Impact and Effectiveness of the Quadrivalent Human Papillomavirus (qHPV) Vaccine

10 Years of Real-World Experience

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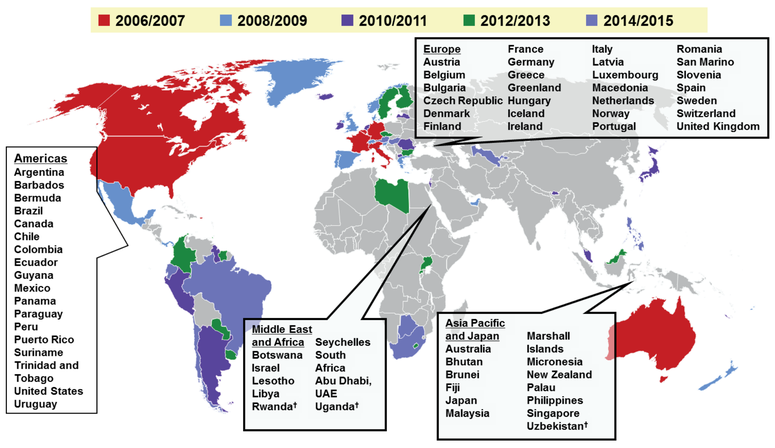
Background

- **HPV genotypes**
  - HPV 16/18 cause 70% of cervical cancers and 80%-90% of HPV-related neoplasms at other sites
  - HPV 6/11 account for 90% of anogenital warts
- **HPV vaccines in widespread use**
  - Bivalent (2vHPV; Cervarix®, GSK): HPV 16/18
  - Quadrivalent (qHPV; Gardasil®/Silgard™, Merck): HPV 6/11/16/18
  - Nonavalent (9vHPV; Gardasil®9, Merck): HPV 6/11/16/18/31/33/45/52/58
- Prophylactic HPV vaccine programs constitute major worldwide public health initiatives

Countries with HPV vaccine in a national immunization program, by year



†Global Alliance for Vaccines and Immunisation (Gavi).

Objectives

- **Rationale**
  - Although high efficacy against multiple endpoints was consistently observed in clinical trials, it is essential to document how trial results translate to real-world settings
- **Aim**
  - To assess the global real-world effect of the qHPV vaccine containing HPV types 6/11/16/18 over its first decade of use

Methods

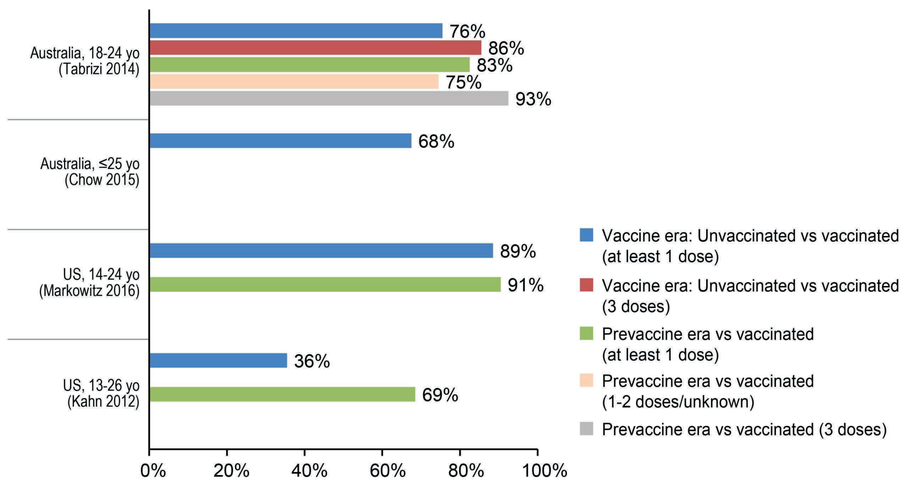
- PubMed and Embase were searched for peer-reviewed manuscripts in any language published after 1 January 2007, using prespecified search terms
- Observational studies of effectiveness or impact of qHPV vaccination on HPV infection or disease were considered for inclusion
  - Studies exclusively of the 2vHPV vaccine, review articles, and clinical trial reports were excluded
- The heterogeneity of study designs and individual circumstances surrounding each study precluded summary estimates

Study Design and Outcomes

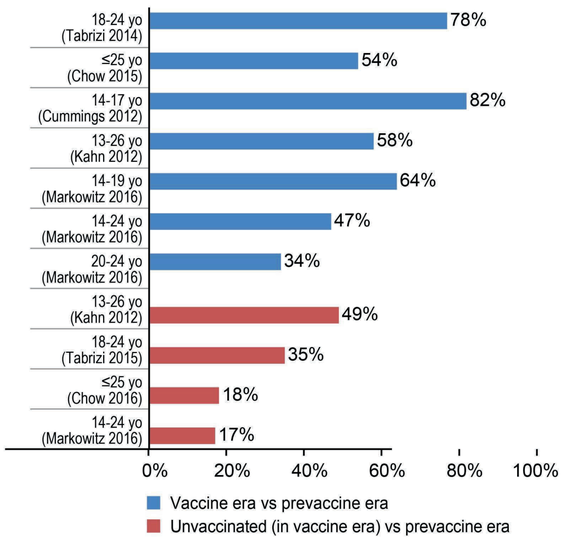
- **Systematic review**
  - To comprehensively synthesize available real-world data to quantify the effectiveness and impact of qHPV vaccination on HPV infection, anogenital warts, and cervical cytological/histological abnormalities
- **Vaccine effectiveness:** Proportion of infection or disease prevented by vaccination
  - Estimated by comparing incidence in vaccinated versus unvaccinated individuals within similar populations
- **Vaccine impact:** Population-prevented fraction of infection or disease
  - Assessed by comparing vaccine vs prevaccine era

Results

Reduction of HPV 6/11/16/18 infection in vaccinated females vs prevaccine era or contemporaneous unvaccinated females



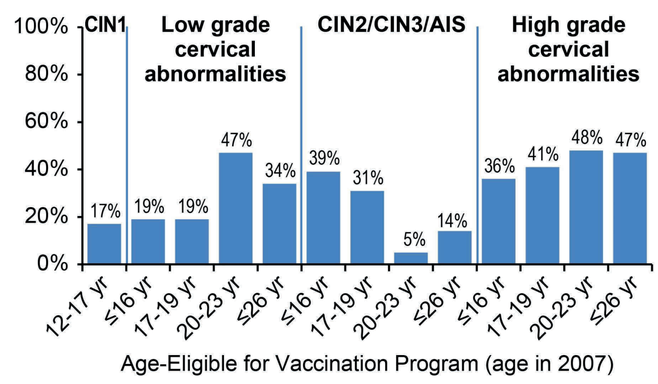
Reduction of HPV 6/11/16/18 infection in vaccine era



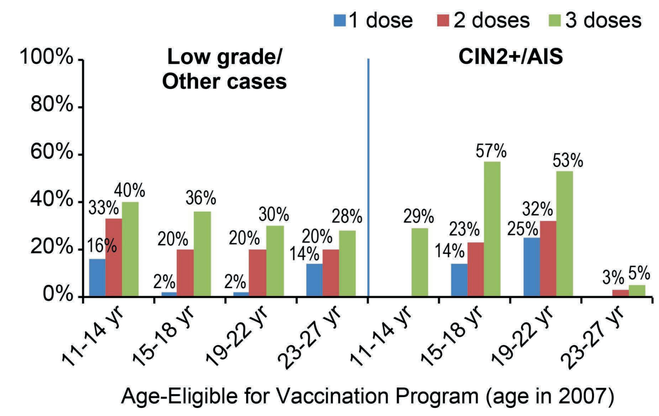
Genital warts—selected studies

Country	Reference	Setting	% Reduction
Australia (high vaccine uptake)	Chow 2015	Melbourne Sexual Health Centre, ≤7 yr after vaccine era	45% annually in females <21 yo
	Smith 2016	National hospital admissions database, ≤4 yr after vaccine era	85%-87%, 10-19 yo 62%-67%, 20-29 yo
	Donovan 2011	National surveillance, ≤2 yr after vaccine era	59%, 12-26 yo
Denmark	Bollerup 2016	National prescription registries, ≤5 yr after vaccine era	43% annually, 12-15 yo 55% annually, 16-17 yo 39% annually, 18-19 yo 21% annually, 20-21 yo 12% annually, 22-25 yo 6% annually, 26-29 yo
Sweden	Herjweijer 2016	National hospital admissions with genital warts diagnosis code, ≤4 yr after vaccine era	82%, 10-16 yo (3 vs 0 dose) 71%, 10-16 yo (2 vs 0 dose) 69%, 10-16 yo (1 vs 0 dose)
United States	Flagg 2013	Large claims database, ≤3 yr after vaccine era	No change, 10-14 yo 38%, 15-19 yo 13%, 20-24 yo

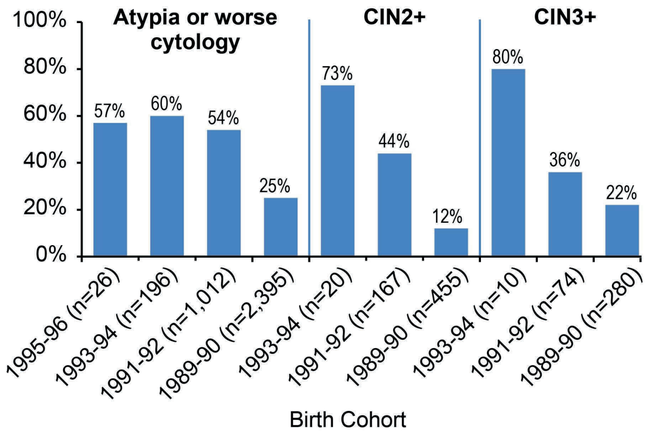
Australia: Reduction in cervical lesions in vaccinated (≥1 dose) vs contemporaneous unvaccinated screened females in Victoria



Australia: Reduction in cervical lesions in vaccinated vs contemporaneous unvaccinated screened females in Queensland



Denmark: Vaccine impact on cervical lesions by birth cohort



n=number of women with lesion in each age group, vaccinated and unvaccinated included.

Factors Influencing Estimates of Impact/Effectiveness	Relevant Considerations	Examples of Possible Bias
Vaccination program	• % uptake/length of time • Age at vaccination • Catch-up cohort	• Higher uptake → possible herd protection • Older age at vaccination → more prior HPV exposure
Vaccination status	• Data sources • Dose number • Age at each dose	• Registry data more accurate than self-reports • Age at dose can help time vaccination relative to sexual debut
Outcome data	• Data sources • Data type	• Pap/histological outcome categorization • HPV typing
Study context	• Location of study • Changes in sexual behaviors • Availability of risk factor data	• Secular trends can be independently associated with lower rates of lesions (not vaccination)
Cervical screening program	• Changes in screening • Population coverage • Age/interval of screening	• Increased screening over time can result in increased detection
Observational study design	• Ecological • Case-control vs cohort • Impact and/or effectiveness	• Individual-level data can help confirm/inform ecological observations
Cohort selected	• Screened/total population • High-risk population • Convenience sample • Comparison cohort • Incomplete vaccination series	• Total population includes those not screened, so no outcome data • Effectiveness can be influenced if individuals with incomplete vaccination series are at higher risk of HPV exposure prior to vaccination
Statistical analysis	• Sample size • Length of/lost to follow-up • Adjustment factors	• Smaller sample size → less stable • Raw or adjusted prevalence ratios or relative risks

Summary

- HPV vaccination programs constitute major public health initiatives worldwide
- This systematic review assessed the global impact and effectiveness of the qHPV-vaccine on HPV infection and disease in real-world settings over its first decade of use
- Substantial reductions were seen in qHPV-vaccine recipients HPV 6/11/16/18–attributable infections and resultant diseases with the shortest incubation periods
  - Genital warts
  - Cervical cytological and histological abnormalities

Conclusions

- Over the last decade, the impact of HPV vaccination in real-world settings has become increasingly evident
  - Especially where broad coverage prior to sexual debut is achieved
- Despite high vaccine effectiveness, the full public health impact of HPV vaccination is unfortunately far from being realized
  - Preventable HPV-related diseases continue to present major challenges to the public health in both developing and developed nations

Disclosures
- Merck manufactures the quadrivalent and nonavalent HPV vaccines under the brand names of Gardasil or Silgard and Gardasil-9, respectively
- The literature extraction was jointly sponsored and supported by Sanofi Pasteur MSD (Lyon, France) and Merck & Co., Inc. (Kenilworth, NJ, USA)
  - The systematic review was designed, managed, and analyzed jointly by the sponsors and invited external experts in the field
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Reference
- Garland SM, et al. Impact and effectiveness of the quadrivalent human papillomavirus vaccine: a systematic review of ten years of real-world experience. *Clin Infect Dis.* 2016; DOI: 10.1093/cid/ciw354.

http://tinyurl.com/hr63vle