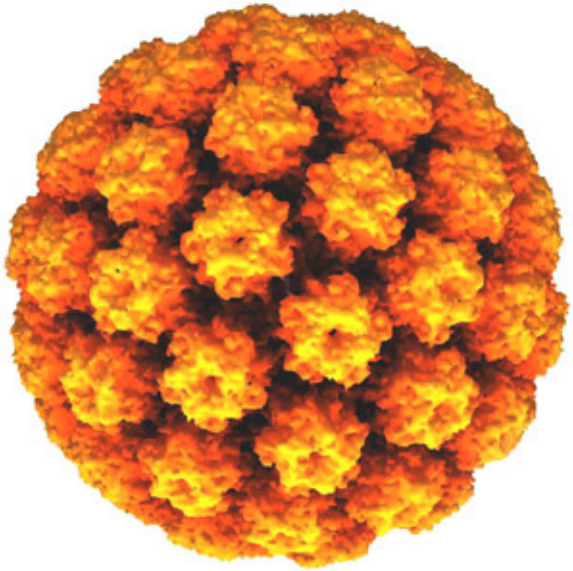




Restructured HPV-based screening program

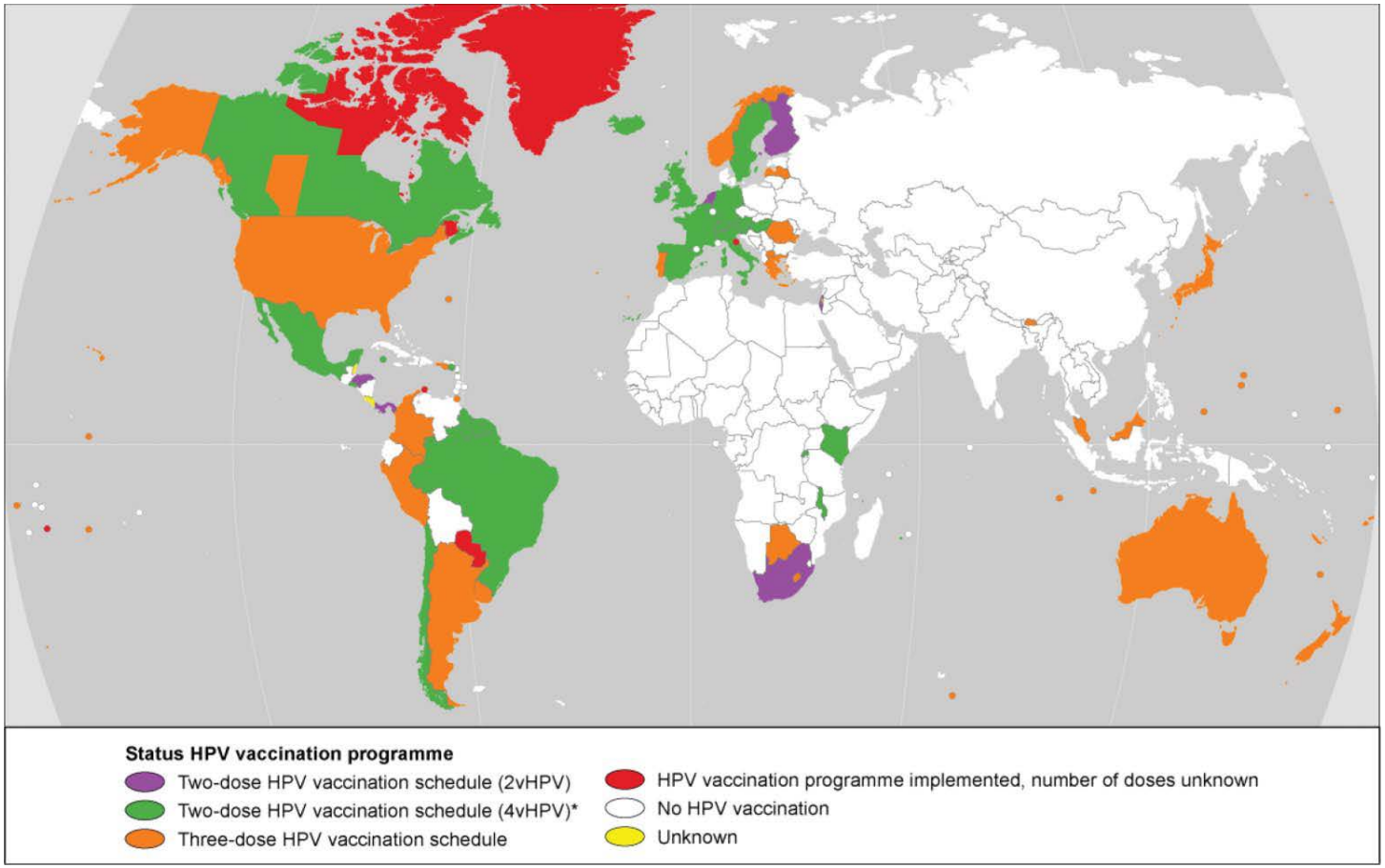
HPV vaccines

- HPV-VLP vaccines available since 2006
  - >95% efficacy if given before sexual debut
- Three vaccines; all target HPV16 and -18
  - associated with majority of (cervical) cancers
  - bi- (Cervarix), quadri- (Gardasil) and nonavalent
- Since 2014, the bi- and quadrivalent vaccines are licensed in a reduced two-dose schedule
- Strong cross-protection reported for Cervarix



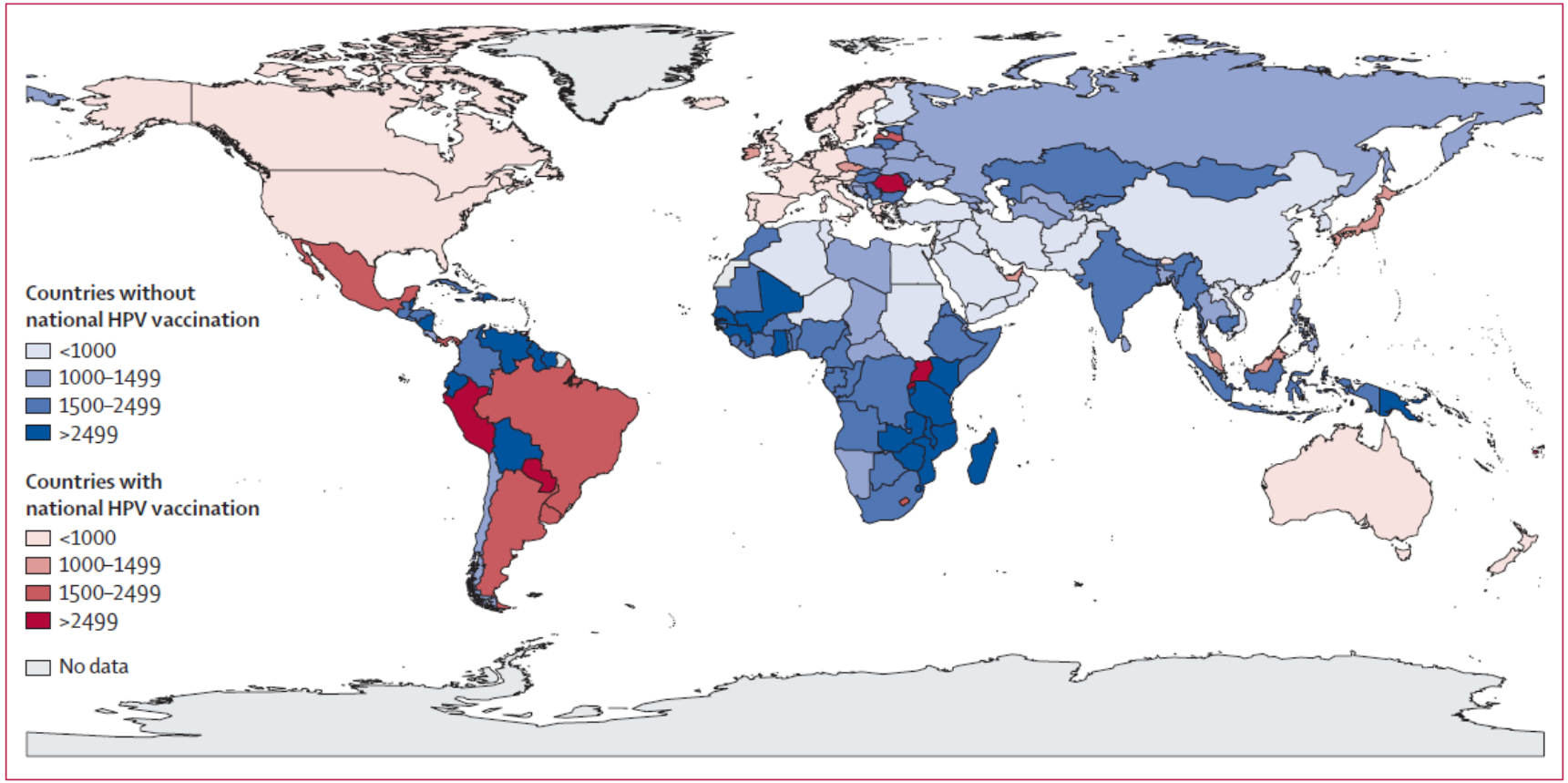
A VLP (virus-like particle) looks exactly like the virus but contains no viral DNA

A decade since the first national introduction of HPV vaccination in Australia, we have seen vaccine introductions in over 50 countries…



Donken et al. (2016), *Hum Vaccin Immunother*

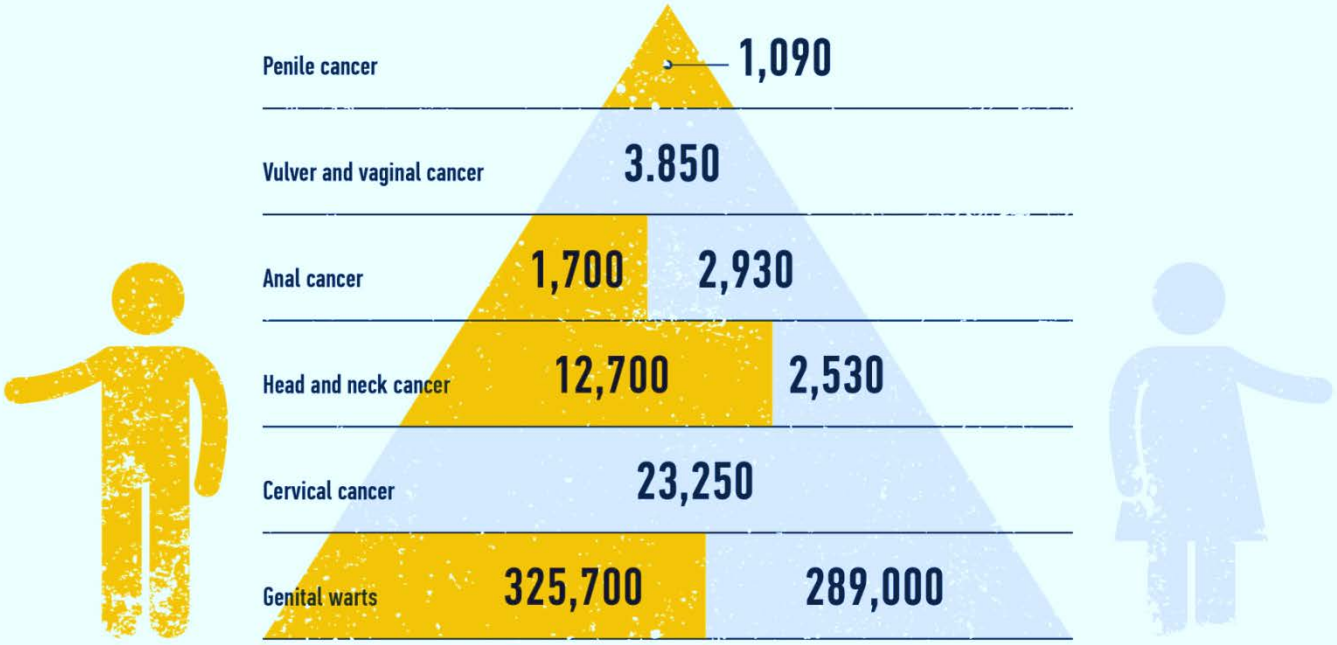
… but introduction in settings with highest burden is lagging behind

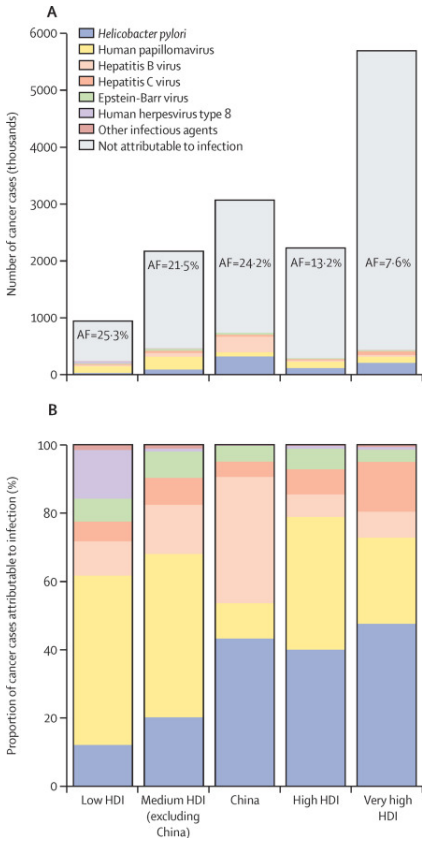


Estimated no. of HPV16/18-related cervical cancers per 100 000 girls

Jit et al. (2014), *Lancet Global Health*

Of 14 million new cancer cases worldwide in 2012, 640 thousand (4.6%) were attributable to HPV, of which 570 thousand (89%) in women

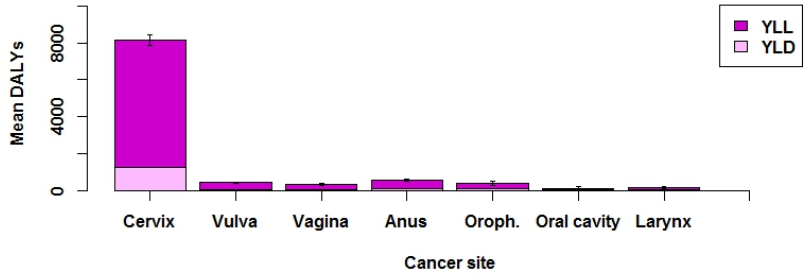




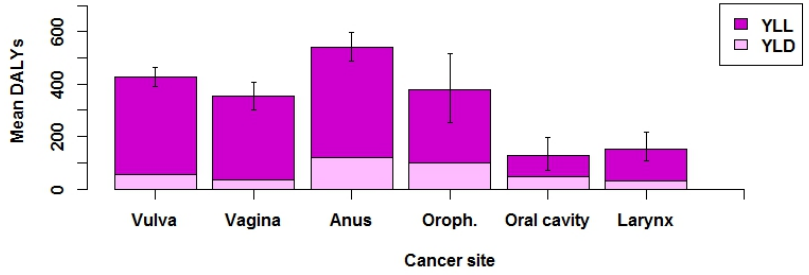
Plummer et al. (2016), *Lancet Global Health*

Disease burden of HPV infection in the Netherlands, 2011-2014: approximately 60% due to cervical disease, 25% in males

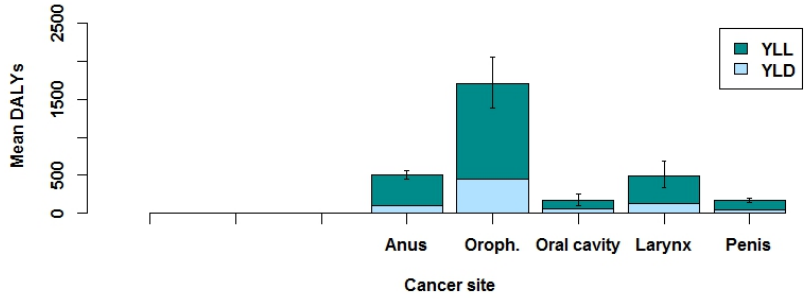
Females



Females excl. cervix



Males



Infectious disease	Est. average annual burden
HPV (2011-2014)	**13,795**
Pneumococcal disease*	9,444
Influenza*	8,670
HIV*	6,987
HPV excl. cervix	**5,627**
Legionellosis*	4,283
Toxoplasmosis*	3,593
Chlamydia*	3,551
HPV excl. females	**3,345**

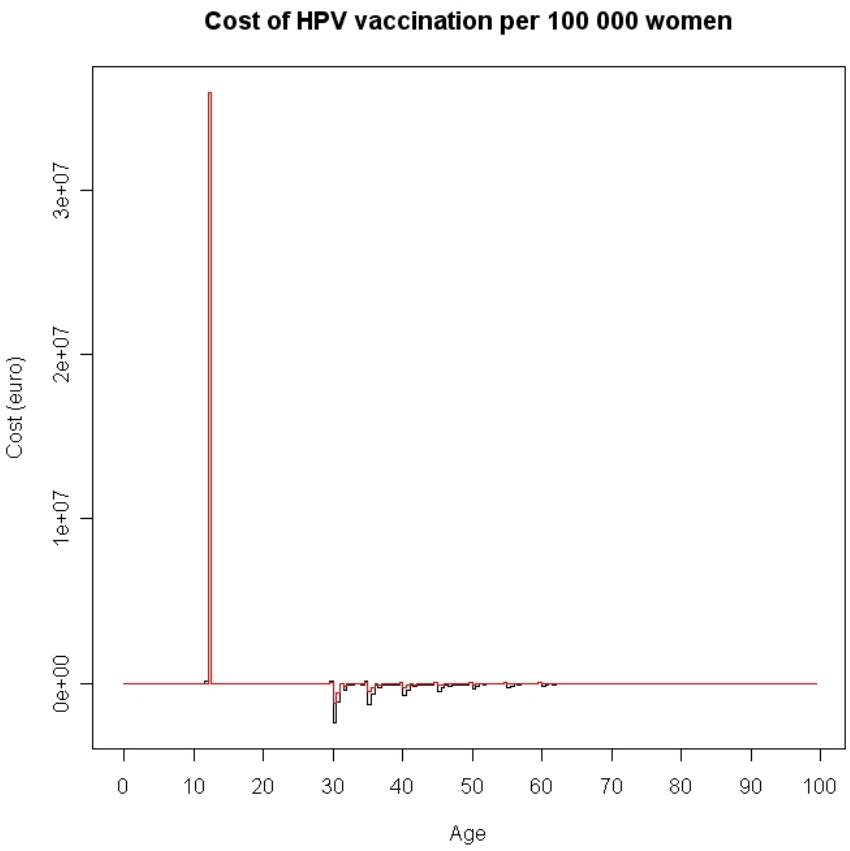
* est. average annual burden 2007–2011

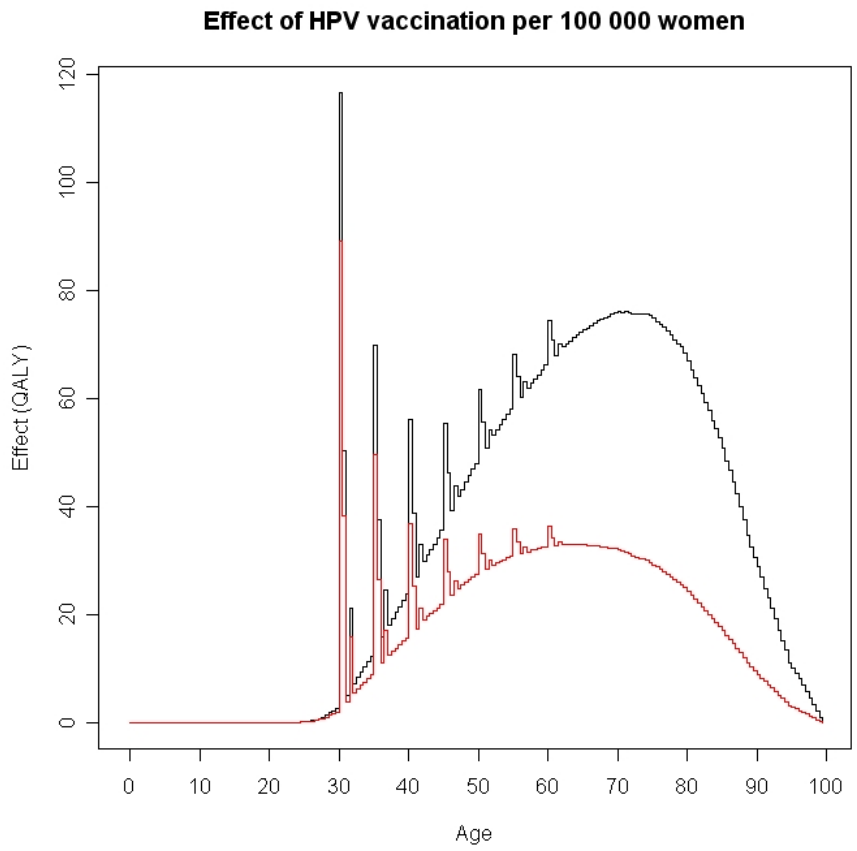
Van Lier et al. (2016), *PLoS One*

McDonald et al. (2017), *Cancer Causes Control*

Cost-effectiveness of cervical cancer prevention by vaccination @ 12y

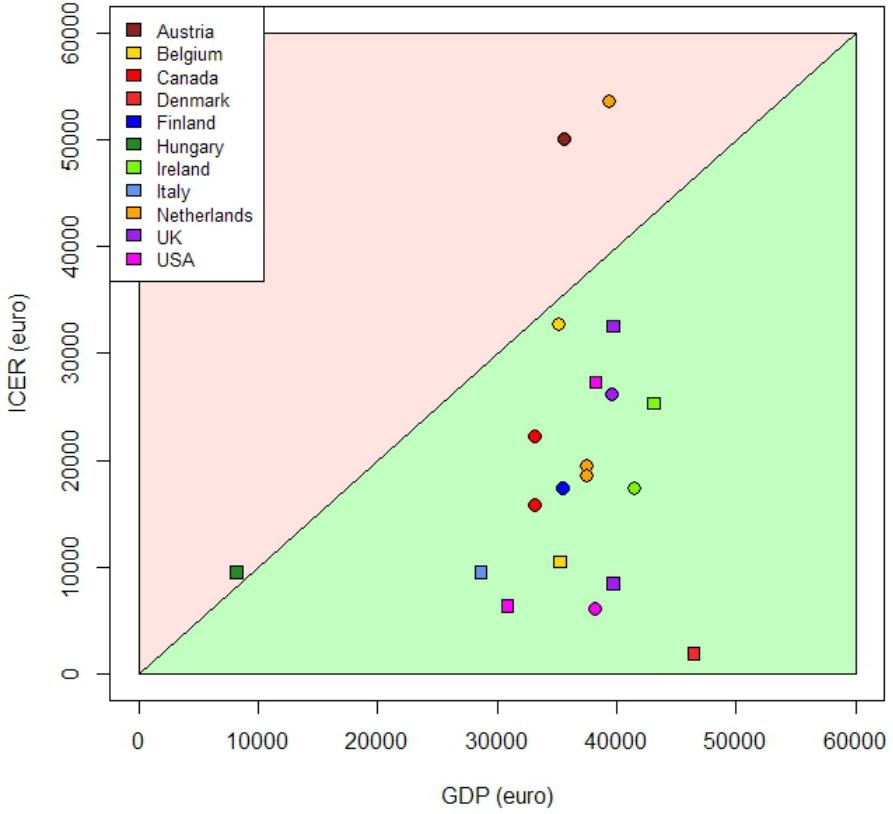
'He who seeks for gain, must be at some expense'

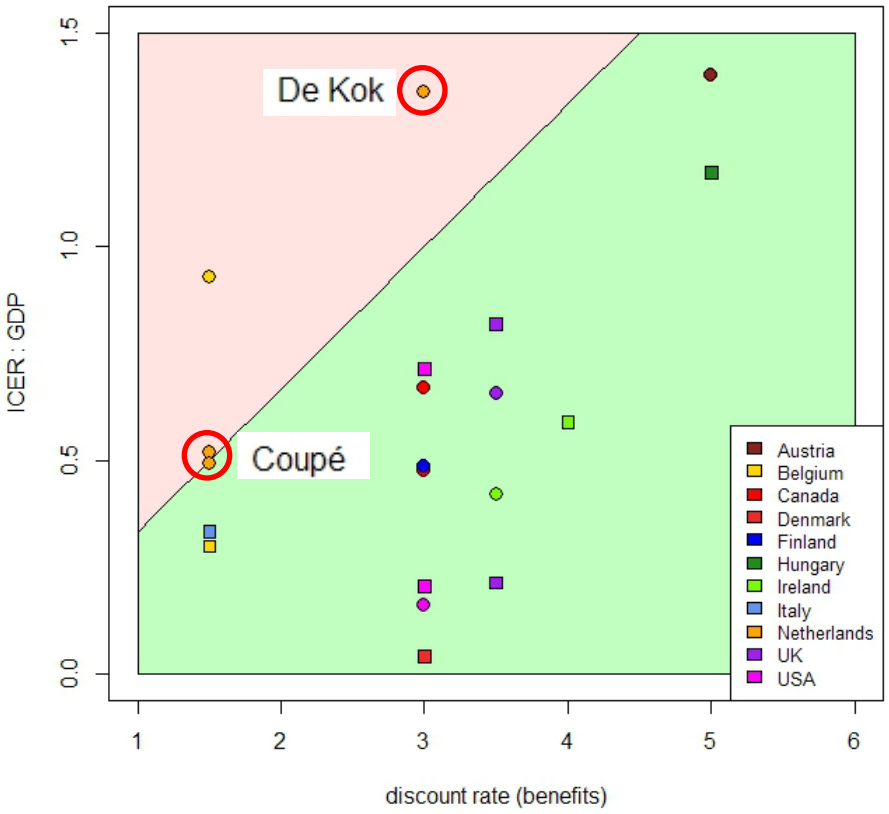




Back to the future: introducing girls-only programs in EU, North America

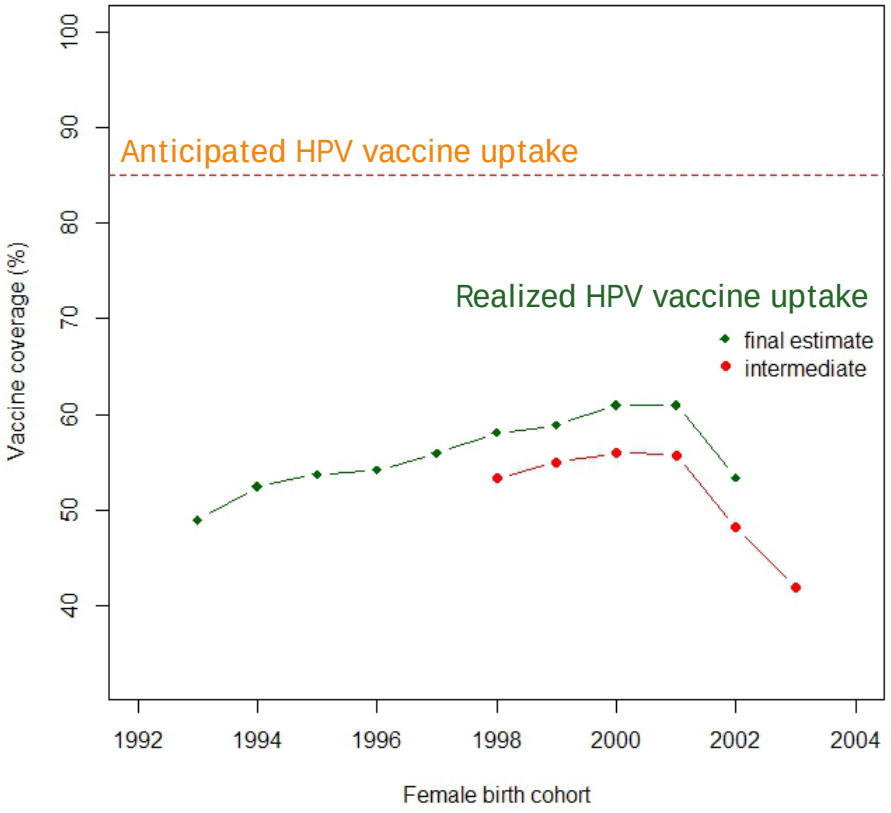
Seto et al. (2012), *Drugs* [Systematic Review, studies published 2007-2010]

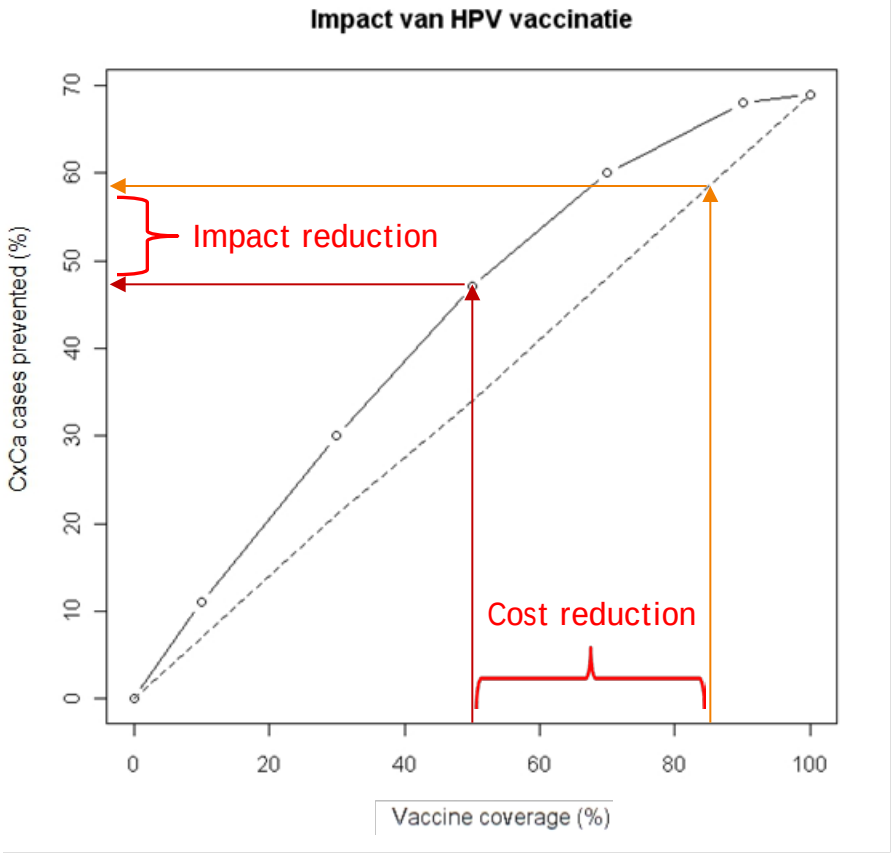




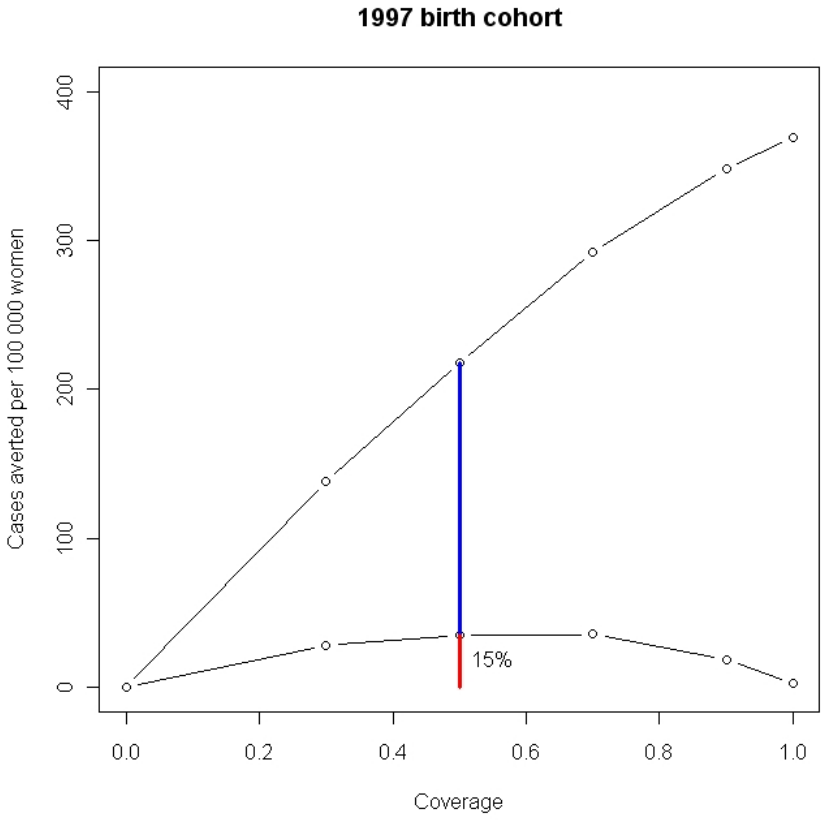
Girls-only vaccination in the Netherlands; the benefit of hindsight pt.1

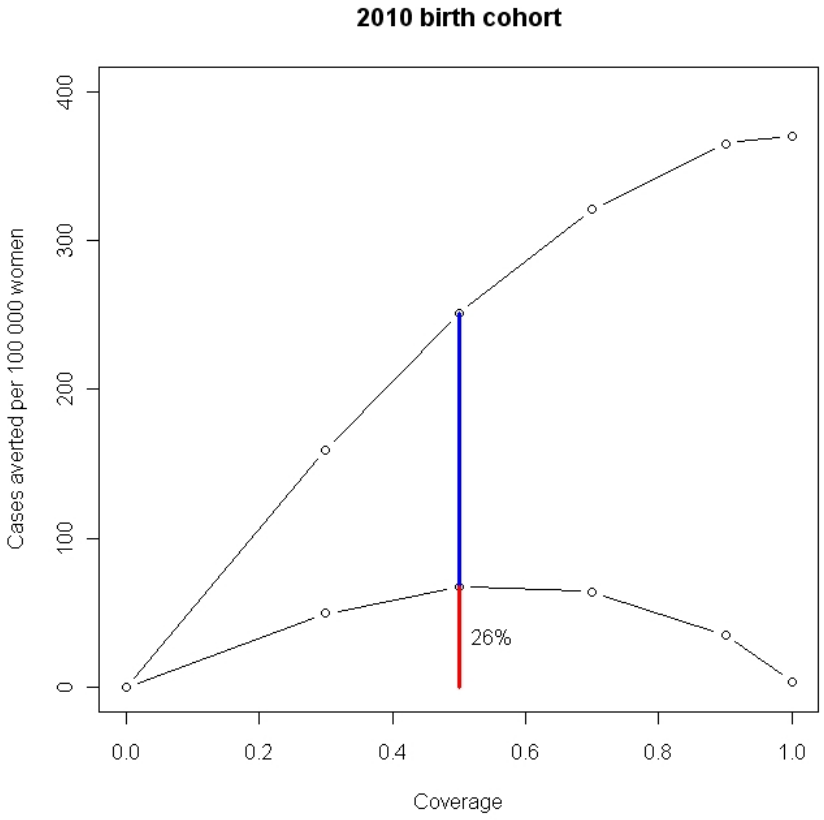
Anticipated and realized participation (and projected impact) of HPV vaccination





Indirect effects of HPV vaccination on cervical cancer prevention: at current vaccine uptake in girls, 1 in 4 cases averted is in non-vaccinated women

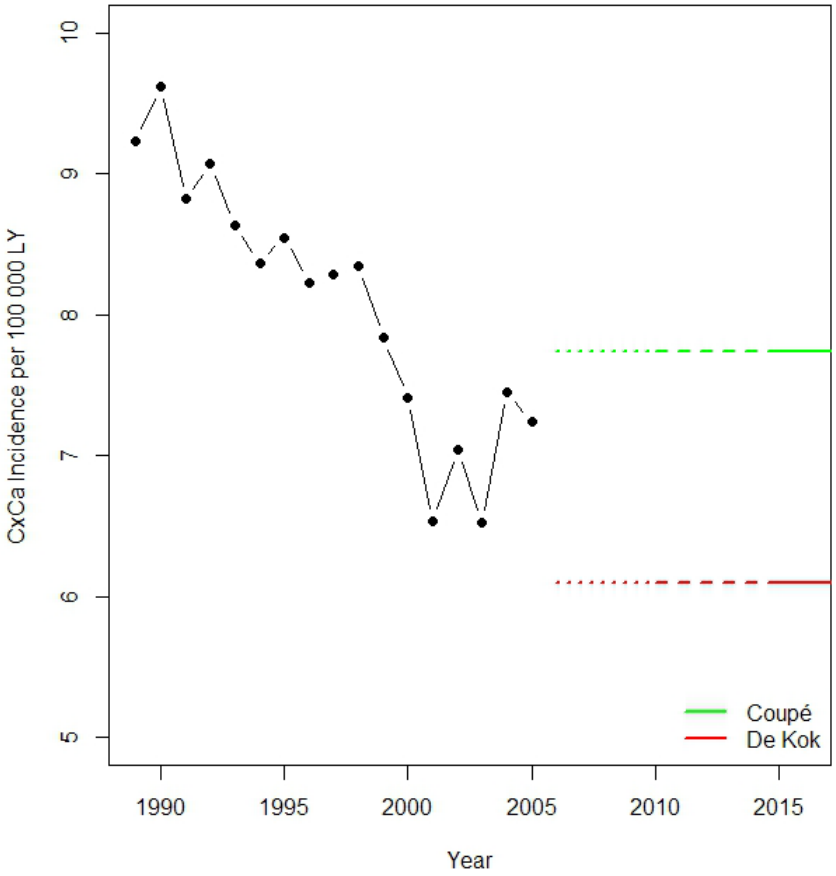


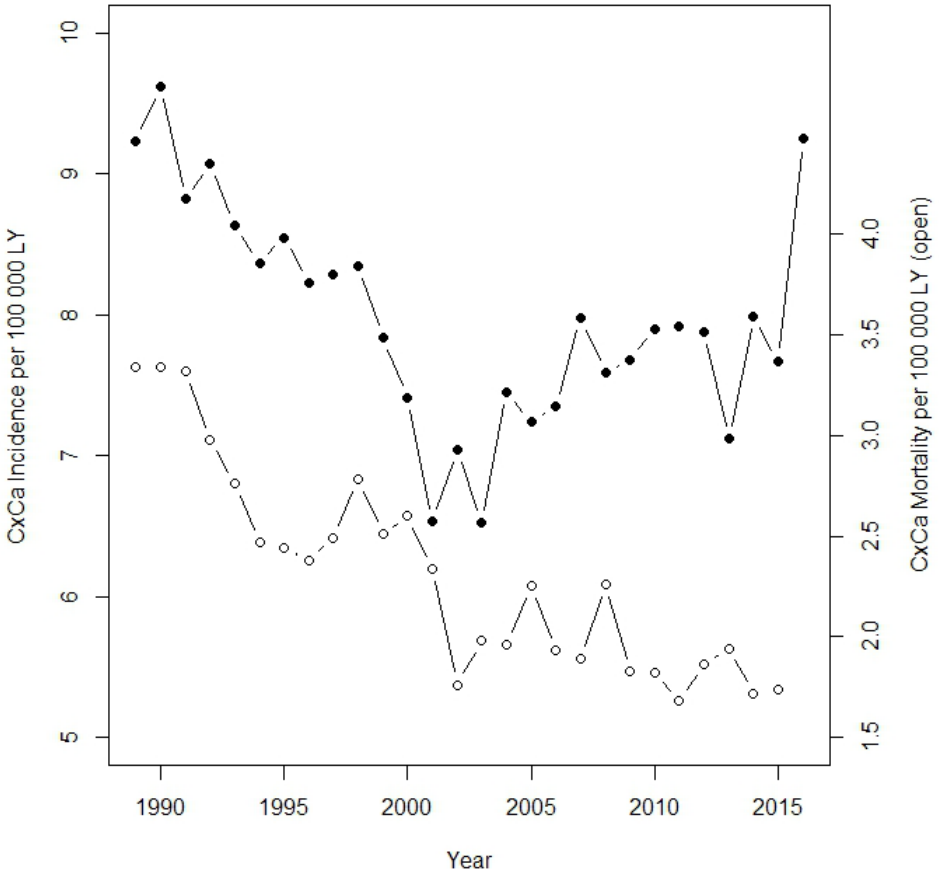


Bogaards et al. (2011), *Epidemiology*

Girls-only vaccination in the Netherlands; the benefit of hindsight pt.2

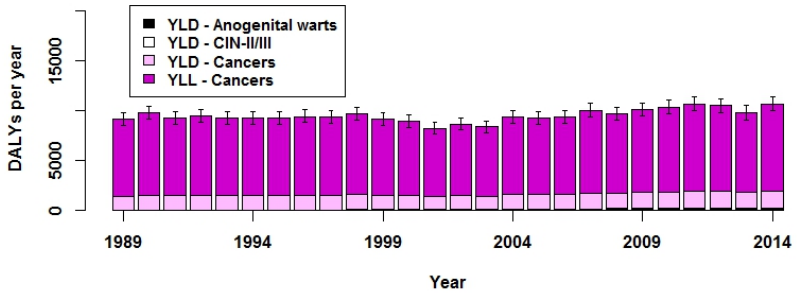
Input to Coupé et al. (2009), *Int J Cancer*; De Kok et al. (2009), *J Natl Cancer Inst*



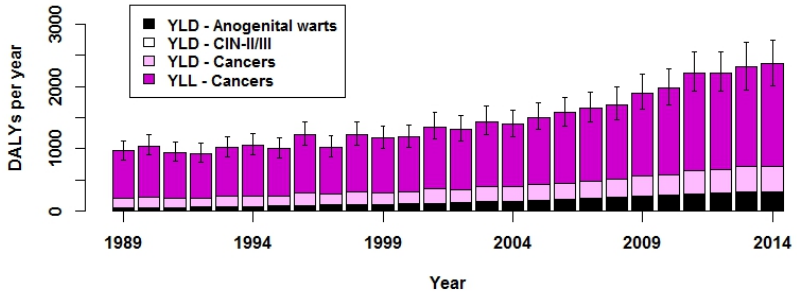


Trends in HPV-related disease burden in the Netherlands, 1989-2014: the gap between females and males is diminishing

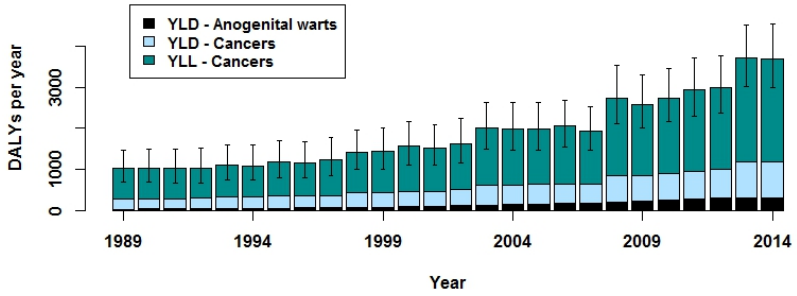
Females

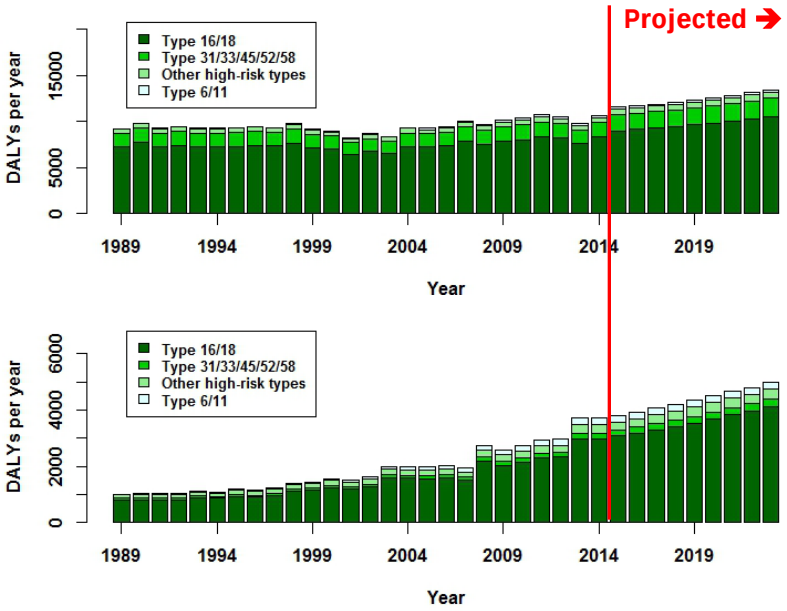


Females excl. cervix



Males

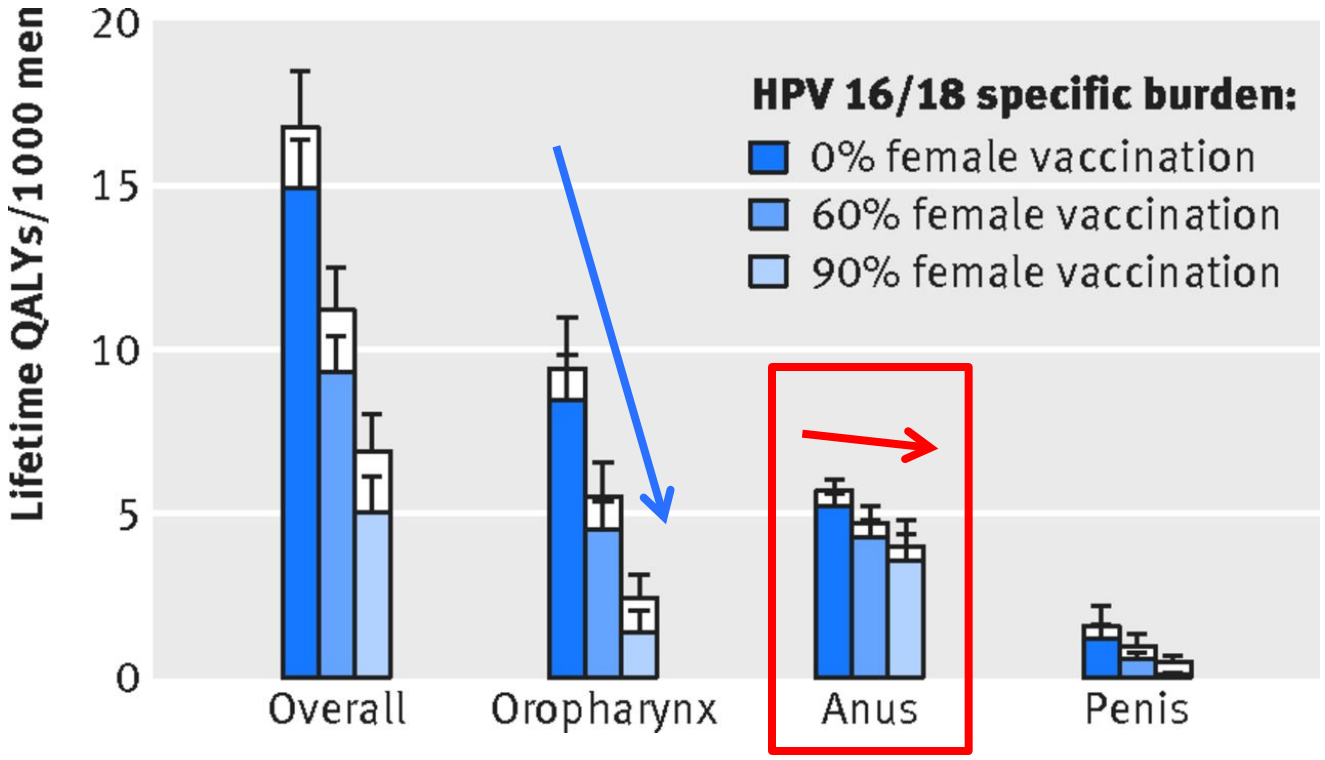




McDonald et al. (2017), *Cancer Causes Control*

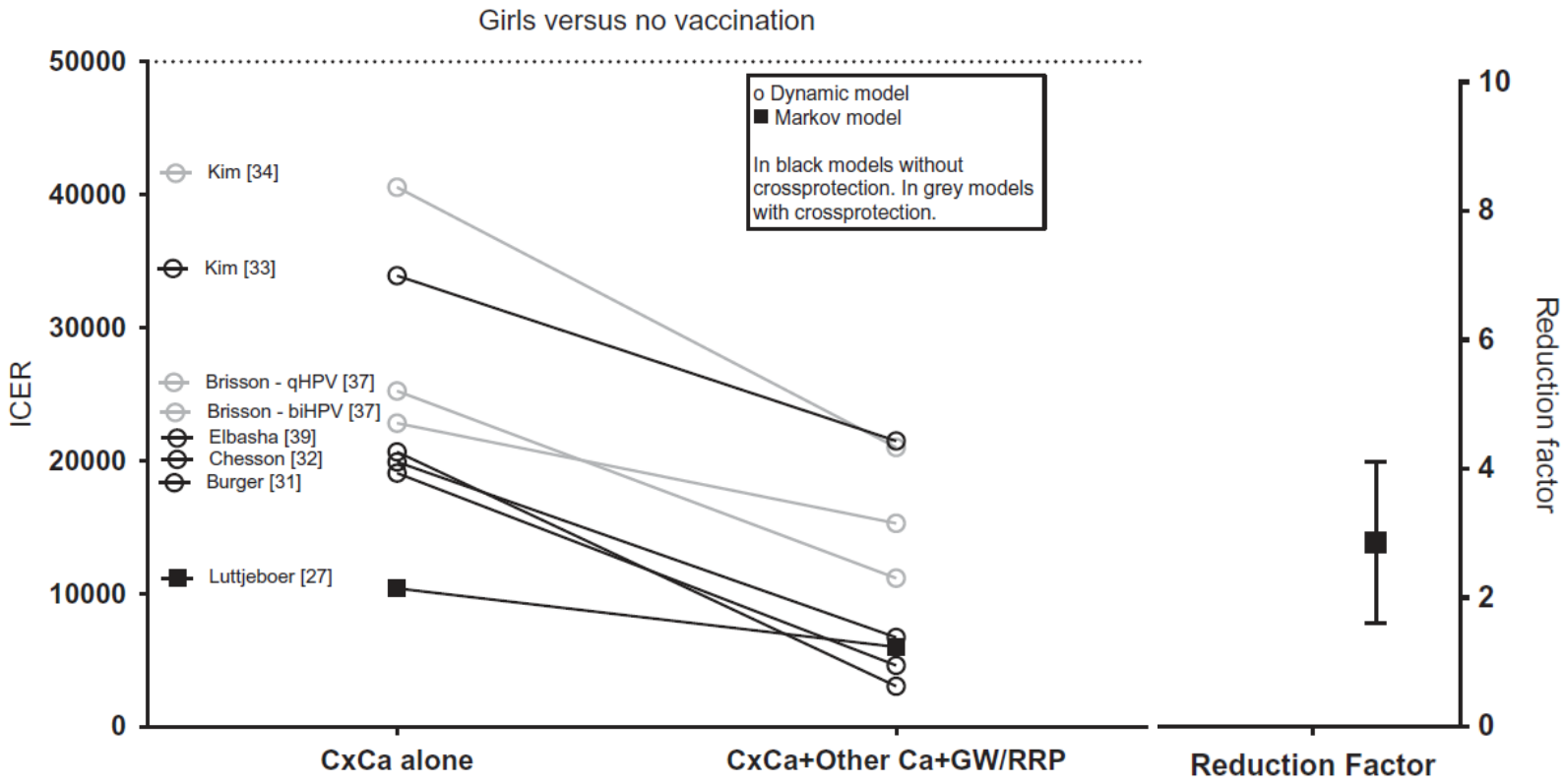
Girls-only vaccination in the Netherlands; the benefit of hindsight pt.3

Long-term impact on HPV16/18-related cancer burden in males



Bogaards et al. (2015), *BMJ*

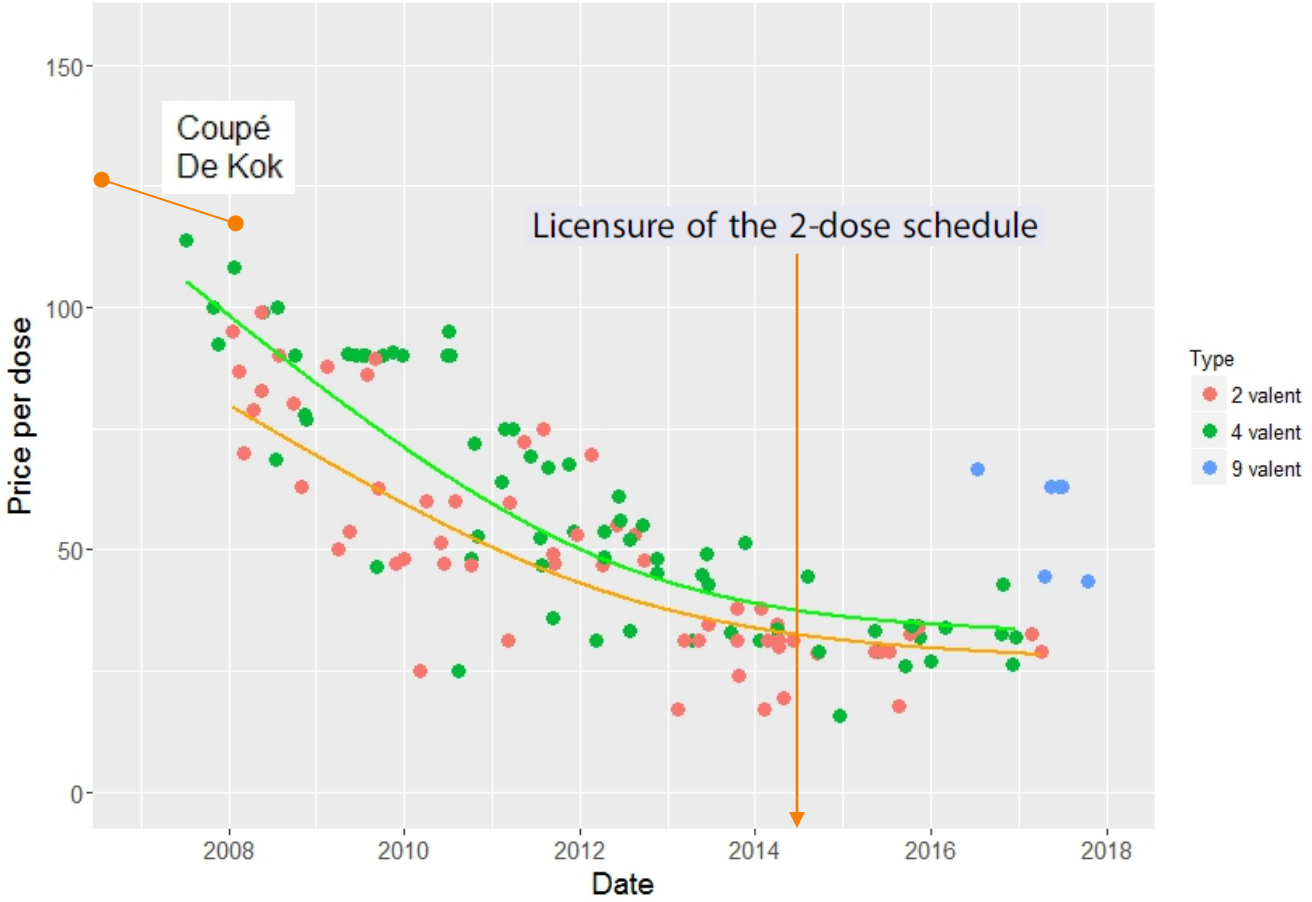
Including non-cervical diseases in economic evaluations of HPV vaccination makes girls-only vaccination about 3 times more favorable



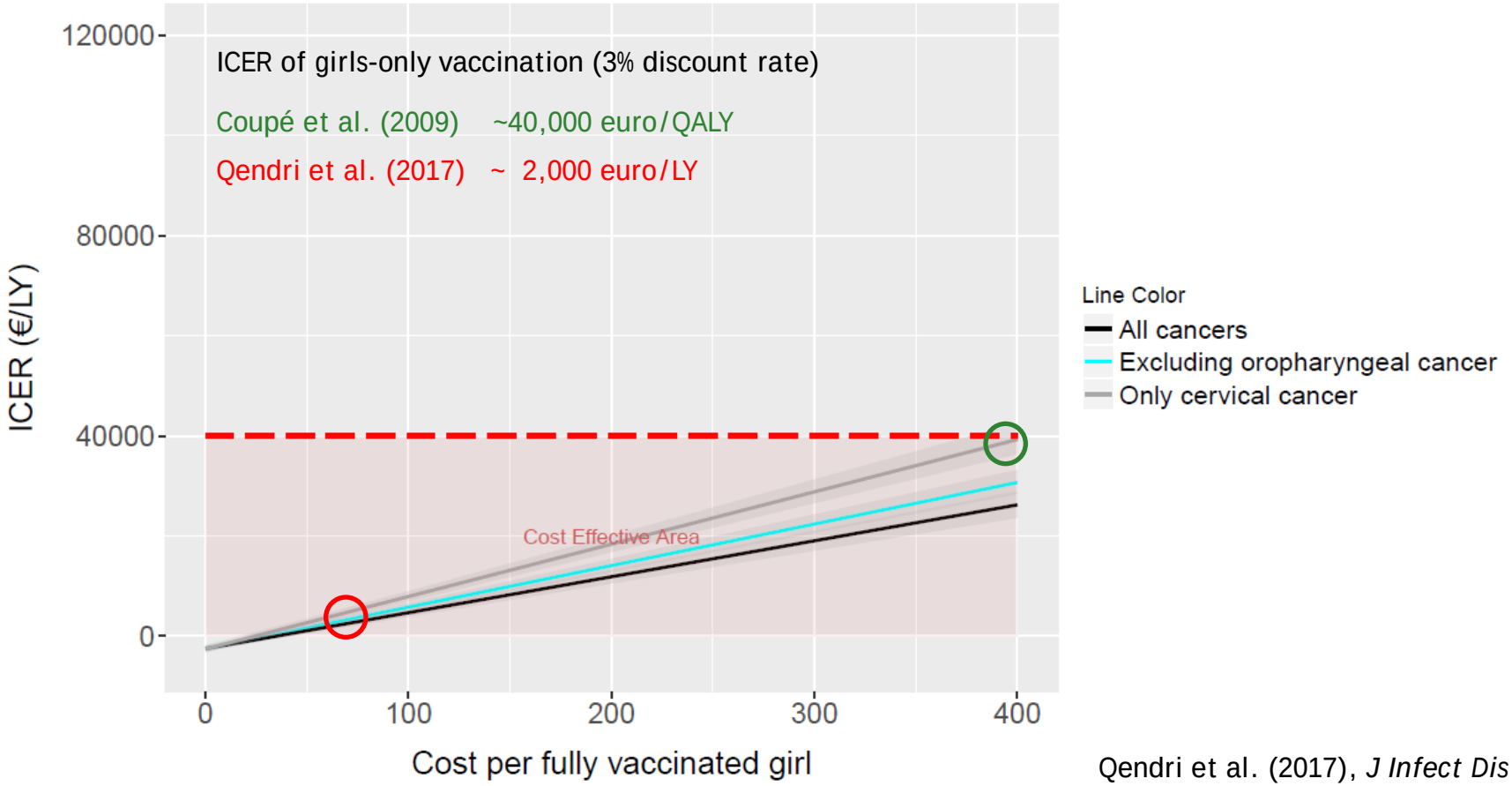
Suijkerbuijk et al. (2017), *Expert Rev Vaccines*

Girls-only vaccination in the Netherlands; the benefit of hindsight pt.4

Qendri et al., Vaccine price development in EU tender-based settings (EUROGIN)



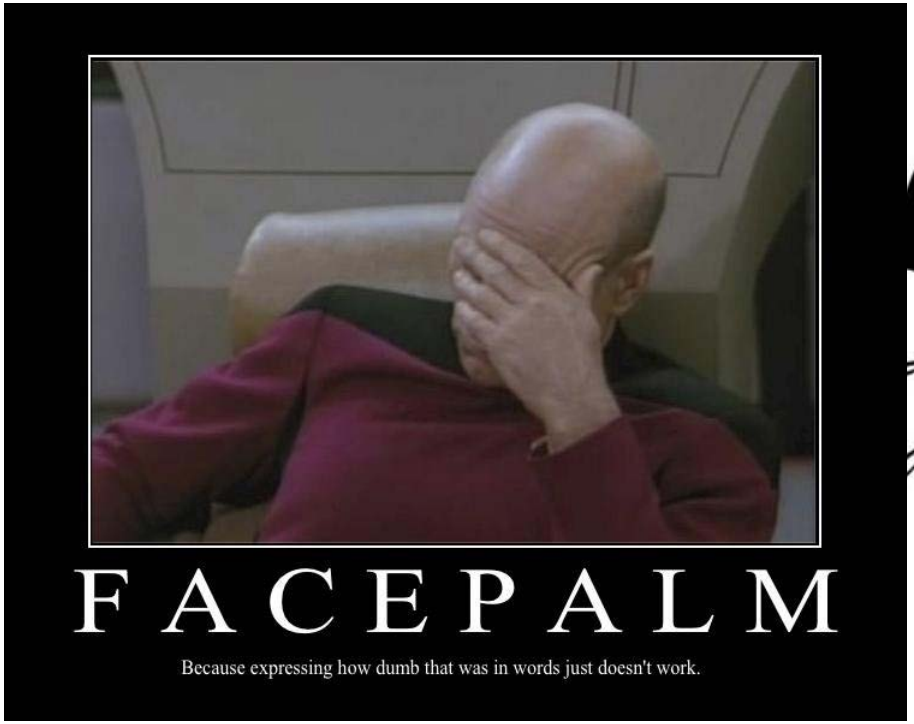
The combined benefit of hindsight: Revised health and economic impact of HPV16/18 vaccination in the Netherlands



Qendri et al. (2017), *J Infect Dis*

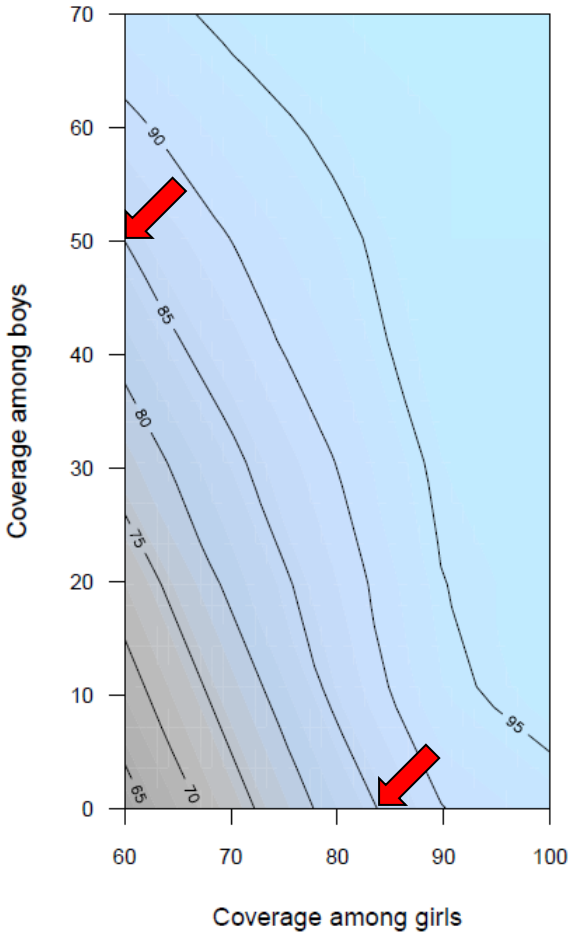
Girls-only vaccination in the Netherlands; combined benefit of hindsight

Revised ICER about 20-fold lower than conventional cost-effectiveness threshold!



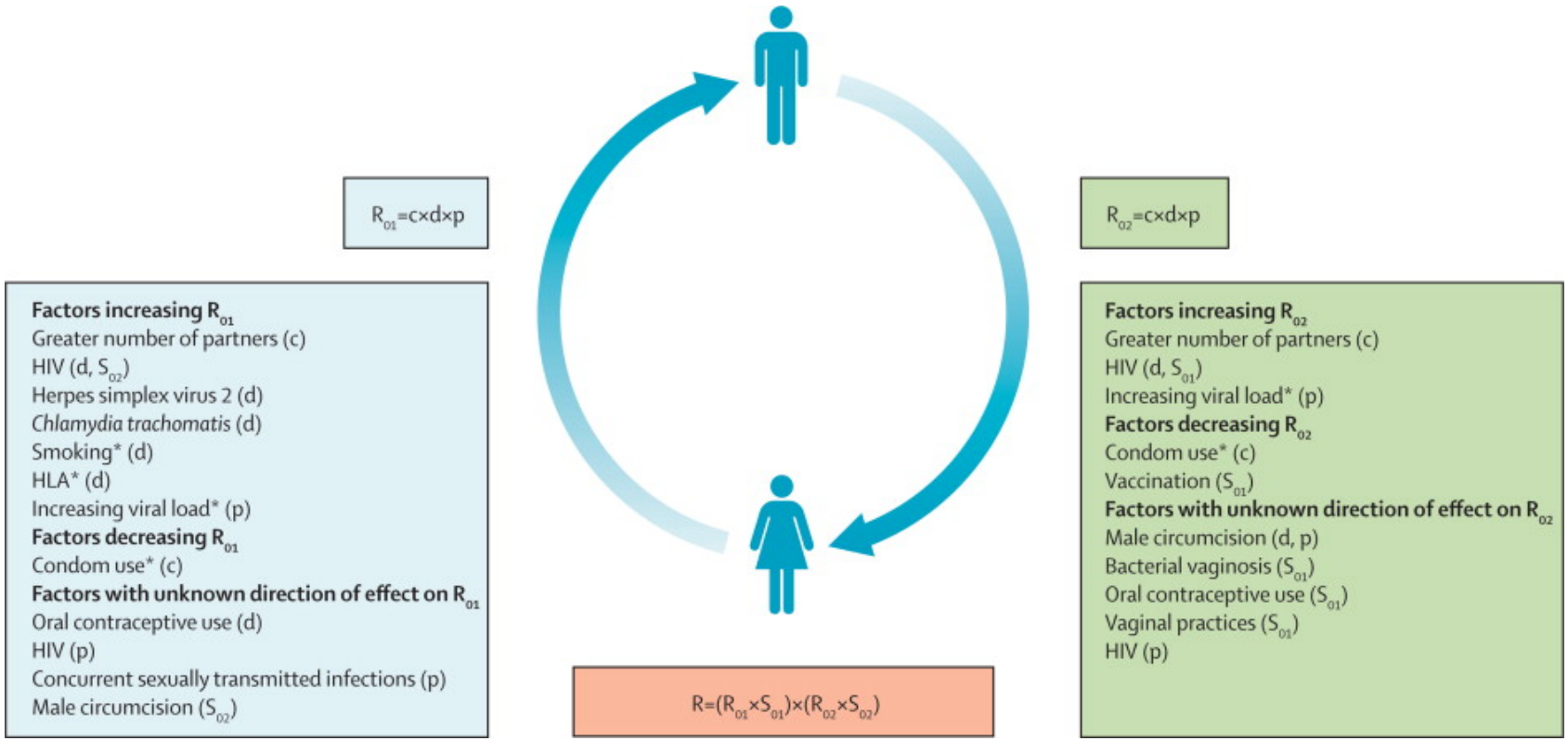
Considerable scope for improved HPV prevention through vaccination

- Girls-only vaccination with 60% coverage will confer a 64% reduction in the life-years lost due to HPV16/18 infections
  - ➢ 71% reduction in women; 37% in men
- Scope for improvement; even more so when considering the total HPV-related burden
- Vaccinating 2 boys leads to a similar further reduction in HPV16/18-related cancer burden as vaccinating 1 'additional' girl
- Differential impact due to gender disparity in burden + asymmetry in transmission dynamics



Qendri et al. (2017), *J Infect Dis*

Factors affecting heterosexual transmission dynamics of mucosal HPV infection: sex-specific reproduction numbers



Veldhuijzen et al. (2010), *Lancet Infect Dis*

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[3] Division of Cancer Epidemiology, McGill University, Montreal, Canada eduardo.franco@mcgill.ca

Effectiveness of vaccinating boys on the transmission of HPV: analysis of the basic reproduction number R_0

Objectives

In many countries universal vaccination of girls against infection with human papillomavirus was recently introduced or will be introduced soon. The decision of whether of not to include boys in the national immunization programmes depends on the strength of indirect effects of vaccinating boys on the incidence in girls and the resulting incremental cost effectiveness. Our aim was to assess the contributions of males and females, respectively, to the transmission dynamics of HPV using the concept of the basic reproduction number.

Methods

Based on a model stratified by age and sexual activity we derived a formula for the basic reproduction number R_0 for HPV. The reproduction number is a geometric mean of two factors describing the average numbers of secondary cases in men by one infected woman and vice versa. Women and men differ in terms of their natural history of infection and their transmission probabilities (Figure 1). Where possible, we based our choices of parameters roughly on available literature data, and otherwise chose plausible values. We assumed that the infectiousness in different stages in women is determined by the viral load, which has been shown to vary between infections with and without lesions (Hesselink et al 2009). We investigated how the reproduction number depends on transmission probabilities, the duration of the infectious period and on vaccination coverage of men and women.

The basic reproduction number R_0 is composed of

R_{mf} the number of secondary infections in women caused by one infected man
R_{fm} the number of secondary infections in men caused by one infected woman

$$R_0 = \sqrt{R_{mf} R_{fm}}$$

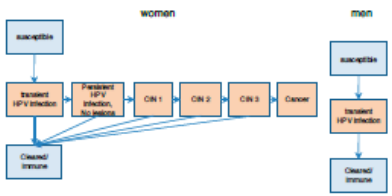

Figure 1

Results

Assuming that persistent infections contribute substantially to transmission, women produce many more secondary infections in men than vice versa. The exact ratio depends on the duration of infectiousness during transient infections, and on the transmission probabilities per partnership. Even with a substantially higher transmission probability from males to females, the transmission chain is driven by female to male transmission (Figure 2).

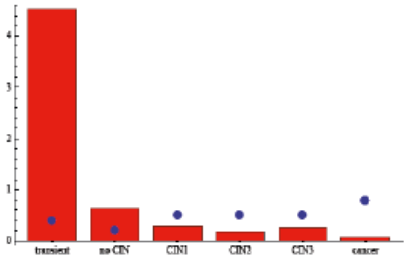

Figure 2: Contribution of different stages of infection to R_{fm} The blue dots represent the transmission probabilities per partnership by stage of infection.

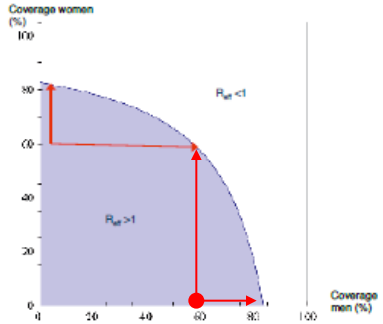

Figure 3: The critical vaccination coverage for women and men.

Conclusions

If vaccination coverage among women is above a critical threshold, vaccination of men does not add anything to effectiveness. If both women and men are vaccinated at the same level of coverage, the fraction of the total population that needs to be vaccinated for elimination is higher than when vaccinating women only (Figure 3). It might be very effective to target intervention to highly sexually active women.

References

Kretzschmar M, de Wit GA, Smits LJ, van de Laar MJ. Vaccination against hepatitis B in low endemic countries. Epidemiol Infect. 2002 Apr;128(2):229-44.

Trottier H, Mahmud S, Prado JC, Sobrinho JS, Costa MC, Rohan TE, Villa LL, Franco EL. Type-specific duration of human papillomavirus infection: implications for human papillomavirus screening and vaccination. J Infect Dis 2008;197(10):1436-47.

Hesselink AT, Berkhof J, Heideman DA, Bulkmans NW, van Tellingen JE, Meijer CJ, Snijders PJ. High-risk human papillomavirus DNA load in a population-based cervical screening cohort in relation to the detection of high-grade cervical intraepithelial neoplasia and cervical cancer. Int J Cancer 2009; 124(2):381-6.

RIVM National Institute for Public Health and the Environment, PO Box 1, 3720 BA Bilthoven, the Netherlands, www.rivm.com

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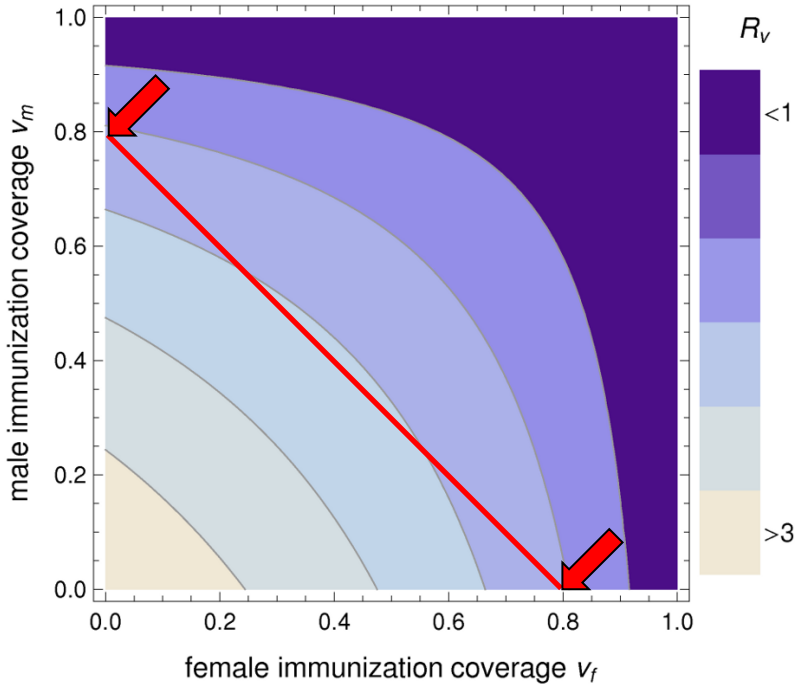
- $R_{fm} > R_{mf}$
  - "women produce many more secondary infections in men than vice versa"
  - Because of an increased prevalence in women!
- $R_0 = \sqrt{(R_{mf} \cdot R_{fm})}$
  - "If both women and men are vaccinated (…), the fraction of the total population that needs to be vaccinated for elimination is higher than when vaccinating women only"
  - Also true for men only!

Kretzschmar & Franco, *18th ISSTDR* 2009

Differential impact of sex-specific immunization on the reproduction number and on the heterosexual prevalence of HPV infection

A



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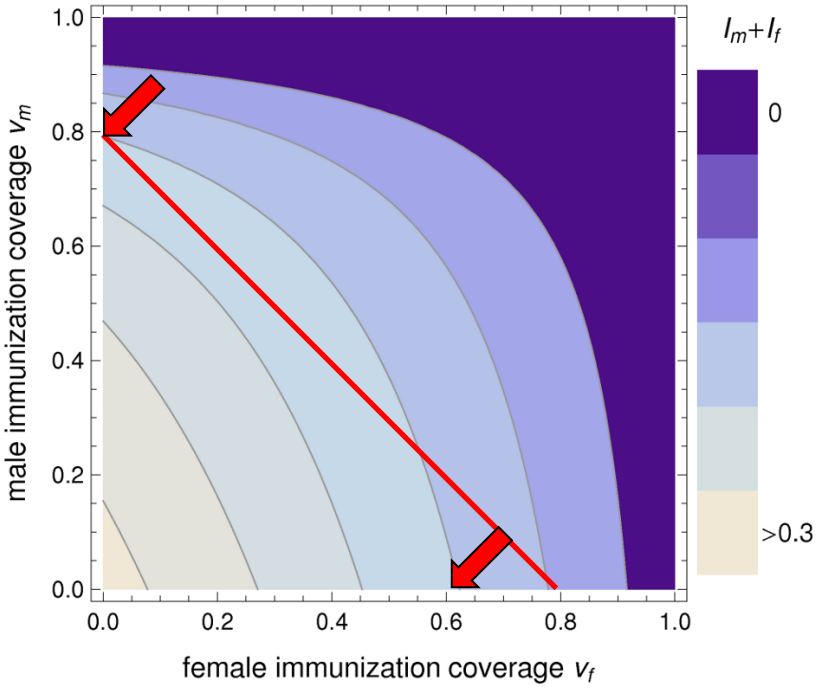


Bogaards et al. (2011), *PLoS Medicine*

Gender-neutral vaccination: neither required nor sufficient for elimination from heterosexual population

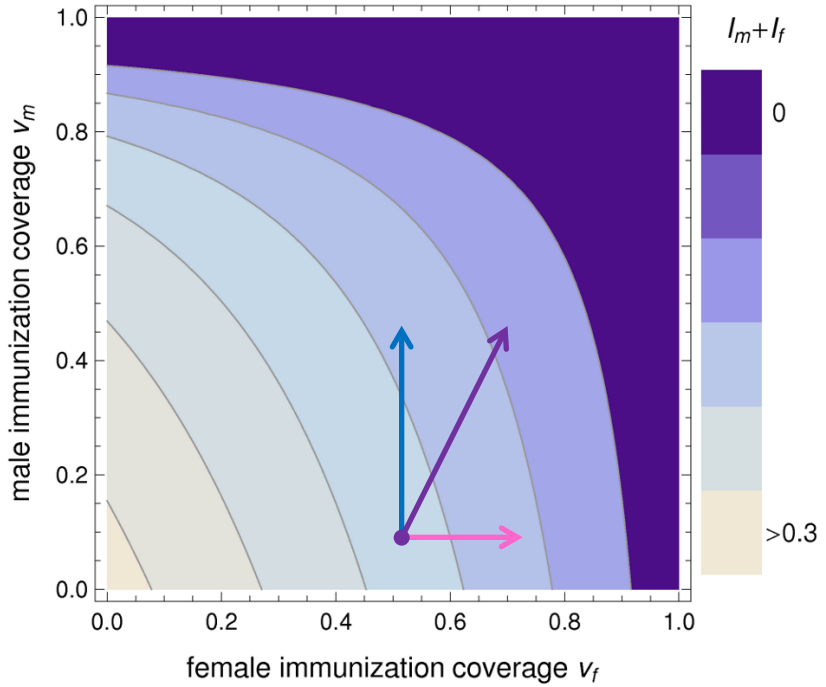
HPV vaccination in boys, girls

Among 13- to 17-year-olds, the vaccination rate for human papillomavirus for boys lags that of girls. Recent vaccination rates, and what parents said their vaccination intentions were for their sons and daughters in the next year:

STATUS/INTENTION		2010	2011
Vaccinated	BOYS	1.4%	8.3%
	GIRLS	48.7%	53%
Somewhat/very likely		27.4%	31.2%
		16.7%	16.9%
Not likely		59.2%	51.5%
		27.9%	25%
Unsure/unknown		11.9%	9.1%
		6.7%	5%

Sources: Immunization Services Division, Centers for Disease Control and Prevention

B

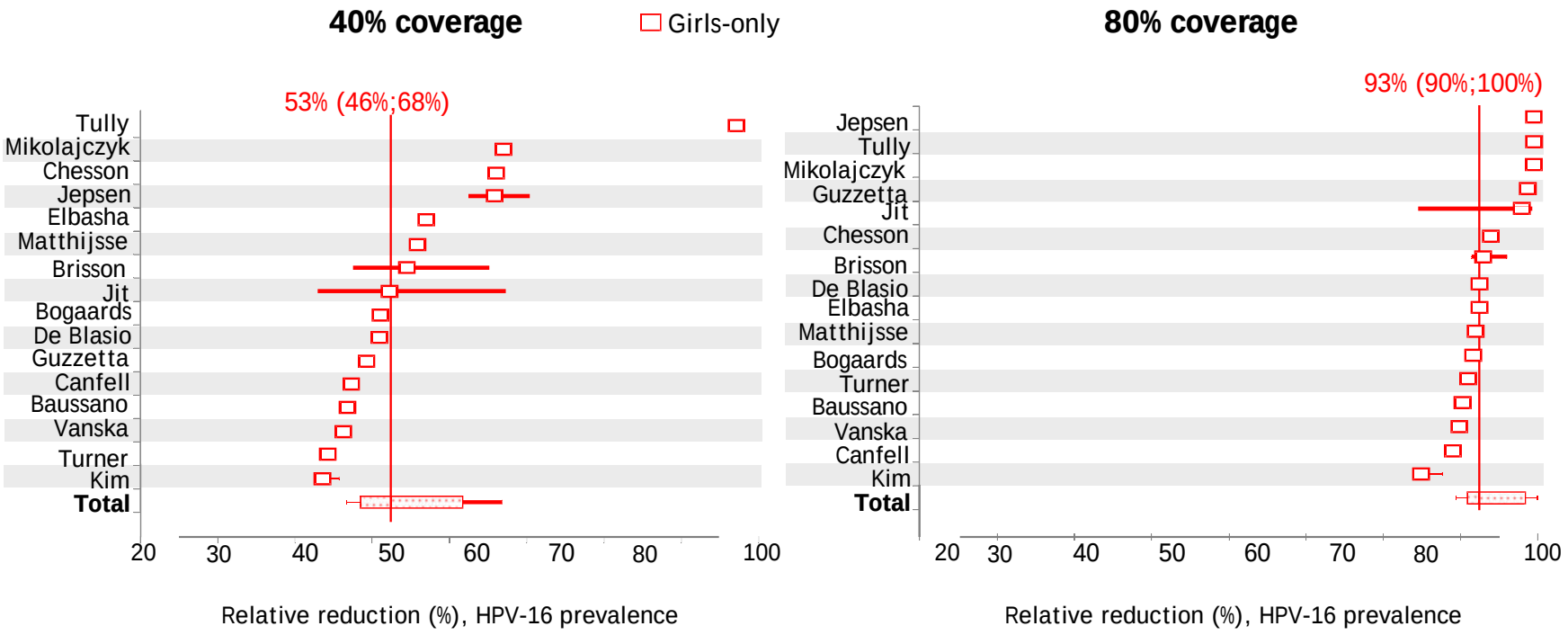


Elimination requires changing attitudes towards HPV vaccination, even more so for boys than for girls

Population-level impact of HPV16 vaccination: meta-analytic predictions

Predictions of 16 transmission-dynamic models

Girls-only vaccination, Vaccine duration=Lifelong, Vaccine efficacy=100%



NOTE: Corresponding author, 16 of 19 Transmission models published in 2009-2014, identified through systematic review

Brisson et al. (2016), *Lancet Public Health*

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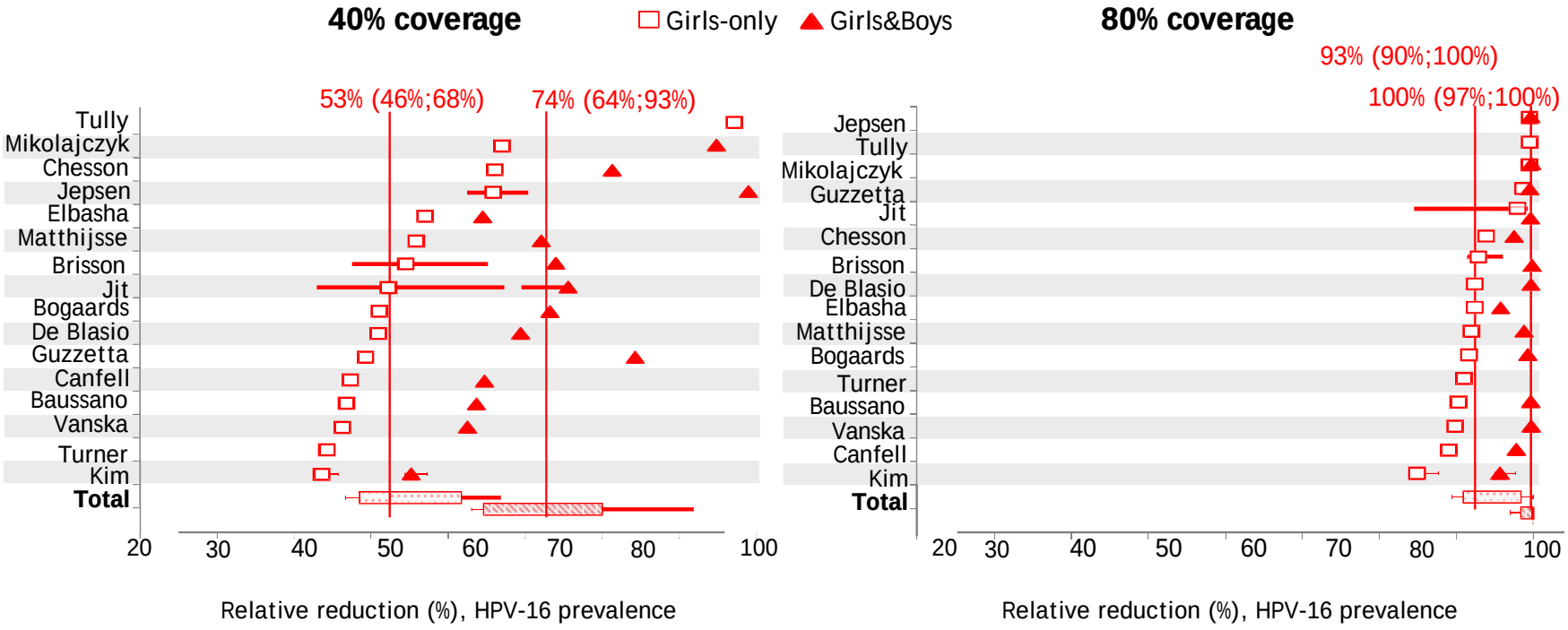


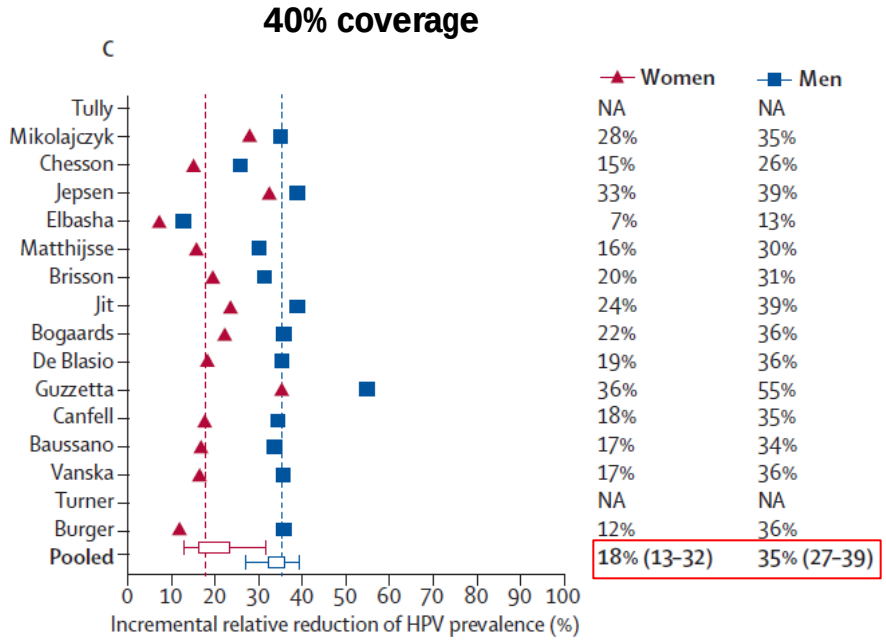
NOTE: Corresponding author, 16 of 19 Transmission models published in 2009-2014, identified through systematic review

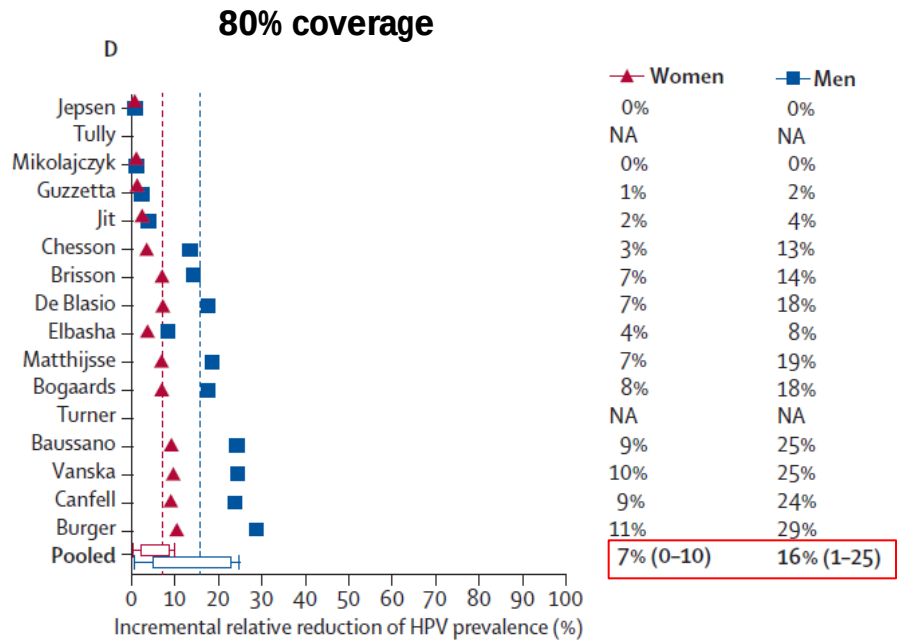
Brisson et al. (2016), *Lancet Public Health*

Incremental effectiveness of vaccinating boys along with girls

Predictions of 16 transmission-dynamic models

Girls-only and Girls & Boys vaccination, Vaccine duration=Lifelong, Vaccine efficacy=100%





Note 1. Incremental effectiveness decreases at high coverage among girls

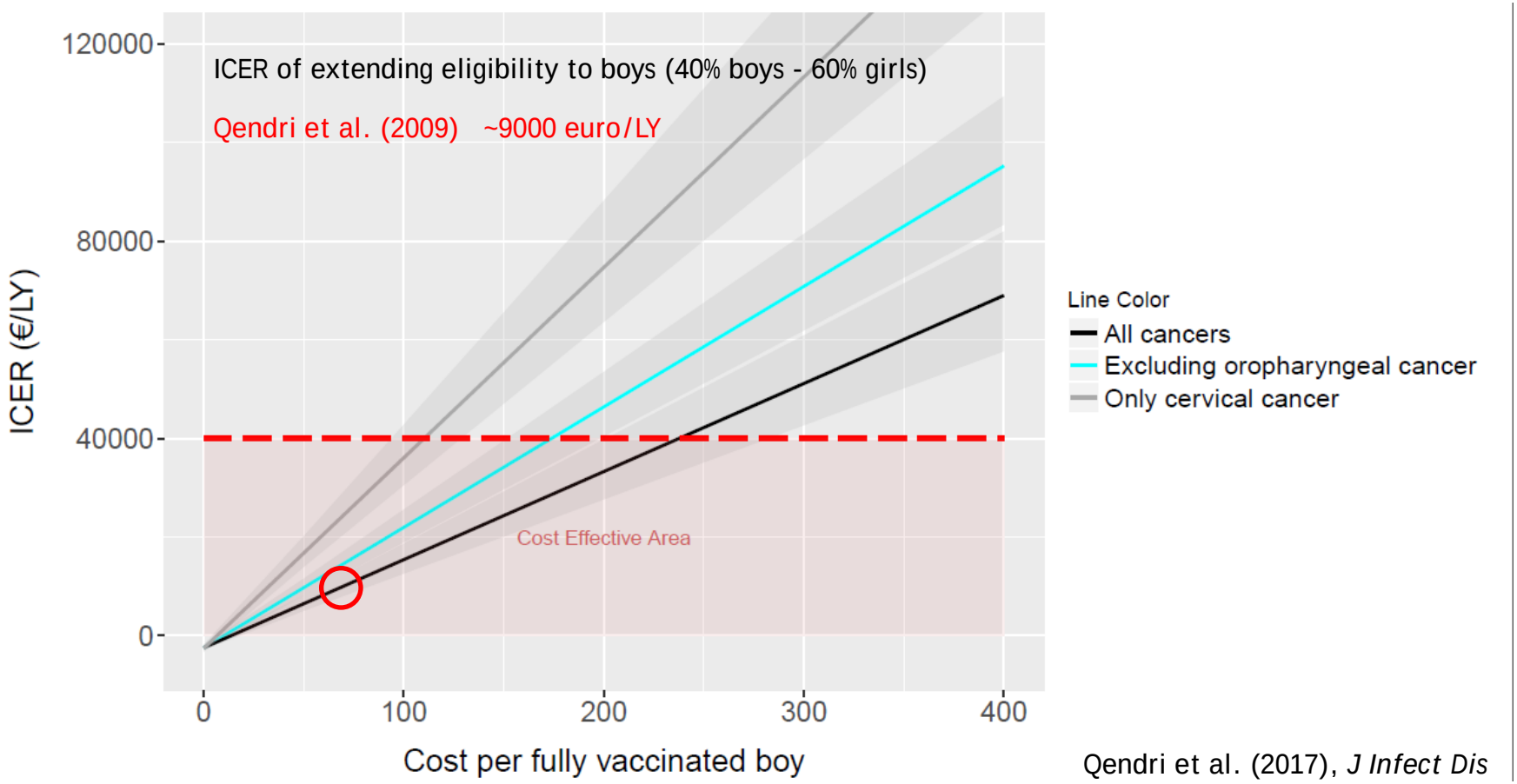
Note 2. Relative uncertainty increases at high coverage among girls

} BLOW-UP of variability in ICER!

Brisson et al. (2016), *Lancet Public Health*

Vaccinating boys along with girls is cost-effective in the Netherlands

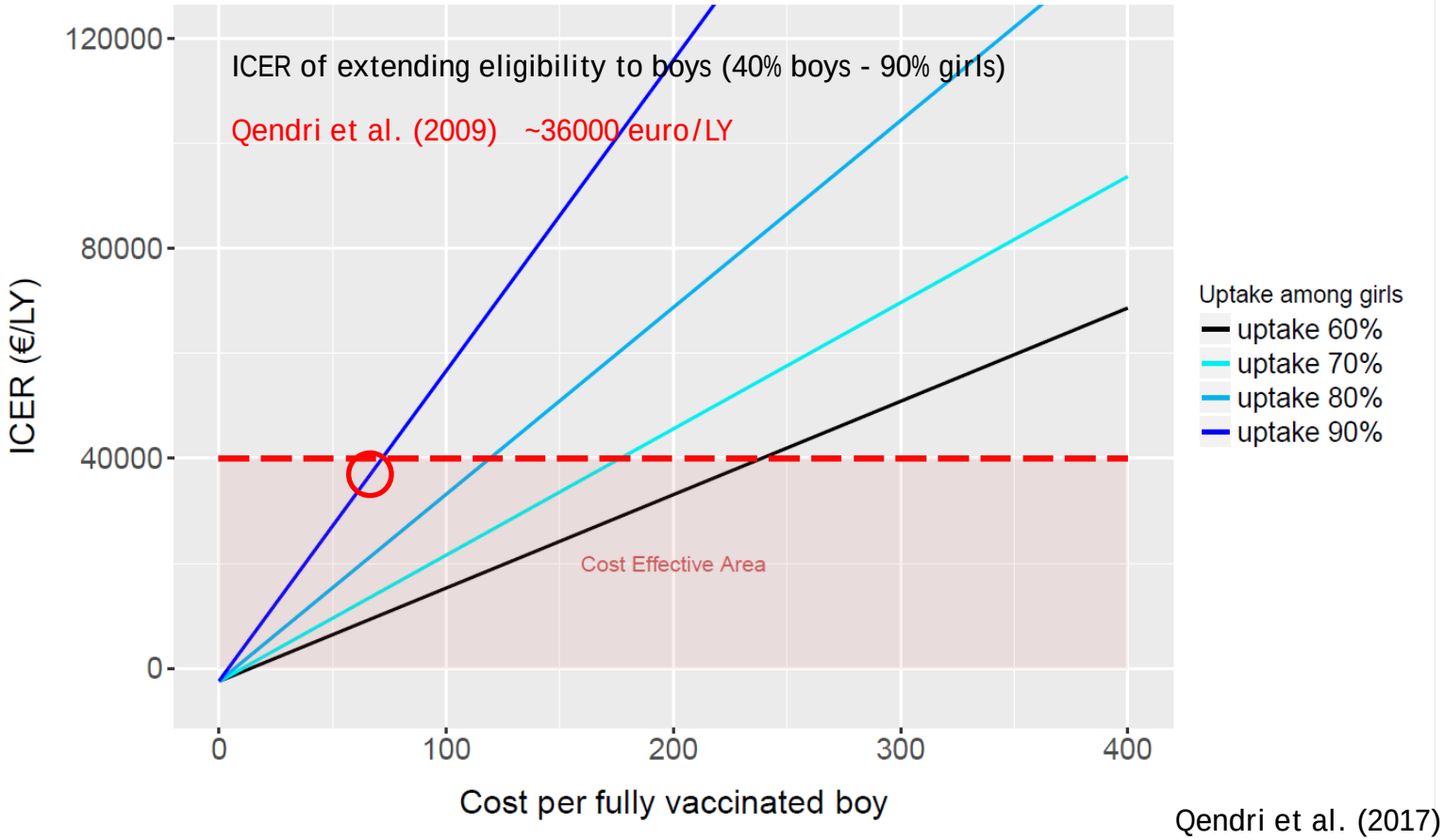
… if the anticipated cost for vaccinating boys were the same as for girls



Qendri et al. (2017), *J Infect Dis*

… and would remain cost-effective at increased coverage among girls

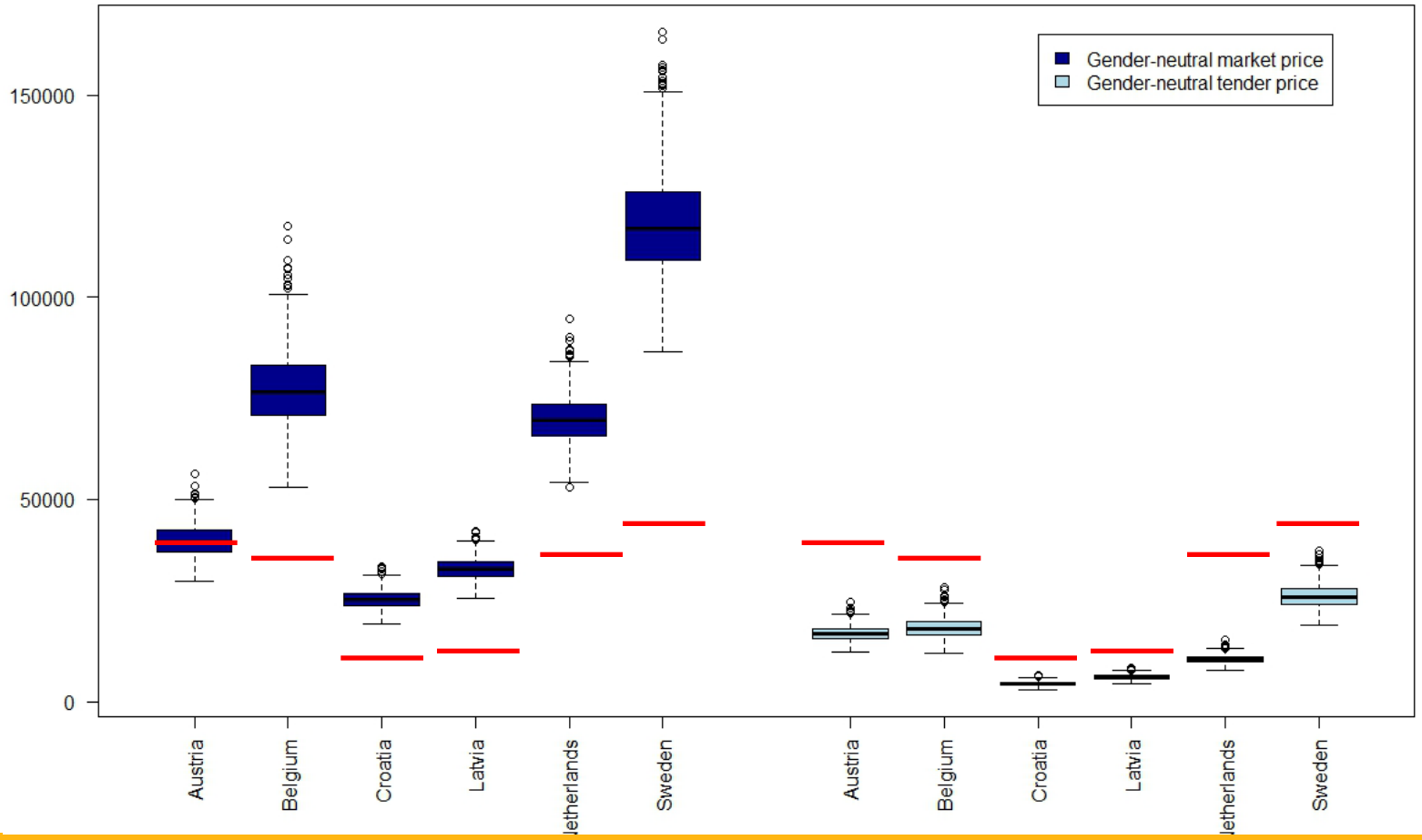
(provided that uptake among girls will not exceed 90%)



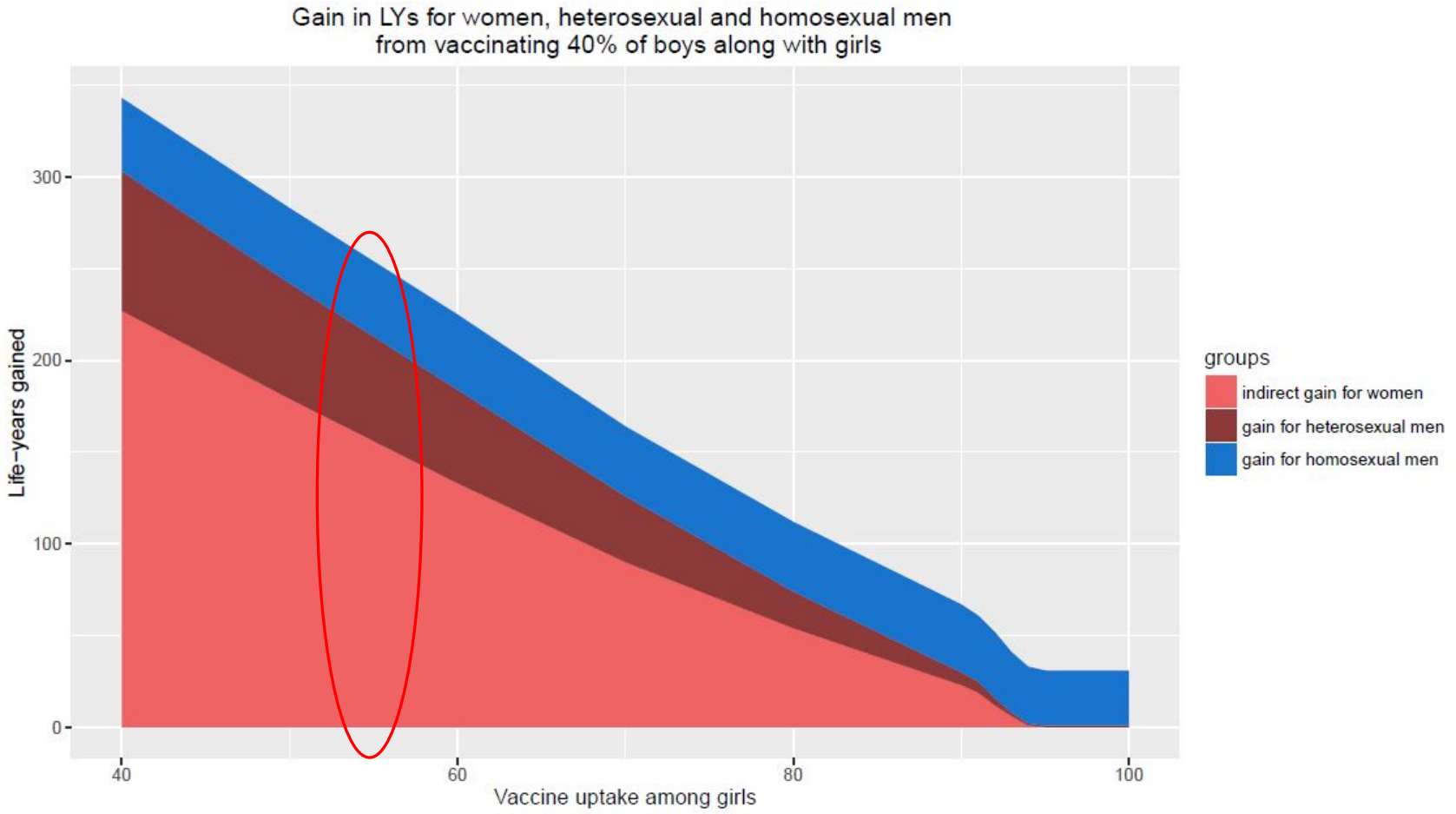
Qendri et al. (2017), *J Infect Dis*

Generalizability to other national immunization programs?

Qendri et al. (FC 13-2), Cost-effectiveness in six EU tender-based settings



Who will benefit from extending vaccine eligibility to preadolescent boys?



Until which age should (wo)men be eligible for HPV vaccination?
> Or: how can modelling help improve existing prevention efforts?

- Topical in settings where HPV vaccination still needs to be introduced
  - ➢ Effectiveness of catch-up campaigns function of individuals' past as much as future
  - ➢ Key drivers of uncertainty: accurate modelling of sexual activity, immunity, latency

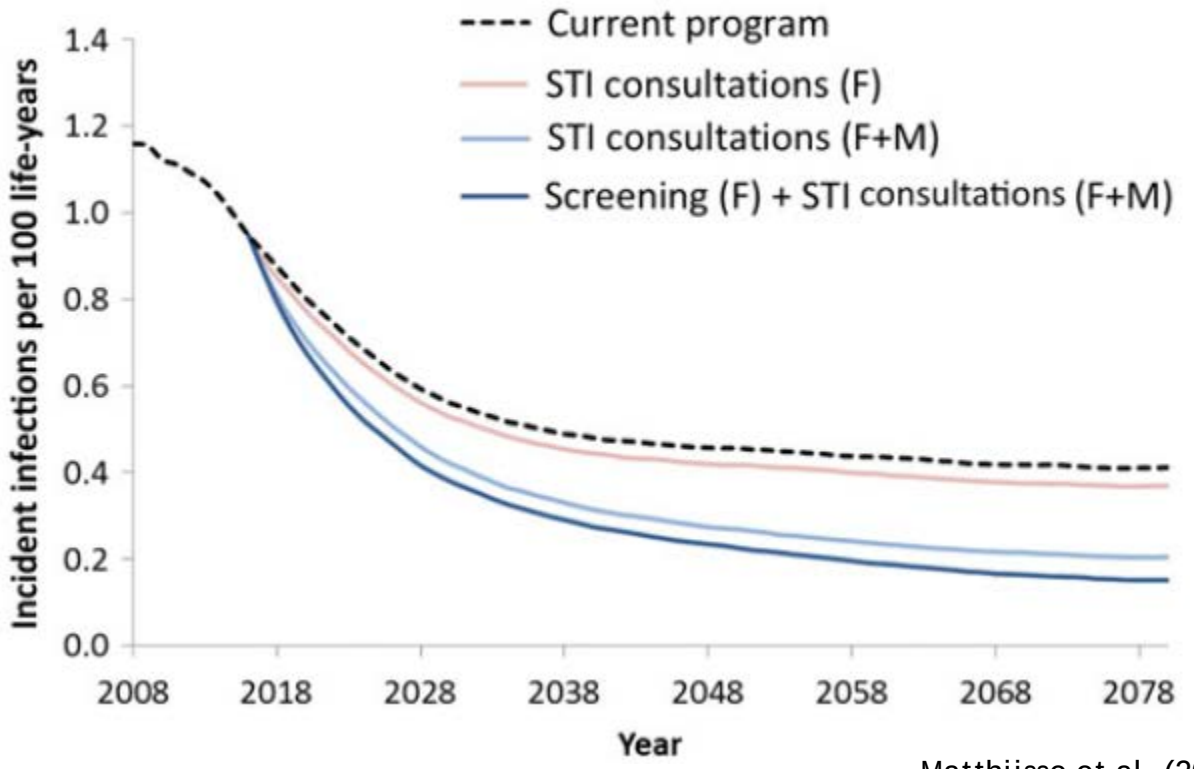
- Also topical in settings where uptake among (pre)adolescents is suboptimal
  - ➢ Expanding vaccine eligibility as a means to improve HPV prevention efforts

- Opportunities to combine vaccination with (HPV-based) cervical screening
  - – Catch-up vaccination at (first?) screening visits to align future cancer risks
  - – 'One size fits all' vs. personalized approach to screening (privacy, equity?)
  - ➢ Feasibility and acceptability of modelled strategies need to be considered

Projected trends in HPV16 incidence under overtly optimistic scenarios

STI consultations: *all* STI clinic visitors <30y are offered and accept HPV vaccine

Screening: *all* screening attenders aged 30y are offered and accept HPV vaccine



Matthijsse et al. (2016), *J Infect Dis*

Should men who have sex with men be targeted for HPV vaccination?
> Or: what is the (temporal) benefit compared to vaccinating boys?

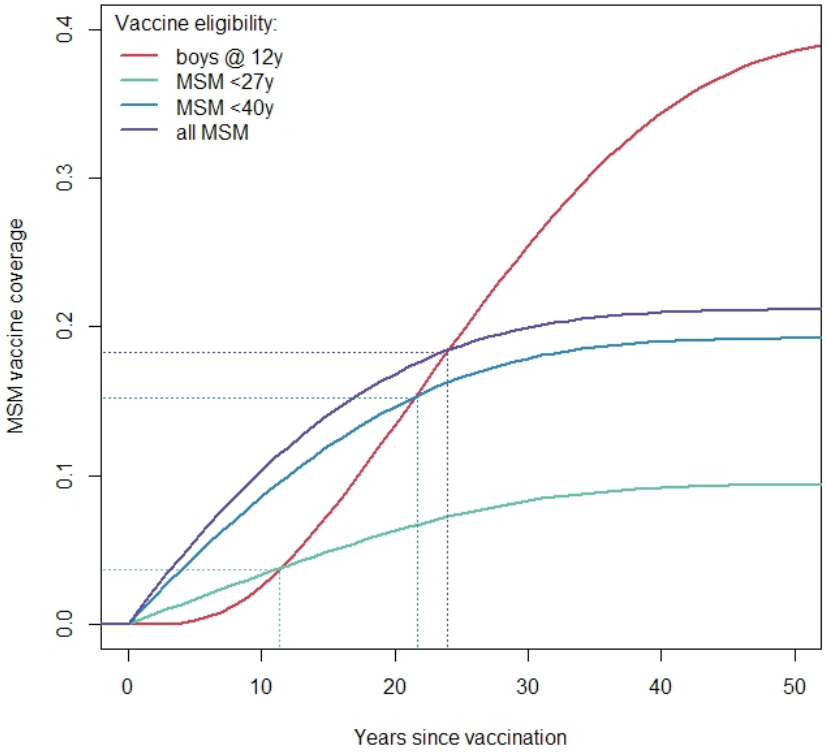
- Modelling MSM vaccination is more involved than preadolescent vaccination
  - ➢ Distinct transmission dynamics (one sex, multiple anatomic locations)
  - ➢ Selective vaccination of MSM can only be realistically achieved after sexual debut
  - ➢ Likewise requires accurate modelling of sexual activity, natural immunity, latency, etc.

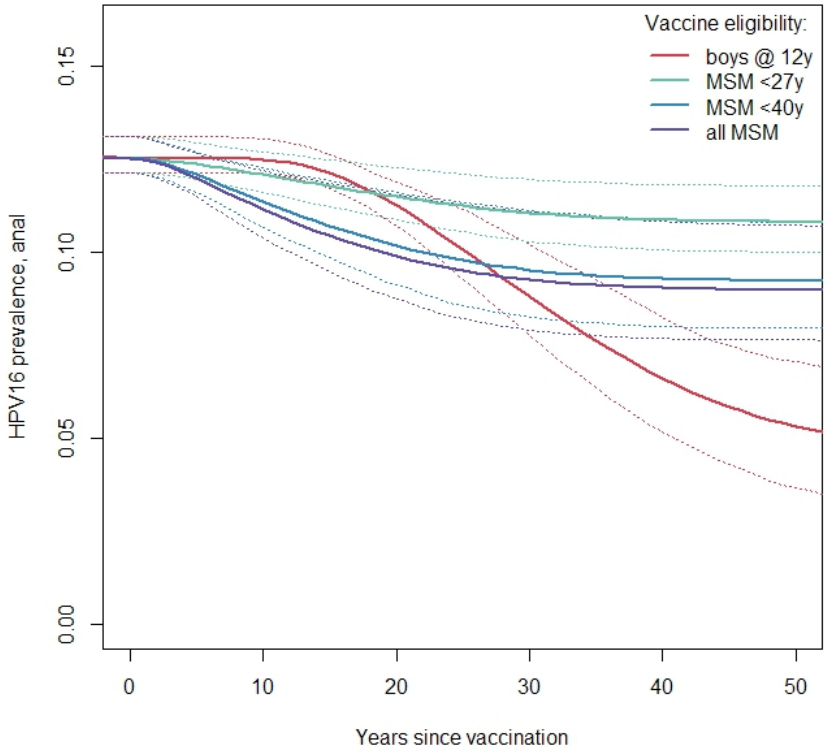
- Large amount of uncertainty around extent and mode of prophylactic efficacy
  - – Distinction between 'leaky' vs. 'all-or-nothing' efficacy becomes important
  - – Effect of previous or current infections on efficacy against future infections?

- Models of selective MSM vaccination should consider the route by which vaccines can be delivered to this group, and implications in terms of vaccine coverage
  - ➢ Explore analogies to selective MSM vaccination against HepB

Projected trends in HPV16 prevalence under optimistic efficacy scenario

Selective MSM vaccination assuming HepB uptake rates vs. 40% boys' uptake @ 12y





Take home message

The current girls-only program is projected to be very cost-effective!

The case for gender-neutral vaccination

- Cervical disease remains the predominant source of HPV burden, at least until the effects of vaccination become apparent
  - Even so, burden in males is considerable by any standard
  - Moreover, the gender disparity in HPV burden is diminishing

- Extending vaccine eligibility to preadolescent boys is only modestly less efficient than increasing vaccine uptake among girls
  - Moreover, it may be easier to include boys than to increase uptake in girls
  - Gender-neutral vaccination is cost-effective at realistic tender prices

How can modelling guide future vaccination policy and implementation?

Opportunities to combine vaccination with cervical screening

- Further development of combined vaccination + screening modalities
  - Prior definition of feasibility to manage computational complexity

Adding boys likely has strong impact on HPV-related diseases in MSM

- But will not protect currently active MSM, who have high risk for anal cancer
  - Targeting interventions to MSM may lead to a reduced acceptability in boys

Feasibility and impact of selective vaccination of MSM is still uncertain

- Unknowns in natural history of infection, prophylactic efficacy, mode of delivery
  - Multi-modelling approach needed to deal with many structural uncertainties

Informing public health strategy by mathematical modelling…

Acknowledgements

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- Venetia Qendri
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- FP7 project www.coheahr.eu