Session III: HPV Surveillance and vaccines

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HPV Vaccination: Myths and Misconceptions

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Topics to cover

- Main findings from RCTs of HPV vaccines
- Importance of universal prophylactic HPV vaccination: equitable benefit
- What are the true gaps in knowledge that require consideration?
- Validity of common arguments against HPV vaccination

Prophylactic HPV vaccines

Characteristic	Gardasil®	Cervarix™
Manufacturer	Merck & Co., Inc., Whitehouse Station, NJ USA	GlaxoSmithKline Biologicals, Rixensart, Belgium
VLP types	6/11/16/18	16/18
Dose of L1 protein	20/40/40/20 μg	20/20 μg
Producer cells	*Saccharomyces cerevisiae* (bread yeast) expressing L1	*Trichoplusia ni* (Hi-5) insect cell line infected with L1 recombinant baculovirus
Adjuvant	225 μg aluminum hydroxyphosphate sulfate	500 μg aluminum hydroxide, 50 μg 3-O-deacylated-4'-monophosphoryl lipid A (ASO4)
Injection schedule	0, 2, 6 months	0, 1, 6 months

Schiller et al., Vaccine 2008

Main findings from RCTs of HPV vaccination

- High efficacy (>95%) in preventing incident and/or persistent HPV infections by the target types (16/18 or 6/11/16/18) and precancer associated with these types in women 15-26 years of age.
- Protection has continued unabated after 6 years of f/up (> 8 yrs for prototype HPV-16 vaccine).
- High titers of neutralizing antibodies among vaccinees.
- Comparable protection among older women and men if not previously exposed.
- No evidence of protection against existing infections; vaccination does not accelerate clearance of infections by target types.
- Evidence of cross-type protection, primarily for HPV 45 and to a lesser extent to HPVs 31 and 33.
- Incidence of adverse events comparable to placebo and within expected background rates in general population.

HPV Vaccination

- Phase II and III trial findings already in the public domain.
- Safety, efficacy, and cost-effectiveness of VLP vaccines documented by numerous peer-reviewed publications in leading medical journals.
- Although clinical experience has just passed 6-8 years, the evidence base is one of the strongest in disease prevention.
- The standard of proof is far more rigorous than that used in the evaluation of candidate vaccines of the past.
- Possibly, the most scrutinized vaccine by the public and media concerning need and safety.

Importance of implementing universal pre-exposure HPV vaccination

Main reason: to provide equitable access to benefit.

Facts:

1) Opportunistic vaccination has already begun;
2) Most cases of cervical cancer represent failures of screening due to insufficient coverage among women of low SES.

What may happen: If only opportunistic vaccination is adopted the existing inequity in cervical cancer prevention will increase.

Franco and Cuzick, Vaccine, 2008

Importance of implementing universal pre-exposure HPV vaccination

The "Like mother, like daughter" principle:

Part 1: The good news (reduction of case loads)

- Mothers who comply with screening will want their daughters to be vaccinated
- Young women who are vaccinated will be like their mothers and are likely to comply with screening later
- Initial enthusiasm with reduction in cervical abnormalities and colposcopy caseloads
- However, because of their high compliance with screening these women would not be likely to develop cervical cancer

Franco et al., Vaccine, 2006

Importance of implementing universal pre-exposure HPV vaccination

The "Like mother, like daughter" principle:

Part 2: The bad news (no change in cervical cancer incidence)

- Mothers who are not screened are less likely to have heard of HPV vaccination and its benefits
- They are unlikely to have their daughters vaccinated
- Like their mothers, these unvaccinated women will be less likely to be screened
- Their lesions will progress undetected with no cytology surveillance
- Until cancer is diagnosed 15-20 years later

Franco et al., Vaccine, 2006

What are the gaps in knowledge?

- Delivery logistics for an adolescent vaccine.
- What to do with cervical cancer screening? Technology changes, age at initiation, frequency.
- Coordination with cancer control programmes.

Example of arguments against HPV vaccination

"Too costly, unaffordable where most needed"

Counter-arguments:

- Procurement programmes reduce costs (e.g., CDC's VFC program, GAVI, PAHO's revolving fund).
- Historically, prices decline with time since deployment.
- Advice from public health and scientific community to vaccine companies to establish thresholds of affordability.
- Competition among manufacturers should force a reduction in prices.
- Ongoing studies on simplified schedules (2 vs. 3 doses).

Example of arguments against HPV vaccination

“No data on long-term duration of protection”

Counter-arguments:

- Sustained Ab response with no indication that humoral immunity will wane before 10 years.
- Even with lowered Ab titers post-vaccination protection has continued unabated.
- Analogy with other subunit vaccines: protection is high even after 20 years.
- We did not wait for such proof before deploying other vaccines.

Example of arguments against HPV vaccination

"It is more effective to get Pap tests"

Counter-arguments:

- Pap cytology is insensitive.
- Screening is secondary prevention: for every case of cancer that is detected there are about 100 cases of cervical abnormalities that require treatment or close follow-up.
- Effective organized screening is complex and costly; coverage alone is not sufficient.

Example of arguments against HPV vaccination

"Screening will continue to be needed"

Counter-arguments:

- Yes, but recent progress on new technologies (HPV testing with Pap triage) will permit extending screening intervals safely and cost-effectively.
- Proper integration of primary and secondary prevention strategies is likely to reduce costs and improve cervical cancer control.

Example of arguments against HPV vaccination

"Protection is limited; vaccines contain only two types"

Counter-arguments:

- Protection is against the ***two most important types***, which translates into a preventive fraction of 70% of all cervical cancers
- Likely to be expanded via cross-protection
- In combination with tailored screening strategies may achieve unprecedented life-long protection

Example of arguments against HPV vaccination

"Risk of type replacement; has happened with pneumococcal vaccine"

What is type replacement?

- The potential for the distribution of HPV types to change gradually as a reflection of the progressive elimination of HPVs 16 and 18 in vaccinated populations.
  - *Note: Evolutionary mutation rate in HPV = one bp every 10,000 years.*

Example of arguments against HPV vaccination

("Risk of type replacement; has happened with pneumococcal vaccine")

Why is type replacement unlikely to happen?

- No epidemiologic proof that HPV types compete for specific niches; several studies have tested this hypothesis.
- Fraction of the population not exposed to HPV 16/18 always high; exposure to HPVs 16/18 does not constrain the pool of susceptible individuals who could acquire other HPVs.

Important: Should not be used as argument to justify conducting prevalence surveys before deploying HPV vaccination. Only ongoing RCTs can properly test the hypothesis of type replacement.

Example of arguments against HPV vaccination

"No proof yet that vaccination can reduce risk of invasive cancers"

Counter-arguments:

- Efficacy in preventing high-grade CIN
- "Absence of evidence" is not "evidence of absence"
- Sensible judgment based on understanding of the natural history of HPV infection and cervical cancer indicates that prevention of precancerous lesions is an acceptable endpoint.

Example of arguments against HPV vaccination

"There is no cervical cancer epidemic"

Counter-arguments:

- The health costs, morbidity, and mortality associated with cervical cancer are sufficiently important to justify action.
- The morbidity and costs associated with diagnosing and managing precancerous lesions are very high.
- Post-screening management of cervical precancerous lesions frequently leads to miscarriage and premature delivery on subsequent pregnancies.

Example of arguments against HPV vaccination

"There is no cervical cancer epidemic"

Counter-arguments (cont'd):

- Vaccination likely to exert substantial protection against other neoplastic diseases, malignant (anogenital and oropharyngeal cancers) and benign (genital warts and laryngeal papillomatosis)
- By analogy, childhood cancer mortality is very low, yet governments would act fast in adopting a preventive measure that could reduce childhood cancer deaths by 50%-70%.

Example of arguments against HPV vaccination

"More research is needed on safety"

Counter-arguments:

- The safety data are among the most well documented for any new vaccine.
- There was no waiting period for the adoption of other vaccines with lesser standards of proof.
- Inaction has a high cost in terms of morbidity and mortality that could have been averted.
- In any case, the most detailed data on safety can only come post-vaccine deployment.

Proper analysis of the vaccine-attributable risk requires knowledge of several epidemiologic parameters

Vaccinated population

N_v

T_v

Follow-up time

Non-vaccinated population

N_n

T_n

Number of cases of adverse event among vaccinated people

C_v

Number of cases of adverse event among non-vaccinated people

C_n

The public only has knowledge of C_v and assumes that this is sufficient to impute causality.

$$\text{Relative risk} = \frac{C_v / (N_v \times T_v)}{C_n / (N_n \times T_n)}$$

After controlling for confounders, the RR measures the excess risk of the event due to vaccination beyond the background rate of the event in unvaccinated persons.

Conclusions

- Unequivocal and large body of evidence in favour of HPV-based preventive strategies.
- Universal HPV vaccination will avoid inequity and will be more effective than opportunistic vaccination.
- Policy adjustments can be made as the new evidence emerges from post-vaccination surveillance and phase IV studies.
- Health professionals serving as opinion leaders should understand the arguments against HPV vaccination and be prepared to oppose them based on scientific facts.