HPV Vaccination of adults: Impact, Opportunities and Challenges – November 2019.

Antwerp, Belgium

November 14-15, 2019

HPV Prevention and Control Board

www.hpvboard.org

Objectives of the meeting (1)

- Provide an overview of the current situation of HPV vaccine for adults.
- Discuss the immunogenicity, safety and efficacy data of existing HPV vaccine studies in adults.
- Gain insight into efficacy of HPV vaccine at mucosal level and systemic level.
- Discuss ways and methods to conduct research on potential benefits of vaccinating exposed adults.
- Understand the evidence of the potential of HPV vaccination to interrupt HPV transmission

Objectives of the meeting (2)

- Discuss challenges and benefits of vaccination of adults including high risk groups.
- Discuss cervical cancer elimination strategies.
- Discuss potential implication of vaccination of adults on vaccine supplies in Low and Middle-Income Countries (LMIC).

Context – Safety

- Cochrane review 2018
- Looking for vaccine-types (VT) vs non-VT vs all
- Looking at different age groups
- 2 safety issues:
  - Serious adverse events (SAEs)
  - Mortality

Context – Safety

- No increased risk of SAEs in older women
- Reported increased risk of mortality in older women
- Cause of deaths not related to vaccine
- Geographical clustering, no temporal relation
- No pattern in death causes
- Finding attributed to chance

Context – Safety

- Mortality: death is the worst SAE
- How to understand these data?
- Understanding the causes of this mortality excess should be a priority
- Provide a background/baseline risk of death, then look whether there is an increased rate
- Design issues, e.g. the effect of unblinding
- What is the rate of loss to follow up in placebo versus vaccine group
- Mortality should be further documented (time after vaccination, clinical details, location, …)
- Who completes the death certificate?

Context – Immunogenicity

- Seropositivity slightly lower in older women
- Always at least 8 times higher than natural infection -> highly immunogenic
- Age-depending decrease but still high above natural infection level -> robust immune response, present for a long time
- High correlation between antibodies in blood and cervicovaginal secretion
- Modelling: antibodies remain present for at least 30 years

Context – Immunogenicity

- Signs for an immunogenic difference between the two vaccines: 2vHPV better in eliciting neutralizing antibodies
- The difference is bigger for HPV 18 than for HPV 16
- Clinical relevance or impact on protection unclear
- So far, no immune correlates of protection

Context – Efficacy

- Moderate to strong efficacy against CIN2+/CIN3+/AIS caused by HPV16/18 in 15-26-year-olds (lower against all HPV)
- Strong efficacy against persistent HPV16/18 infection in 15-26-year-olds
- Limited efficacy against CIN2+ caused by HPV16/18 in 24-45-year-olds
- Limited efficacy against persistent HPV16/18 infection in 24-45-year-olds
- Better if women were HPV negative at enrolment

Context – Immune cross talk towards infection prevention

- Assay: xMAP, different HPV types simultaneously, high throughput, small samples, 2 international standards included,
- Two population-based studies 2006 / 2016 in the Netherlands
- Gender differences in seroprevalence: lower levels of seroprevalence in the males versus an increase in seroprevalence in non-vaccinated women, in most age groups
- Nevertheless, large part of the population is seronegative (which does not rule out previous infection), eligible for vaccination?

Context – Immune cross talk towards infection prevention

- Mucosal antibodies: considerable levels of HPV 16 & 18 in CVS, correlated with concentration in serum
- Cross-protection against 31, 35, 45 and 52 in adolescents and young adults
- One-dose study, especially in LMIC? Looked at all girls receiving 1 dose only. Lower levels than 2 or 3 doses, but still much higher than non-vaccinated girls
- Avidity is similar regardless of number of doses, as are subclass-responses. 1 dose induces lower number of memory cells, immune response wanes more quickly

Context – Immune cross talk towards infection prevention

- Very early effects after immunization, in adults, seronegative for high-risk types. Half with 2vHPV, half with 9vHPV.
- Euroflow method, able to phenotype >200 cell types, innate panel, T cells, B cells, etc.
- However, will these effects have a bearing on the eventual immune system and protection?

Context – Vaccine-induced antibodies in cervicovaginal secretions (CVS)

- Levels vary during menstrual cycle: reduction just before ovulation (but high enough to provide protection)
- Mucosal immunization not promising
- Detection in CVS lower than in blood
- Higher titers in CVS after 2vHPV
- No standard sampling method; softcup // first void urine
- Not able to look at neutralizing antibodies
- Normalization through division by total IgG
- Influencing factors: menstrual cycle/blood contamination/age
- Key question: do transudated antibodies protect against transmission

Context – the potential impact of cervical sample collection on HPV infection

- In mouse model, physical/chemical disruption necessary for HPV infection
- Disrupted epithelium makes it possible for capsids to bind
- Cervical sample collection is based on surface disruption
- Dramatic results in macaque model: 1000x higher infection after pap smear, almost entirely inhibited by carrageenan

Context – HPV vaccination post treatment

- Vaccination after conization -> lowers risk of recurrence
- Speranza (Italy). After 4 years FU, the risk was reduced by 81.2%
- In Spain, three groups were vaccinated post treatment: 1) women who decided to pay for vaccination (treated > 1 year before introduction of guideline), 2) women who were recalled (treated < 1 year before guideline), 3) women who got vaccine after procedure (from date of guideline)
- Free vaccine raised acceptance of the vaccine
- 3.3% in vaccinated vs 10.7% in non-vaccinated had persistent/recurrent disease
- Effective for vaccination of older women with high-grade disease

Context – HPV vaccination post treatment

- Denmark: selected all CIN3+ cases, via PIN linked to vax register, reduces loss to FU
- Registered new episodes of CIN2+
- FU from 1 year after vaccination, to exclude relapse
- Women vaccinated before treatment much better outcome
- Not true for women vaccinated after treatment
- NOTE: potential reduction of recurrences in males, after AIN and condyloma
- NOTE: potential benefit after RRP (reduction in number of surgical interventions)

Context – Transmission Reduction and Prevention with HPV Vaccination

- The Hitch study showed transmission reduction, however, only 10% was vaccinated
- Designed to address the need for evidence that vaccination can interrupt transmission
- RCT: 2x2 study with both males and females vaccinated, both placebo, male+, female- and male-, female+
- Relation less than 6 months (tried 3 months, enrolment failed)
- First results by end of next year
- Costly endeavour, many sponsors
- Challenge in recruitment

Context – Predicting cohort-specific CaCx incidence from population-based HPV prevalence surveys

- Key problem: how long does it take from infection to cancer
- HPV prevalence + cancer incidence to decipher rate of progression
- Worldwide surveys available, using GP5+/6+, in places with cancer registries
- At risk population (HPV+) and cancer prevalence in same age cohort
- From prevalence to incidence, based on average age at sexual debut
- A plateau is reached by age 35, regardless of age at sexual debut

Context – Health Economics Models for HPV Vaccination of Mid-Adults

- Five models used
- Differences in structure/calibration
- All models favourable cost-effectiveness result for current vaccination program
- Little extra benefit of vaccination up to 45 years of age
- Cost per QALY ranging from 100,000 to 1,400,000
- Even worse with slow progression and high natural immunity
- Based on an 1% annual increase in vaccination coverage in mid-adults

Context – Directionality of HPV Infection transmission

- Longitudinal, not cross-sectional studies needed
- Discordant HPV infection needed to investigate transmission
- Genotyping needed
- 7 studies of which 2 new
- Lot of heterogeneity, in FU, age, relation status, differences in genotyping assays
- Low transmission rates except for Hernandez and Widdice
- Slightly higher in F2M than M2F, but not significant

Context – HPV Vaccination for sex workers: pros and cons.

- Large STI clinic, special clinic for sex workers
- Prevalence anal/vaginal much higher than in general population and remains high with age
- Intention to vaccinate: high if free, going down with increasing cost
- Pro vaccination: high-risk group, not previously vaccinated; immunogenicity regardless of sexual activity; vaccine may reduce transmission
- Against: Prophylactic, not therapeutic; not needed if self-clearing; difficult to establish past infections; clearance vs latency

Context – HPV Vaccination for sex workers: pros and cons.

- Silverberg + Wilkin + van der Zee – no indication of effect
- Public health view - Aim to protect sex workers?
- Public health view - Aim to protect community?
- Physician - Aim to protect individual sex workers?
- Studies needed to investigate the impact of SW vaccination on transmission.

Context – HPV Vaccination for MSM in Scotland

- Vaccination of MSM under 45 since July 2017
- Vaccine uptake around 65%; completion much lower, uptake mainly in 20-29 age group
- Decrease in genital warts in Scotland, both in males and females, not shown for MSM
- 1 year after introduction, based on 1235 samples
- Decrease in HPV 16/18, small but significant
- Still early in program, without info on vaccination status

Context – Towards cervical cancer elimination: the context of HPV Vaccination.

- Three models used plus a hiv+ model, especially for Africa
- three scenarios
  - S1 – girls only, same screening
  - S2 – girls only, 1 lifetime screen
  - S3 – girls only, two screens, 2nd 10 y later
- Assumptions: 90% coverage of girls, lifelong duration of vaccine, 100% efficacy
- S1 will go below 10/100 000 not reach 4/100 000
- S2 around 4
- S3 most likely below 4

Context – Towards cervical cancer elimination: the context of HPV Vaccination.

- Shortage expected to last for 5 years, with impact on vaccine introduction in LMIC, and hence, on the number of deaths due to CaCx, as these are high-risk countries
- Number needed to vaccinate to avoid one case of any HPV related cancer: girls in Uganda 78, girls in Canada 560, boys in Canada 5480, adults in US >8500
- Ethics of adding other cohorts in the light of vaccine shortage: can HIC be asked to pause/delay vaccination of boys, of adults, of risk groups?
- Vaccination of boys is essential, shift in HPV-related cancer from almost purely female to 50/50 male/female, due to increase in OPC
- Vaccination of boys also impactful in countries with “low” coverage in girls, even for CaCx

Pros and cons of vaccinating of older cohorts

- PRO: Primary protection from types not yet encountered
- PRO: Secondary protection of transmission to partners*
- PRO: When trying to reduce transmission - herd immunity - catch-up is important -> vaccinating older cohorts is just another catch-up program
- PRO: Reduce risk of progression by preventing auto-inoculation leading to transformation zone or endocervical infection*
- PRO: Neutralize shed virus, reducing transmission from infected women*

* More data is required to confirm this impact

Pros and cons of vaccinating of older cohorts

- CON – the cost is very substantial, even with a 1-dose schedule
- CON – vaccination won't clear infection in those already infected
- CON – current shortage in vaccine worldwide (but plan well ahead, vaccine ordered now will be delivered in 2 years)
- CON – efficacy is limited above 25 years of age

Lessons learned

- Two sites to block infection by antibodies: 1) binding of virus to the basement membrane, 2) binding of virus to L1 binding sites on keratinocyte
- For protection, low levels of antibodies might be sufficient but high avidity is necessary
- Differentiate purposes of vaccinating older cohorts: 1) benefit of the community by reduction of transmission or reduction of healthcare cost; 2) benefit for the individual, although the latter might be limited
- If not vaccinating entire older cohorts, focus on risk groups such as MSM, or HIV+ women at increased risk of CaCx?

Lessons learned

- Should carrageenan be used as a standard for pelvic exams
- Three trials using carrageenan currently underway; preliminary evidence that it is 40% efficacious
- HCW are important to spread the message that vaccination helps reduce persistence/recurrence after conization
- Free provision of vaccine after conization improves the vaccination rate
- 10 years ago, we thought only HPV-naïve could be vaccinated. Now we are discussing to make it much broader.

Lessons learned

- Prioritize on target groups: high coverage in girls and boys first
- Vaccination of boys is not directed at CaCx, it is about HPV-related cancer.
- Let's not think about elimination just yet. Increase coverage first.
- Elimination only possible with screening and treatment, too costly for many LMIC.
- Don't underestimate the impact of a message to pause/delay the use of a valuable vaccine, may have a negative effect on vaccine acceptance in HIC, the language must be much clearer.

Recommendations – further studies needed?

- Revisit efficacy in older women now that more data are available
- Investigate reduction in transmission, by tissue-culture experiments or through RCTs showing reduced risk
- Develop more sensitive assays to detect mucosal antibodies
- Demonstrate that shed virus can be neutralized
- Investigate how long it takes from primary infection to CaCx at different ages
- RCTs on pap smear +/- carrageenan?
- Belgium: large data set, genotyping on pap smears. Change of sampling device, look for effect on glandular disease before and after new device.
- Find a small population, preferably on an island, give everybody 1dose, this should have a profound impact on transmission. Assess the potential for elimination.

Recommendations – further studies needed?

- Look at intradermal immunization to spare antigen, so a delay in LMIC may be avoided
- Studies needed to investigate the effectiveness of vaccination of SW

Recommendations

- So far, goals and policies for HPV vaccination have been focused on benefits for those vaccinated
- Think fundamentally: block transmission to have a rapid drop in HPV transmission
- If we really want to eliminate CaCx, we need to immunize whole populations. Cost should not be an issue. However, eradication of CaCx may not be an option. Less than 4/100 000 is not eradication.
- Think globally, the need for vaccine is in younger cohorts first.

Conclusion

- Too early to routinely introduce vaccination of adults
- Information incomplete, many further studies suggested, see above
- Given the limited vaccine supply, do not compete, the need for vaccine is in younger cohorts first, especially in LMIC, as that is where the burden is highest