

The state of HPV vaccination in the world

Building Trust, Managing Risk: Vaccine Confidence and Human Papillomavirus Vaccination
London School of Hygiene & Tropical Medicine, London

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Botswana



Cameroon



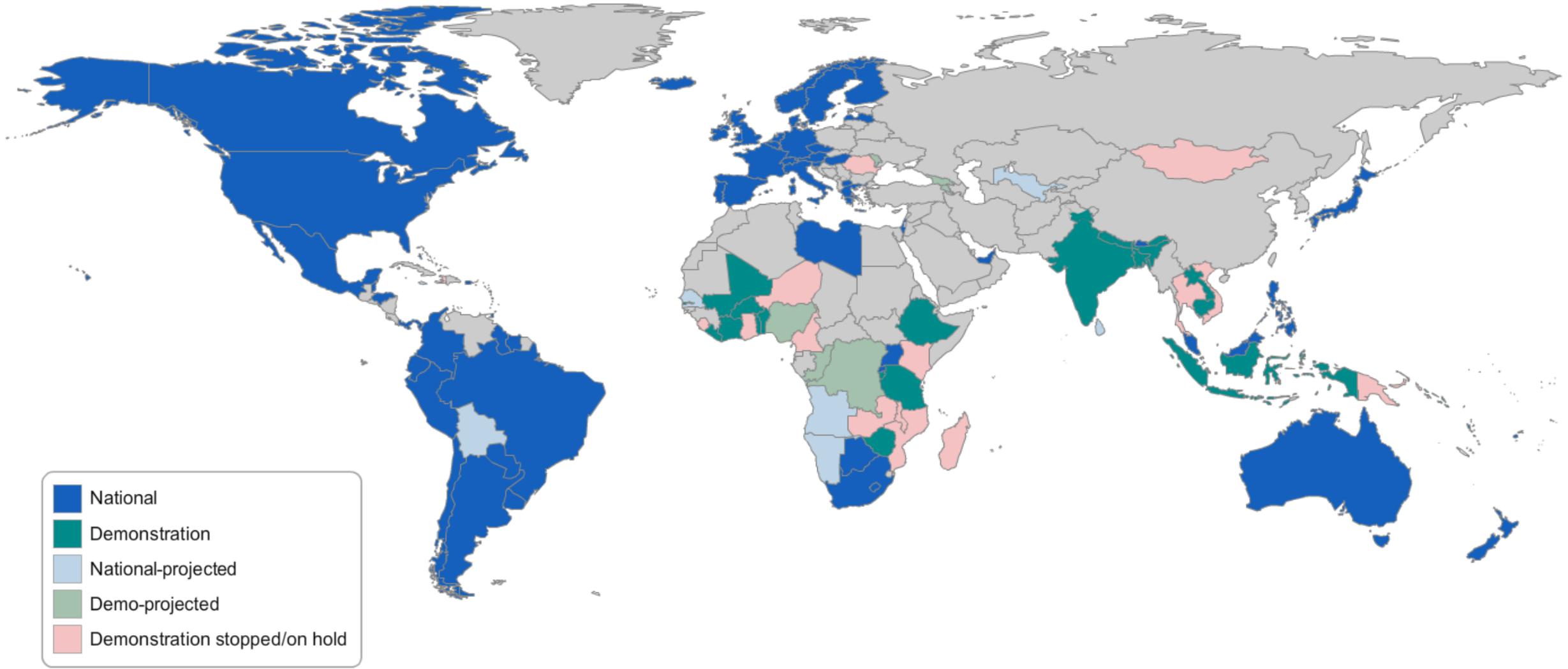
Solomon
Islands



Mozambique

Nations or Territories with National, Demonstration, or Projected (National or Demo) HPV vaccine programs by Year

2017

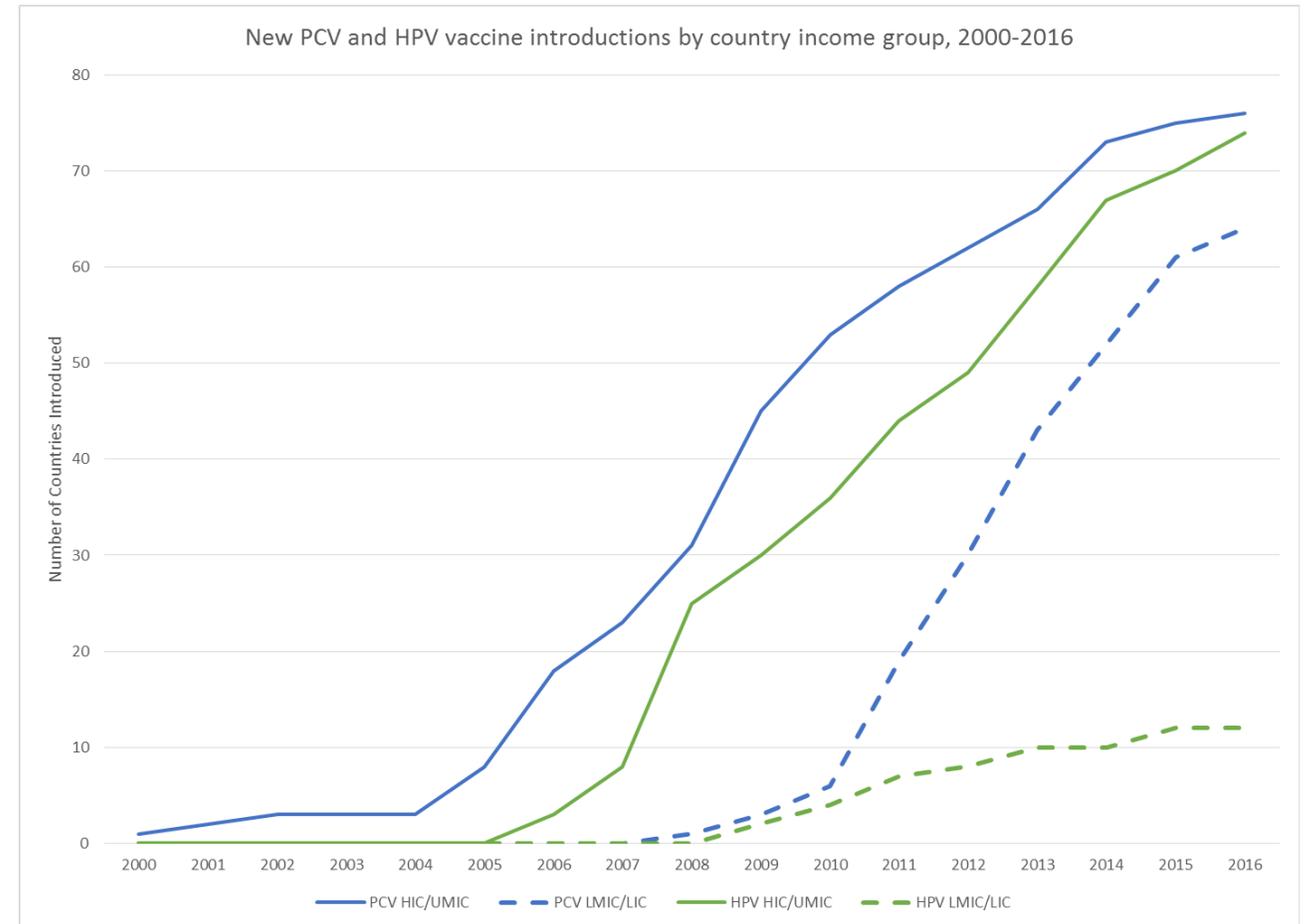


- National
- Demonstration
- National-projected
- Demo-projected
- Demonstration stopped/on hold



HPV vaccine introductions in high and upper-middle income countries

- 30 HIC/UMIC countries introduced in first 3 years of vaccine availability; now totals 74 [1]
- Focus on adolescent girls with catch-up provided up to age 18 for several years (UK, Australia, Sweden) [2]
- Primary target 11-12 year old girls; a few countries providing routinely to boys (Australia, Austria, Barbados, Israel, Lichtenstein, Switzerland, US) [2]
- School-based programs achieving highest coverage
- Estimated 34% of 10-20 year old females in HIC fully vaccinated (by Oct. 2014) [3]
- 48 countries now using 2-dose schedule [1]



[1] Brotherton JML, et al. Current Obstet Gynecol Rpts 2016

[2] Markowitz LE, et al. MMWR 2014

[3] Bruni L, et al. Lancet Global Health 2016

LaMontagne DS, et al. HPV World 2017 (in press)

Challenges of HPV vaccine in high income countries

- Vaccine safety has been primary concern in HICs
- Initial reports of frequent syncope led to post-vaccination waiting periods [4,5]
- Safety concerns persisted and impacted several country programs – Romania, Trinidad & Tobago, Fiji [1]
- Particularly entrenched safety issue persists in Japan [6,7], despite numerous reviews by GACVS reaffirming positive safety profile of the vaccines after more than 200 million doses distribute globally
- Communication strategies focused on infection/transmission, informed choice, behavior change theory; concern about sexual disinhibition [8]



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5 November 2015
EMA/714950/2015

Review concludes evidence does not support that HPV vaccines cause CRPS or POTS

Reports of CRPS and POTS after HPV vaccination are consistent with what would be expected in this age group

[4] Buttery JP, et al. Med J Aust 2008

[5] Global Advisory Committee on Vaccine Safety 2009

[1] Brotherton JML, et al. Current Obstet Gynecol Rpts 2016

[6] Richards S, et al. Arch Dis Child 2012

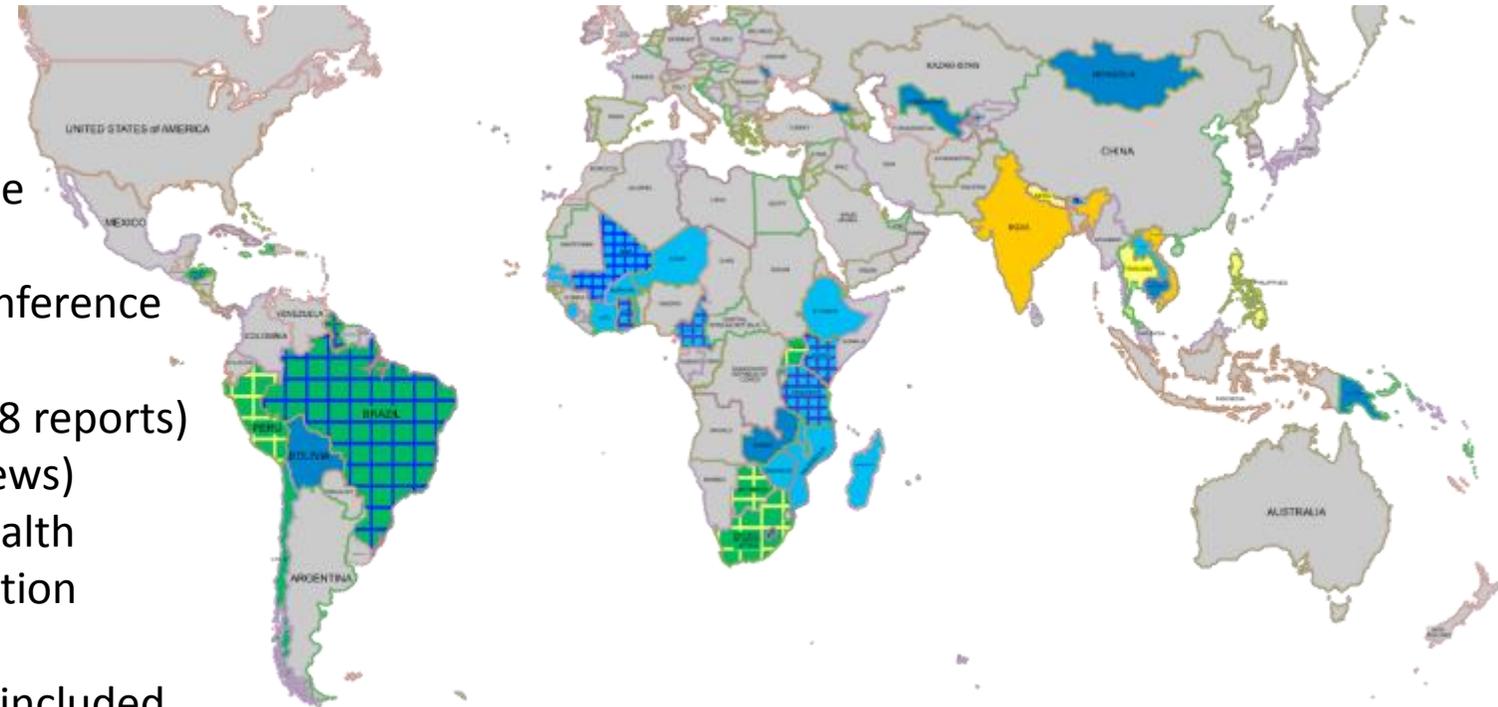
[7] Kinoshita T, et al. Intern Med 2014

[8] Bednarczyk RA, et al. Pediatrics 2012

Study methods

This review [9] included:

- 46 selected countries after mapping exercise
- 3 data-collection approaches:
 1. Systematic review (61 articles, 11 conference abstracts)
 2. Review of unpublished literature (188 reports)
 3. Key informant interviews (56 interviews)
- Data extraction was based on the World Health Organization's (WHO) new vaccine introduction guidelines
- 9 countries that did not apply to Gavi were included (5 interviews)



Note: Demo=demonstration project; GAP=GARDASIL® Access Program; Gavi=Gavi, the Vaccine Alliance; National=national programme.

[9] Gallagher KE, et al. *PLoS One* 2017



ACHIEVEMENTS



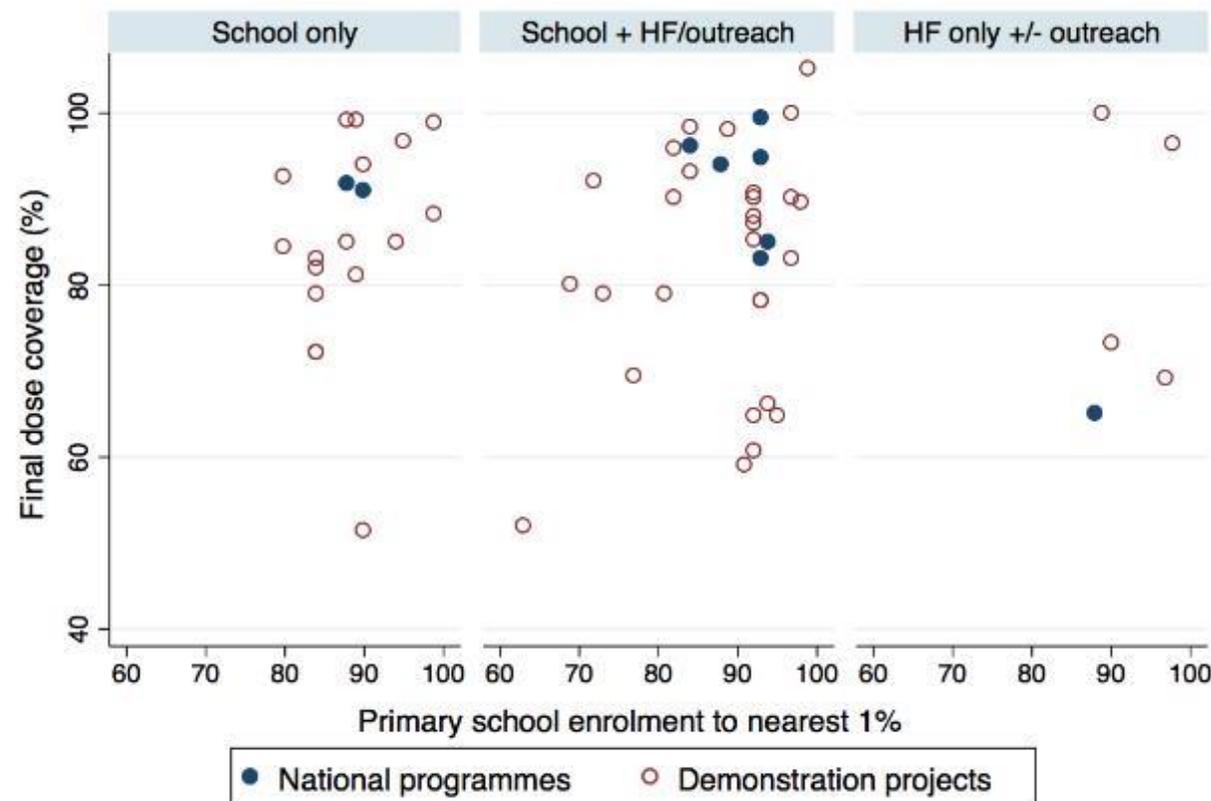
Key findings: achievements

Vaccine coverage

- 60 estimates of coverage available (of potentially 92)
- 50 used 3-dose schedule, 10 used 2-dose
- >80% reported final dose coverage of $\geq 70\%$ [10]
- Minimal data from health facility strategies (5 experiences; 65-96%)
- 17 estimates in 13 countries from coverage surveys.

Uptake and dropout

- First-dose coverage: 64- 100%
- Completion: 70-99%
- Majority reported drop-out rate of 10% or less



Graphs by vaccine delivery strategy

[10] Gallagher KE, et al. *Papillomavirus Research* 2017 (under review)



DELIVERY



Lessons learnt: delivery

- In schools, grade-based delivery simpler to implement than age-based, but can be challenging to communicate and calculate coverage [9]
- Delivery of all doses within 1 school year minimised dropouts and facilitated tracking to complete all doses
- Engaging community health workers increased acceptance and helped identify non-completers or out of school girls
- Scope of 'mop-up' activities governed by country-context: daily absenteeism rates and resources



LSHTM/ Deborah Watson-Jones

[9] Gallagher KE, et al. *PLoS One* 2017



Lessons learnt: communications

- Key messages: HPV vaccine prevents cervical cancer, is safe, will not harm fertility, endorsed by government and WHO
- Face-to-face interaction most effective way to mobilise parents and the community
- Most effective influencers: teachers, health workers, community leaders
- Mobilisation activities conducted at least one month prior to vaccination were most effective
- Reasons for vaccine refusal: fear of adverse events, lack of awareness or absenteeism
- Reasons for vaccine non-completion: absenteeism, rumours and logistical challenges in reaching vaccine sites
- Opt-in consent (where not standard EPI practice) increased rumours; lengthy consent procedures decreased uptake



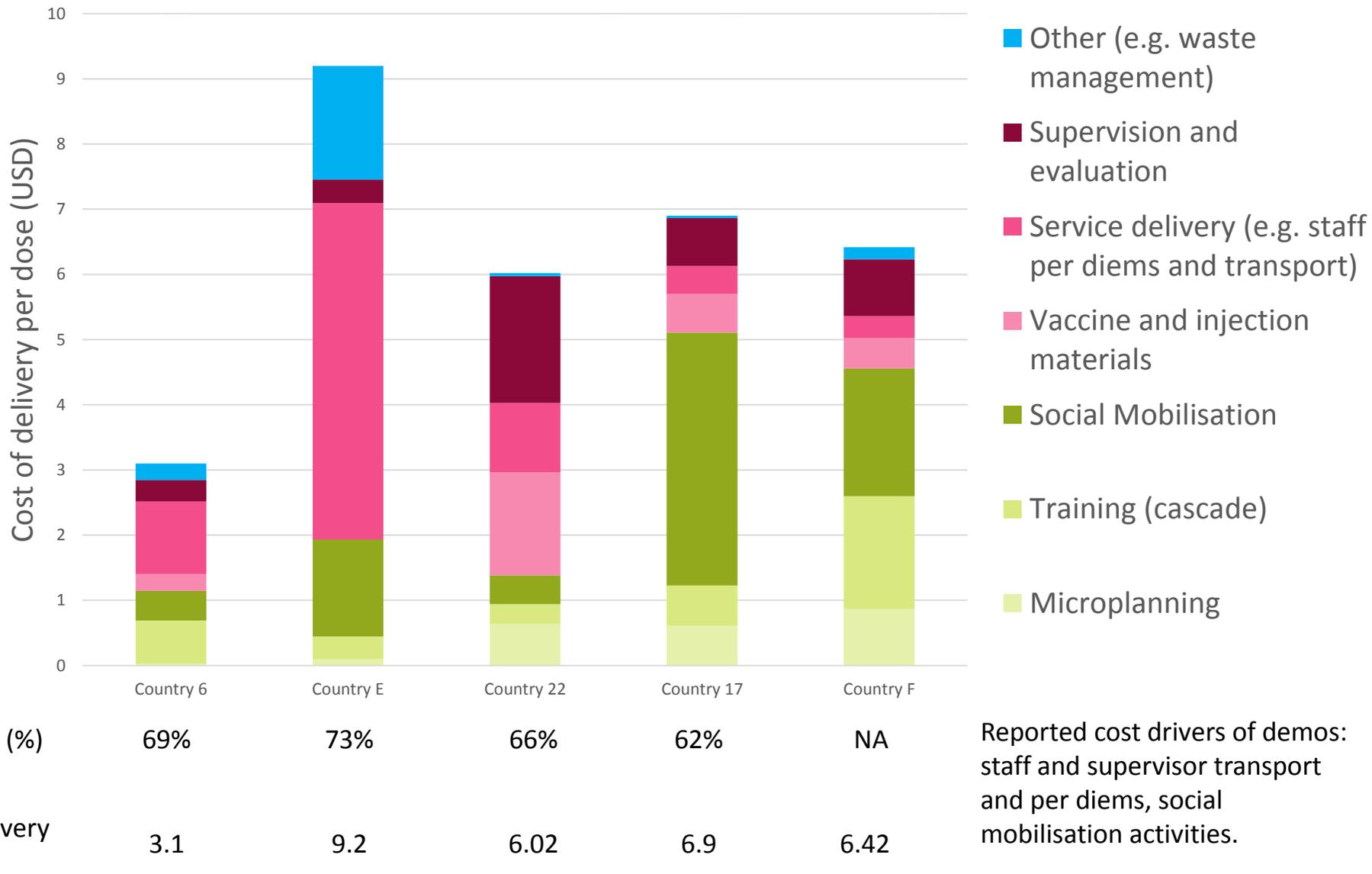
[11] Kabakama S, et al. *BMC Public Health* 2016



SUSTAINABILITY



Financial cost per dose Gavi demo projects (n=5)





PITFALLS



Lessons learnt: pitfalls

- Lack of political commitment early in the process caused delays later in the programme.
- Failure to coordinate early with national immunisation programme staff, the MOE and MOF led to planning, social mobilisation and delivery problems.
- Not allowing enough time for planning led to poor decision-making, lack of availability of funds, and untimely disbursement.
- Not engaging, or engaging too late, with local community leaders derailed social mobilisation efforts in some cases.
- Insufficient training of school staff/teachers and lack of a crisis communications plan perpetuated rumours.
- Failure to engage sufficiently or early enough with private schools early led to resistance by school leaders and parents.
- Limited focus on strategies to deliver HPV vaccine to out-of-school girls led to low coverage in that group.
- Failure to correctly enumerate the target population resulted in difficulties in accurately estimating coverage.

[12] Howard N, et al. *Human Vaccines & Immunotherapeutics* 2016

HPV vaccine delivery comparisons

High and Upper Middle Income Countries

- School-based delivery, few primary care models in countries
- Target age post-puberty, 11-14 years + catch-up
- Active decision making, seek service
- Individual consents, behavior change approach
- Government adoption based on cost-effectiveness
- Cautious conversion to 2-dose schedule
- Significant impact on infection/disease with girls only programs
- Boys (same age target) included in national schedule

Low and Lower Middle Income Countries [12]

- School-based delivery, mixed strategies for out of school girls
- Target age pre-puberty, 9-10 years, single cohorts
- Passive service, government brings to girls
- Community consent, social mobilization approach
- Government adoption based on costs and sustainability
- Rapid deployment of 2-dose schedule
- Evaluation of program based on operational successes, not impact
- Including boys will double costs

[12] LaMontagne DS, et al. *Intl J Gynecol Obstet* 2017

HPV vaccine impact on infection and disease outcomes

METHOD

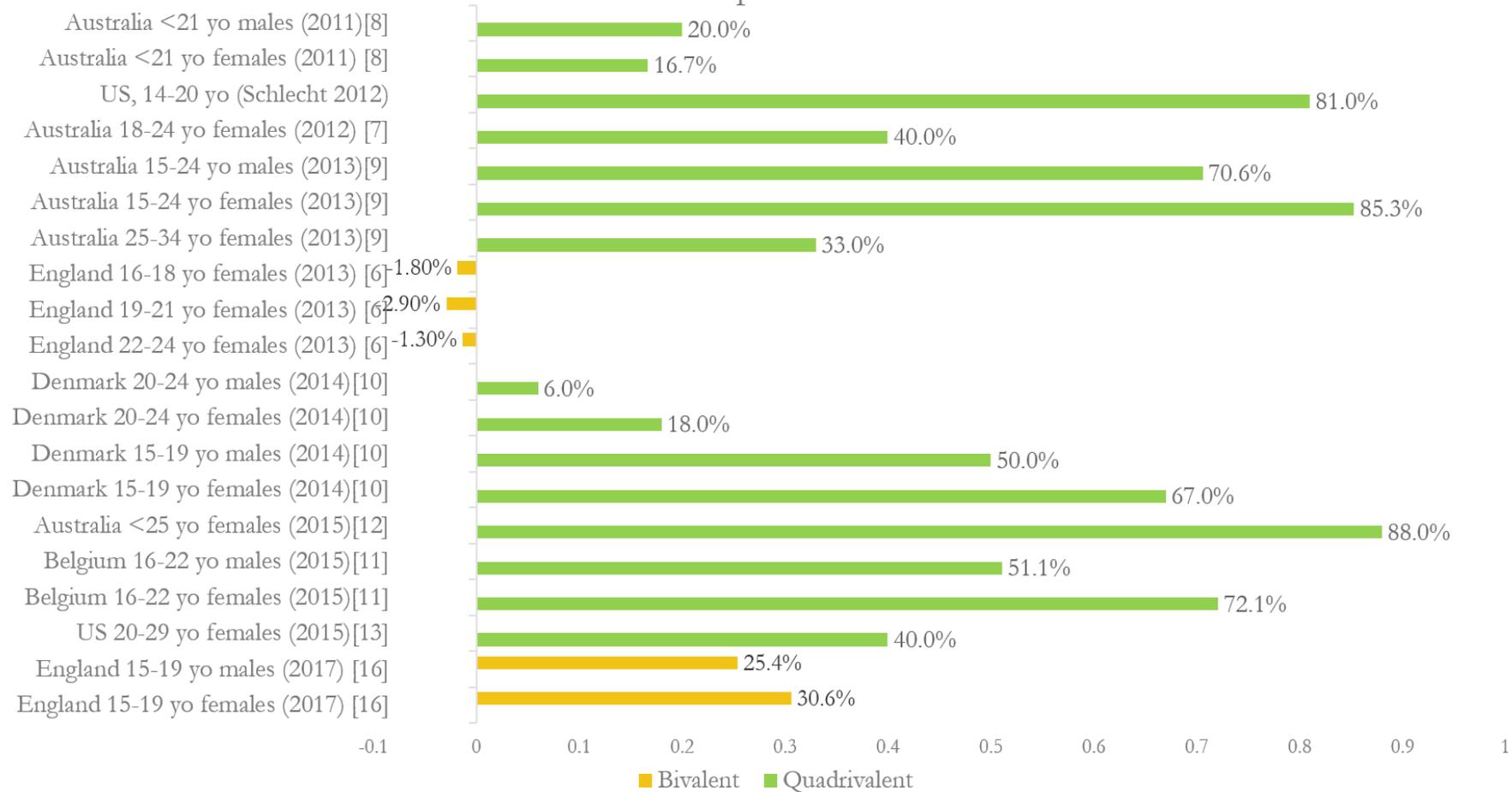
- More than 40 studies of HPV impact were reviewed.
- Studies published from 2009 to 2016.
- Data were extrapolated from studies to provide insight on HPV vaccine impact measures.
- Measures assessed included decreases in HPV infections (6/11/16/18) broadly, decreases in HPV infections (6/11 and 16/18) in vaccinated populations compared to prevaccine era, decreases in HPV infection (6/11) during vaccine era, and decreases in CIN (as a consequence of HPV 16/18 infection).

REVIEW QUESTIONS

1. **Is the vaccine working?**
 - The simplest approach comparing population level rates of infection prior to vaccination starting (prevaccine era) with rates during the period of vaccine availability (vaccine era)
2. **How is the vaccine working directly between those that receive it and those that do not during the same time period?**
 - These studies are a closer approximation to direct measurement of the vaccine's effectiveness after introduction.
3. **Does the vaccine provide any benefit to those not vaccinated during the time when vaccine is available?**
 - In other words, these studies look at possible herd effects among populations not vaccinated by virtue of others being vaccinated.
4. **What has been the impact on pre-cancer disease outcomes?**
 - These studies compared decreases in cervical intraepithelial neoplasia in vaccinated populations.

Is the vaccine working?

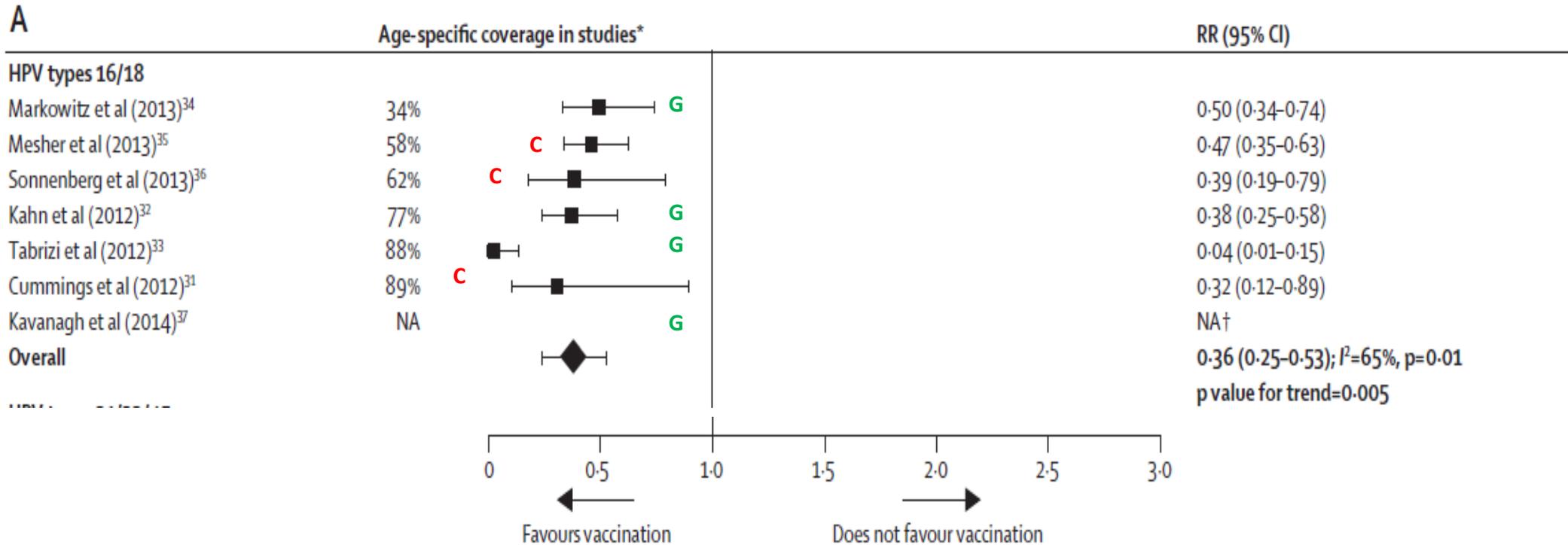
Figure 2. Percent reduction of genital warts (combined HPV 6/11 infections): vaccine era vs prevaccine era



[6] Mesher D, et al. *Vaccine* 2013
 [7] Tabrizi SN, et al. *JID* 2012
 [8] Read TRH, et al. *STI* 2011
 [9] Ali H, et al. *BMC Infect Dis* 2013
 [10] Sando N, et al. *Acta Dermato Venereologica* 2014
 [11] Dominiak-Felden G, et al. *PLoS One* 2015
 [12] Chow EPF, et al. *STI* 2015
 [13] Dunne EF, et al. *Cancer Causes Control* 2013
 [16] Canvin M, et al. *STI* 2017

HPV impact outcomes relative to vaccination levels in the population

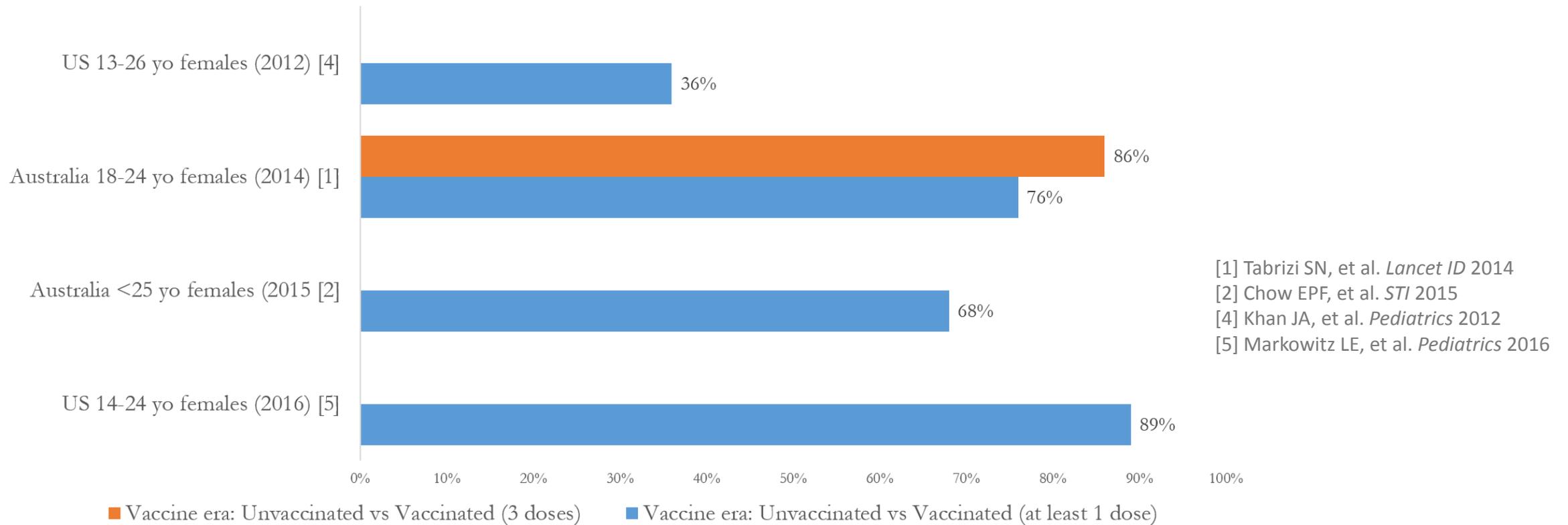
Prevalence of infections with HPV16/18 between periods before and after start of vaccination in 13–19 year olds



Drolet et al. *Lancet Infect Dis* 2015

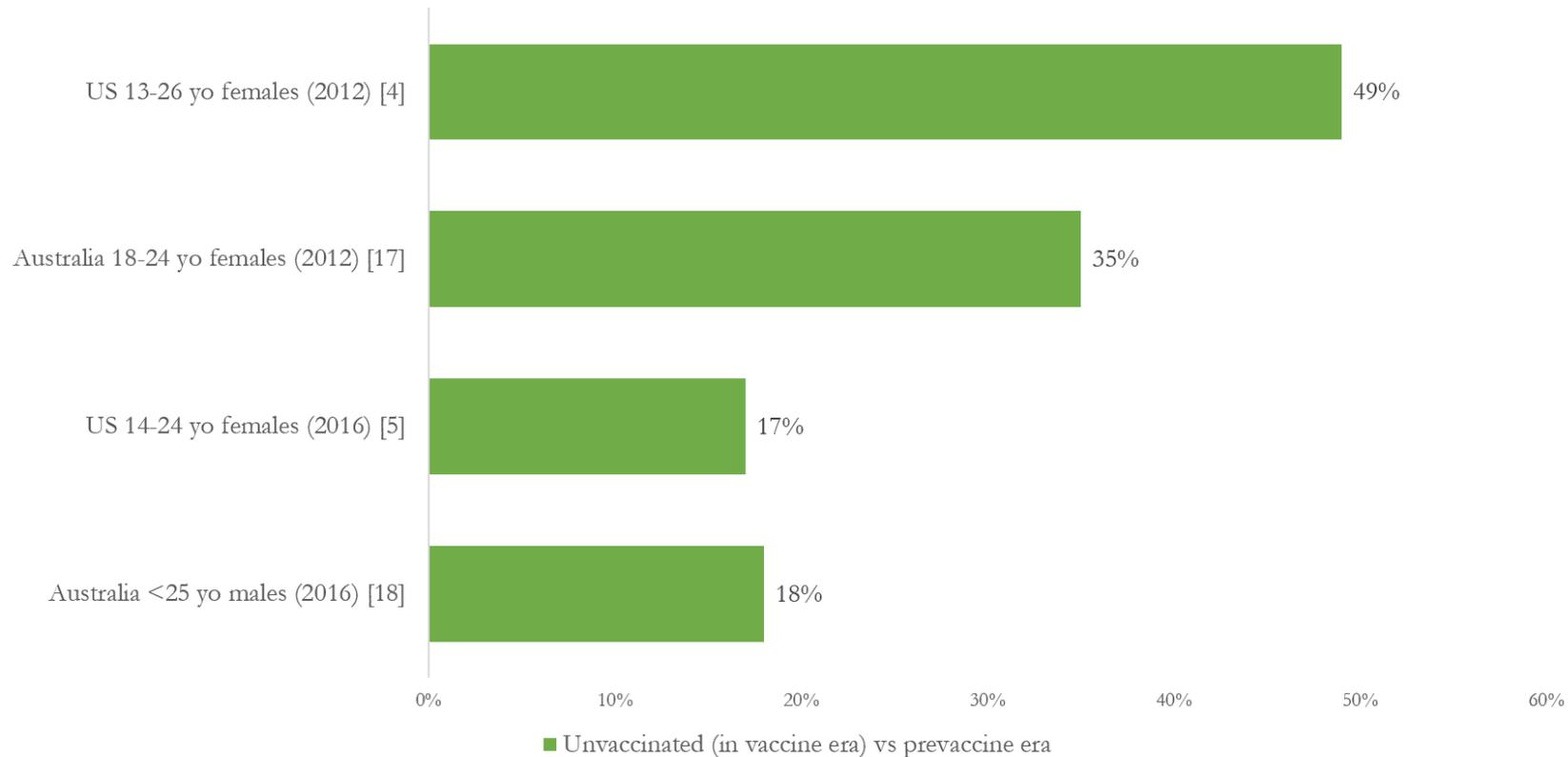
How is the vaccine working directly between those that receive it and those that do not during the same time period?

Figure 5. Percent reduction in prevalent HPV 6/11/16/18 infection among vaccinated compared to unvaccinated during the vaccine era



Does the vaccine provide any benefit to those not vaccinated (herd effect) during the time when vaccine is available?

Figure 6. Percent reduction of prevalent HPV 6/11/16/18 infections among the unvaccinated during vaccine era



[4] Khan JA, et al. *Pediatrics* 2012
[5] Markowitz LE, et al. *Pediatrics* 2016
[17] Tabrizi SN, et al. *JID* 2012
[18] Chow EPF, et al. *Lancet ID* 2016

What has been the impact on pre-cancer disease outcomes?

Table 2. Percent reduction in cervical neoplasia incidence

Country (year of pub.) [ref#]	Population	CIN stage	Percentage decrease in incidence (time period)
United States (2015) [21]	Females 18-20 yo	CIN 2+	95% (from 94 to 5 per 100,000, 2008-2011 California)
			87% (from 450 to 57 per 100,000, 2008-2012 Connecticut)
			86% (from 299 to 43 per 100,000, 2008-2012 New York)
			82% (from 202 to 37 per 100,000, 2008-2012 Oregon)
	Females 21-29 yo	CIN 2+	23% (from 762 to 589 per 100,000, 2008-2012 Connecticut)
			40% (from 770 to 465 per 100,000, 2008-2012 New York)

[21] Hariri S, et al. *Cancer* 2015

What has been the impact on pre-cancer disease outcomes?

Table 4. Incidence of CIN among vaccinated compared to unvaccinated populations

Country (year of pub.) [ref#]	Population	CIN stage	Incidence rate per 100,000 (time period)
Finland (2013) [25]	Females 16-17 yo, HPV-vaccinated (2002-03)	CIN3	0.0 / 100,000 (2007-2012)
	Females 16-17 yo, placebo-vaccinated (2002-03)		87.1 / 100,000 (2007-2012)
	Females 18-19 yo, unvaccinated (2003-05)		93.8 / 100,000 (2007-2012)

[25] Rana MM, et al. *Int J Cancer* 2013

What can we expect next?

- New HPV vaccines
 - Nonavalent
 - Chinese candidates (Innovax & Walvax)
 - Tech-transfer (India)
- Dosing schedule reductions (1-dose sufficient?)
 - “natural” experiment (India 1 v. 2 v. 3 dose trial)
 - 1 v. 2 dose efficacy and non-inferiority trial (Costa Rica)
 - Other 1 dose trials (Tanzania and The Gambia)
- Strengthened impact data
 - For different levels of coverage
 - For disaggregated and advanced CIN outcomes

Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study



Rengaswamy Sankaranarayanan, Priya Ramesh Prabhu, Michael Pawlita, Tarik Gheit, Neerja Bhatia, Richard Muwonge, Bhagwan M Nene, Pulikottil Okuru Esmay, Smita Joshi, Usha Rani Reddy Polj, Parimal Jivarajani, Yogesh Verma, Eric Zomawia, Maqsood Siddiqi, Surendra S Shastrj, Kasturi Jayant, Sylla G Malvi, Eric Lucas, Angelika Michel, Julia Butt, Janki Mohan Babu Vijayamma, Subha Sankaran, Thiraviam Pillai Rameshwari Ammal Kannan, Rintu Varghese, Uma Divate, Shila Thomas, Geeta Joshi, Martina Wilthauack-Fleckenstein, Tim Waterboer, Martin Müller, Peter Sehr, Sanjay Hingmire, Alka Kriplani, Gauravi Mishra, Sharmila Pimple, Radhika Jadhav, Catherine Sauvaget, Massimo Tommasino, Madhavan Radhakrishna Pillai, for the Indian HPV vaccine study group



Summary

Background An increase in worldwide HPV vaccination could be facilitated if fewer than three doses of vaccine are as effective as three doses. We initially planned to compare the immunogenicity and frequency of persistent infection

Lancet Oncol 2016; 17: 67-77

Efficacy of fewer than three doses of an HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica Vaccine and PATRICIA trials



Aimée R Kreimer*, Frank Struyf*, Maria Rowena Del Rosario-Raymundo, Allan Hildesheim, S Rachel Skinner, Sholom Wacholder, Suzanne M Garland, Rolando Herrero, Marie-Pierre David, Cosette M Wheeler, for the Costa Rica Vaccine Trial and the PATRICIA study groups†

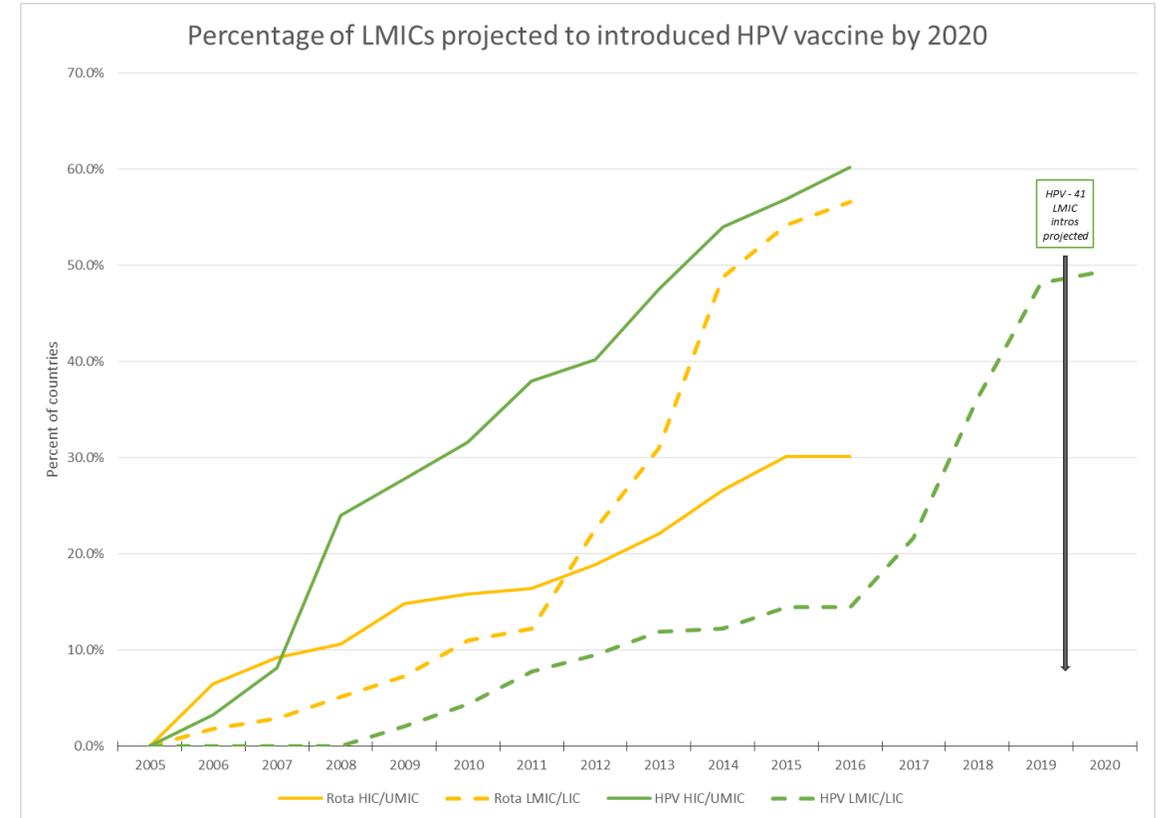
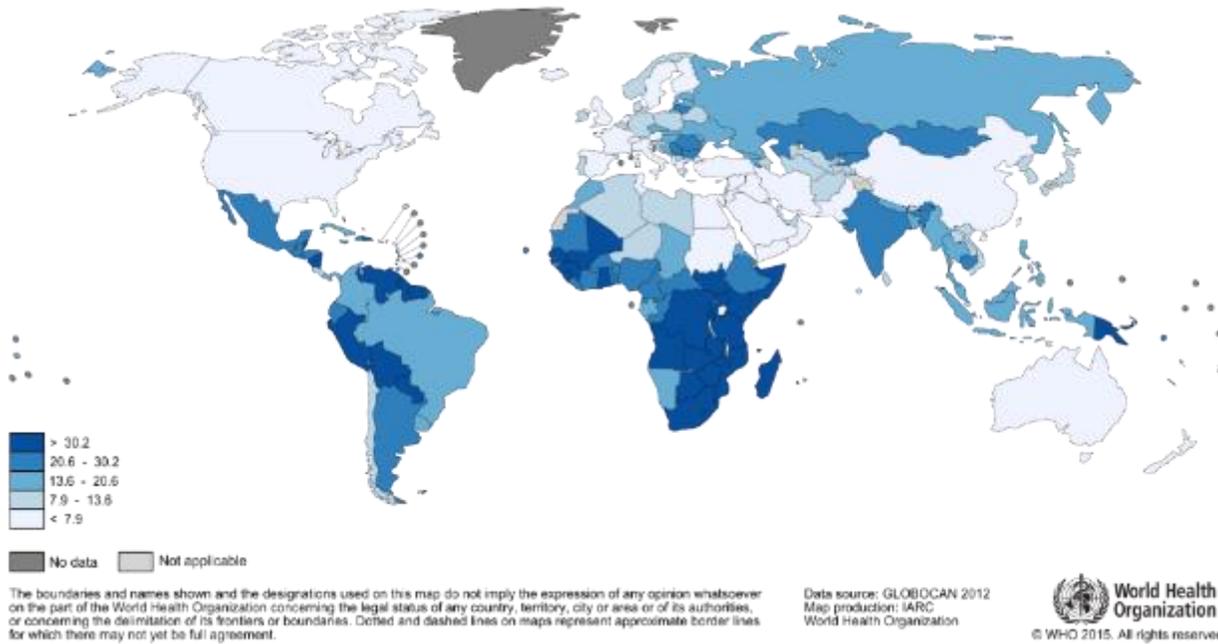
Summary

Background There is some evidence to suggest that one or two doses of the HPV vaccine provides similar protection

Lancet Oncol 2015

Expanded access and uptake in LMICs

Age-standardized incidence rates of cervical cancer, 2015



Thank you

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<http://path.org/our-work/cervical-cancer.php>

<http://www.rho.org/HPVlessons>

