Why are we reviewing the evidence on HPV immunization of adolescent girls & what are the questions for SAGE today?

Prof Claire-Anne Siegrist
SAGE Member
Estimated cervical cancer incidence worldwide

2012:
528,000 new cases
266,000 deaths due to cervical cancer.

> 85% of cervical cancer deaths are in developing countries

Data Source: International Agency for Research on Cancer
Two available vaccines: bivalent (bHPV, Cervarix®) and quadrivalent (qHPV, GARDASIL®).

Both are prepared from purified L1 protein, the major capsid protein, and contain HPV VLPs adjuvanted on aluminium hydroxyphosphate sulfate (qHPV) or AS04 (bHPV).
Bases for the introduction of HPV vaccines

- Both licensed based upon the demonstration of clinical efficacy against CIN2-3 lesions in young adult women (16-25 years) ↔ assumed efficacy against cervical cancer.

- Mechanism of protection: assumed to be neutralizing antibody-mediated (supported by animal models in which passive transfer of hyperimmune serum from donors immunized with L1 VLPs is protective).

- The age-based license extension for adolescent girls, in whom efficacy trials would not be feasible, was granted through “immunological bridging”.
Bases for the introduction of HPV vaccines

- Phase III immunogenicity study (qHPV) in male and female adolescents and young adult women *(Block SL, Pediatrics 2006)*

- Non-inferiority of antibody titers $\leftrightarrow$ 1.7 – 2.7 times higher in adolescents elicited by the same 3 dose (0-2-6 months) schedule

Merck, unpublished data, ACIP presentation by Eliav Barr, February 2006
Countries with HPV immunization in the national immunization programme; and planned introductions, 2014

More than 50 countries
Yet few developing countries (3)

Data Source: WHO/IVB Database, as at 23 January 2014
Map production: Immunization Vaccines and Biologicals, (IVB), World Health Organization
Date of slide: 24 January 2014

- Introduced* to date (52 countries or 27%)
- Not Available, Not Introduced /No Plans (142 countries or 73%)
- Not applicable

* Includes partial introduction

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
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Main challenge for HPV immunization

WANTED: increased implementation and increased coverage!

Today's Questions

May the HPV immunization schedule for adolescent girls be reduced from 3 to 2 doses?

- **cost savings**
  - reduced vaccine and delivery costs

- **simpler logistics**
  - increased flexibility of the intervals
  - annual doses easier for school-based delivery

If yes, with which schedule?
If yes: does this apply to both qHPV and bHPV vaccines?
Correlates of protection against HPV

Protection: assumed as only antibody-mediated

Protective threshold undefined - markedly below (100x ?) detection levels of current assays (no failure despite apparent “Ab loss”)
Correlates of protection against HPV

Vaccine-induced antibodies
• much higher (10 – 100x)
• of higher “potency” than infection-induced antibodies

Protection is expected as similar if antibodies are non inferior (titers, neutralizing capacity / avidity)

(Scherpenisse M, Plos One 2013)
Duration of protection ↔ duration of antibody persistence

- long-lived plasma cells ↔ Ab plateau (12 mo) ↔ slow decay ↔ slow waning

Immunological correlates of long term protection:

Prime First 1(-2) dose(s): generate memory cells to trigger their affinity maturation

Boost Last dose (≥ 6 mo): reactivate memory cells to differentiate into plasma cells
Duration of protection ↔ duration of antibody persistence

- long-lived plasma cells
  ↔ Ab plateau (12 mo)
  ↔ slow decay
  ↔ slow waning

Immunological correlates of long term protection:

Prime  First 1(-2) dose(s): generate memory cells to trigger their affinity maturation ↔ 100% adol. primed after 1 dose

Prime

Boost Last dose (≥ 6 mo): reactivate memory cells to differentiate into plasma cells ↔ 2x higher peak titers in adolescents ↔ antibody plateau ↔ slow decline
PROCESS

Ad hoc Expert Consultation

Review of evidence

Review background document

Report to SAGE
HPV Vaccine Schedules
Ad-hoc Expert Consultation

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May the HPV immunization schedule for adolescent girls be reduced from 3 to 2 doses?

Are antibody responses after 2 adolescent doses non inferior to 3 doses in women (efficacy demonstrated) and/or adolescents

• peak titers
• plateau “immunological bridging”

If yes, with which schedule?

• prime – prime (0 – 2 months)
• prime – boost (0 - ≥ 6 months)

If yes: does this apply to both qHPV and bHPV vaccines?