Review of Effectiveness Studies HPV Vaccine 2-Dose Schedules

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Introduction

- Evidence review for 2 doses of HPV vaccine:
  - Immunogenicity
  - Efficacy
  - Post-licensure effectiveness
- Data on 2-dose immunogenicity and efficacy previously presented
- Systematic review of vaccine efficacy and effectiveness for 2 doses

Methods

- Search for studies on HPV vaccine effectiveness
  - 930 papers on vaccine impact or effectiveness identified
  - Studies selected if effectiveness evaluated by number of doses
  - 13 papers discuss vaccine effectiveness with 2 doses
- Studies presented by vaccine, then outcomes evaluated
  - HPV infection, genital warts, or cervical precancers
- Detailed data for studies evaluating outcomes by timing of interval

Limitations of post-licensure effectiveness studies

- Many methodological challenges to using post-licensure effectiveness studies within context of 3-dose program to evaluate 2-dose effectiveness
  - Most vaccinees received (M0,1) or (M0,2) interval
  - Many studies conducted during ‘catch-up’ vaccination period
  - Partially vaccinated population different than fully vaccinated
    - Implications for exposure to HPV prior to vaccination

- Overview of 2-dose studies for complete review of evidence

9vHPV effectiveness by number of vaccine doses

- No studies on 2-dose effectiveness of 9vHPV

4vHPV effectiveness by number of vaccine doses

- **8** studies

- HPV infection
  - Sankaranarayanan Lancet Oncol 2016

- Genital warts
  - Herweijer JAMA 2014
  - Dominiak-Felden PLOS ONE 2015
  - Blomberg Clin Infect Dis 2015

- Cervical precancer
  - Hofstetter JAMA Peds 2016
  - Crowe BMJ 2014
  - Gertig BMC Medicine 2013
  - Brotherton Papillomavirus Res 2015

4vHPV effectiveness by number of doses & interval, HPV infection

Country	Outcome Evaluated	Study Population	Vaccination	Incidence (95% CI)
India Sankaranarayanan, 2016	Overall incidence and persistent infection in females aged 10–18 years	Females aged 10–18 years	3 doses	0.4% (0.0–1.3)
			2 doses at (M0,6)	0.8% (0.2–1.9)
			2 doses at (M0,2)	1.3% (0.6–2.4)
			1 dose	1.1% (0.6–2.1)

- Conclusion:
  - No persistent infections
  - 2 doses at (M0,6) interval similar to 3 doses
- Limitations:
  - Randomized trial stopped early

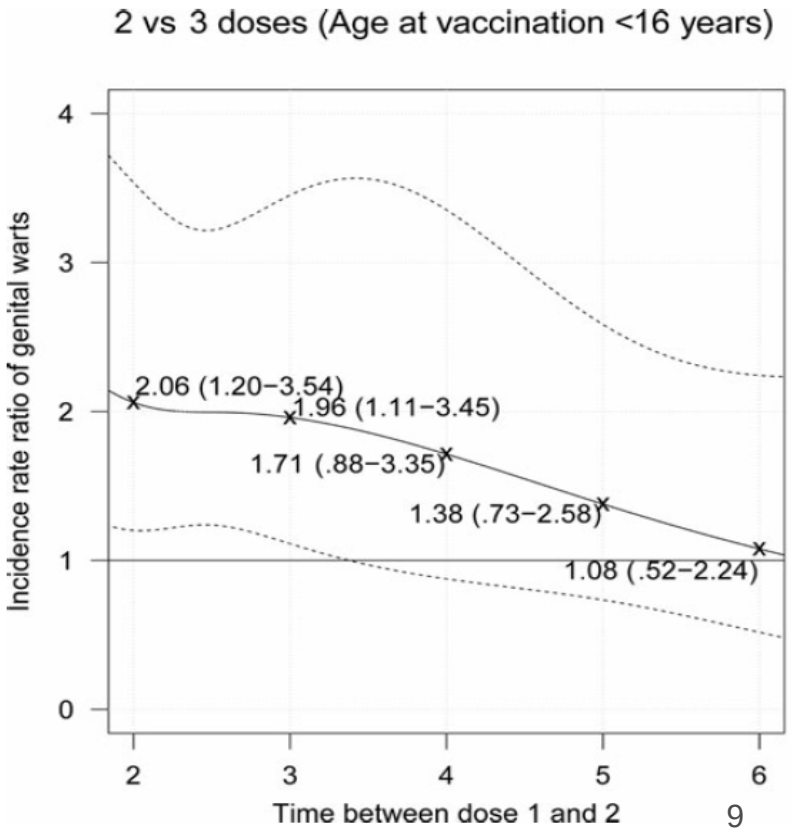
4vHPV effectiveness by number of doses, genital warts

Country	Study Population	Study Design
Sweden Herweijer, 2014	Females aged 10–24 years, vaccinated from 10–18 years of age	Retrospective cohort study using population-based health registries
Belgium Dominiak-Felden, 2015	Females aged 16–24 years, vaccinated from 12–18 years of age	Retrospective cohort study using sick-fund/ insurance data
Denmark Blomberg, 2015	Females aged 12–26 years, vaccinated from 12–26 years of age	Retrospective cohort study using national registries

- Conclusion:
  - All concluded that maximum vaccine effectiveness with 3 doses
- Limitations:
  - All evaluated partially vaccinated in setting of 3 recommended doses
    - Different than fully vaccinated
    - Most received (M0,2) interval

4vHPV effectiveness by number of doses & interval, genital warts

- Conclusion:
  - Effect of 2 doses, when given at a longer interval, approaches 3 doses
- Limitations:
  - Limited number of vaccinees with longer interval



Blomberg Clin Infect Dis 2015

4vHPV effectiveness by number of doses, cervical precancer

Country	Study Population	Study Design
United States Hofstetter, 2016	Vaccine eligible females from select clinics, with cervical screening prior to 2014	Retrospective cohort study using medical center records
Australia Gertig, 2013	Females vaccinated up to age 17, with first cervical screen from 2007 –2011	Retrospective cohort using linked regional data registries
Australia Crowe, 2014	Females vaccinated from age 12–26, with first cervical screen from 2007 –2011	Case control study using linked data from population registries
Australia Brotherton, 2015	Females vaccinated up to age 26, with first cervical screen from 2007 –2011	Retrospective cohort using linked regional data registries

- Conclusion:
  - All concluded that maximum vaccine effectiveness with 3 doses
- Limitations:
  - All evaluated partially vaccinated in setting of 3 recommended doses
    - Different than fully vaccinated
    - Most received (M0,2) interval

4vHPV effectiveness by number of doses & interval, cervical precancer

Vaccination	Time between doses	Hazard Ratio
3 doses	-	0.71 (0.64–0.80)
2 doses	<6 months	1.25 (1.03–1.51)
2 doses	≥6 months	1.05 (0.72–1.55)

- Conclusion:
  - Interval ≥6 months had lower hazard ratio, but neither ratio was significantly lower than the unvaccinated population
- Limitations:
  - Partially vaccinated females older at vaccination, younger at first cervical screening, lower SES
  - <5% of population received 2 doses at ≥6 months

Brotherton Papillomavirus Res 2015

2vHPV effectiveness by number of vaccine doses

- **5** studies

- HPV infection
  - Kavanagh BJC 2014
  - Cuschieri BJC 2016
  - Kreimer (efficacy) JNCI 2011
  - Kreimer (efficacy) Lancet Oncol 2015

- Cervical Precancer
  - Pollock BJC 2014

2vHPV effectiveness by number of doses, HPV infection

Country	Study Population	Study Design
Scotland Kavanagh, 2014	Females aged 20–21 years, residual samples from first cervical screening	Cross-sectional study using registry data and state labs
Scotland Cuschieri, 2016	Females vaccinated from age 12–17 years of age with residual cervical sample	Cross-sectional study using registry data and state labs

- Conclusion:
  - First study found no risk reduction with 2 doses
  - Second study found risk reduction with 2 doses, but less than reduction from 3 doses
- Limitations:
  - All evaluated partially vaccinated in setting of 3 recommended doses
    - Older than fully vaccinated
    - Most received (M0,1) interval

2vHPV efficacy by number of doses, HPV infection

Country	Study Population	Study Design
Costa Rica Kreimer, 2011	Females aged 18–25 years: **Costa Rica Vaccine Trial**	Post-hoc analysis of a 3 dose randomized controlled clinical trial
Multiple Kreimer, 2015	Females aged 15–25 years: **Costa Rica Vaccine Trial** or **PATRICIA** trial	Post-hoc analysis, combing data from 2 randomized controlled trials

- Conclusion:
  - Both showed high efficacy with 1, 2 and 3 doses
- Limitations:
  - Evaluated partially vaccinated from those randomized to receive 3 doses
  - Pregnancy was most common reason for incomplete series

2vHPV efficacy by number of doses & interval, HPV infection

Vaccination	Interval	Vaccine efficacy (95% CI)
3 doses*	—	77.0% (74.7–79.1%)
2 doses	1 month	75.3% (54.2–87.5%)
2 doses	6 months	82.6% (42.3–96.1%)

- Conclusion:
  - High efficacy with both a (M0,1) and (M0,6) interval
- Limitations:
  - Small percent of study participants received longer interval

* Population included in analysis is CRVT + PATRICIA Trial participants

Kreimer Lancet Oncol 2015

2vHPV effectiveness by number of doses, cervical precancer

Country	Study Population	Study Design
Scotland Pollock, 2014	Females vaccinated at 12–17 years of age, with a colposcopy	Retrospective cohort study using linked national registry data

- Conclusion:
  - No risk reduction with 2 doses
- Limitations:
  - Evaluated partially vaccinated in the setting of 3 recommended doses
    - Partially vaccinated females older, graduated from school
    - Primarily a (M0,1) interval
    - Small proportion of population received 2 doses

Summary

- **13** studies evaluated 2-dose effectiveness
- Study design
  - 3 post-hoc analyses of clinical trials
  - 10 post-licensure effectiveness studies evaluating partially vaccinated individuals in settings of a 3 dose schedule
- Dosing interval
  - 4 included evaluations of (M0,6) interval

Conclusion

- 3 studies found similar outcomes for 2 doses compared to 3 doses
  - All 3 were post-hoc analyses of clinical trials
- 10 studies found 2 doses were not as effective as 3 doses
  - All 10 were post-licensure effectiveness studies performed within settings of a recommended 3-dose schedule
    - Most received a (M0,1) or (M0,2) interval
  - Persons who only received 2 doses different than those completing series
    - Older, lower SES, earlier cervical screening
    - Implications for exposure to HPV prior to vaccination

Conclusion

- Of the 4 studies that evaluated a (M0,6) interval compared to a shorter interval
  - 1 study showed a longer interval was more effective
  - 3 studies suggest a longer interval impacts vaccine effectiveness

Conclusion

- Many methodological challenges to using post-licensure effectiveness studies within context of 3-dose program to evaluate 2-dose effectiveness
- Data from post-licensure effectiveness studies may not be applicable to current policy question due to differences in:
  - Age at vaccination
  - Interval between 2 doses
  - Population in the studies receiving 2 doses compared to 3 doses
- These factors impacted studies included in GRADE

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For more information, contact CDC
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