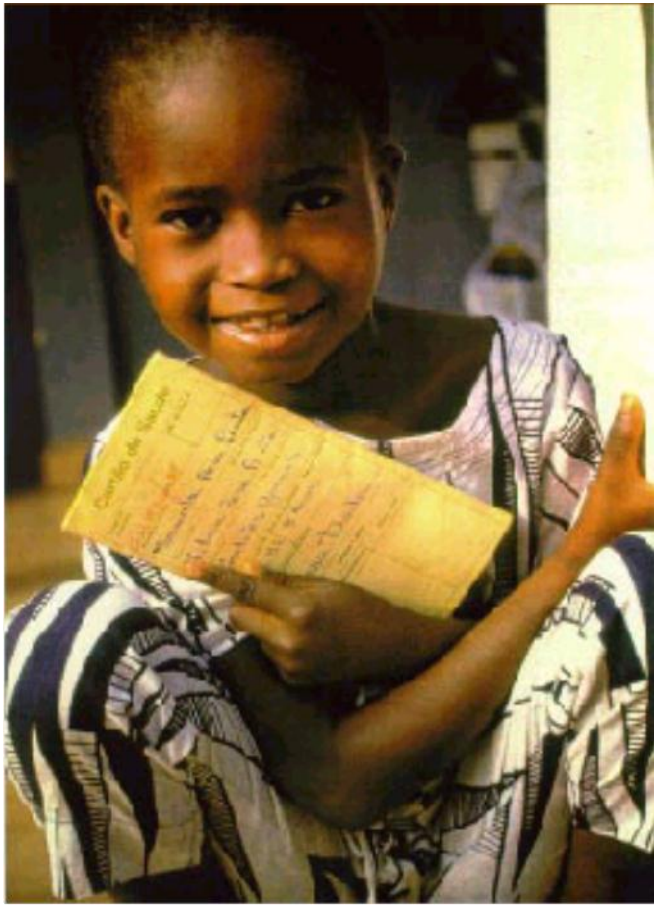
Why are we reviewing the evidence on HPV immunization of adolescent girls & what are the questions for SAGE today?



Prof Claire-Anne Siegrist

SAGE Member

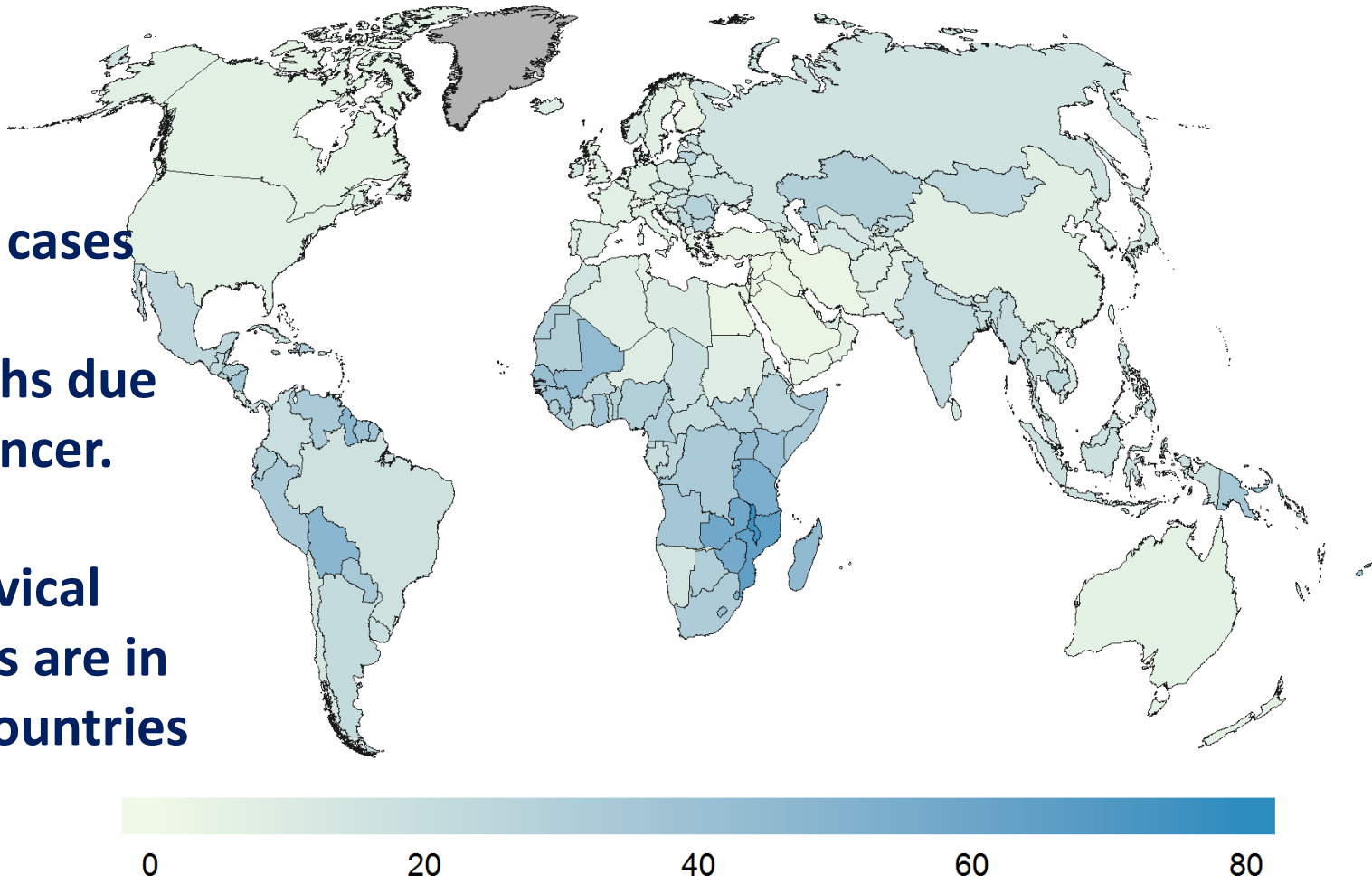
Estimated cervical cancer incidence worldwide

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

International Agency for Research on Cancer

World Health Organization

Bases for the introduction of HPV vaccines

Two available vaccines : bivalent (bHPV, Cervarix®) and quadrivalent (qHPV, GARDASIL®).

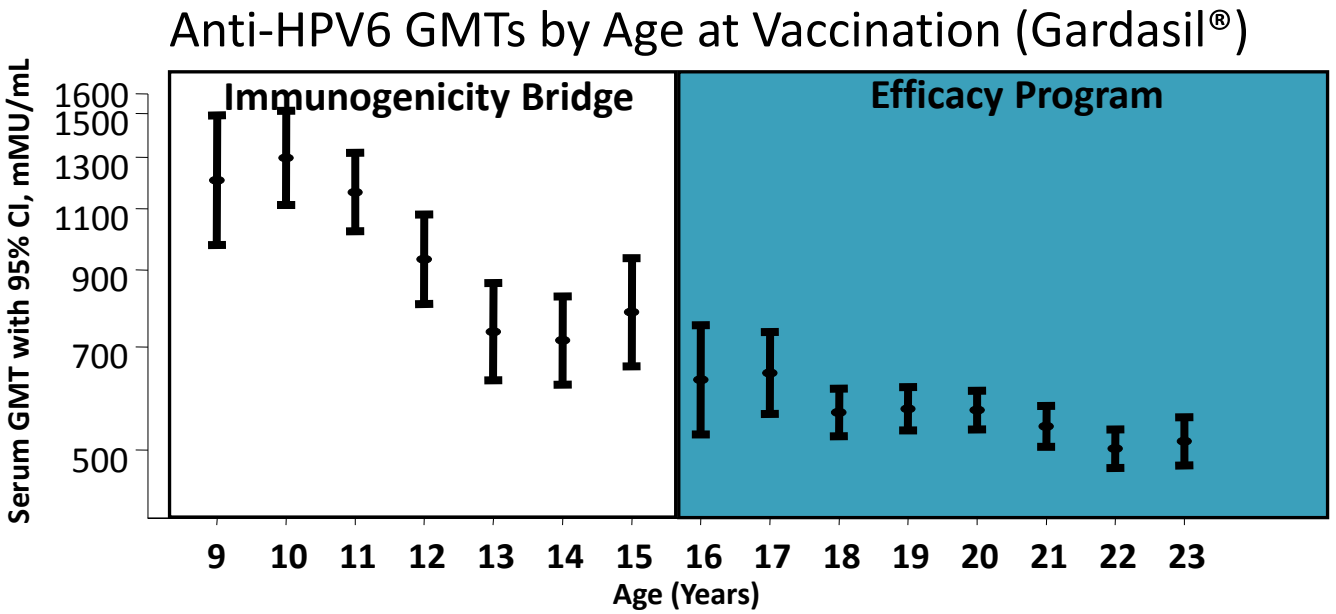
Both are prepared from purified L1 protein, the major capsid protein, and contain HPV VLPs adjuvanted on aluminium hydroxyphosphate sulfate (qHPV) or AS04 (bHPV).

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".**

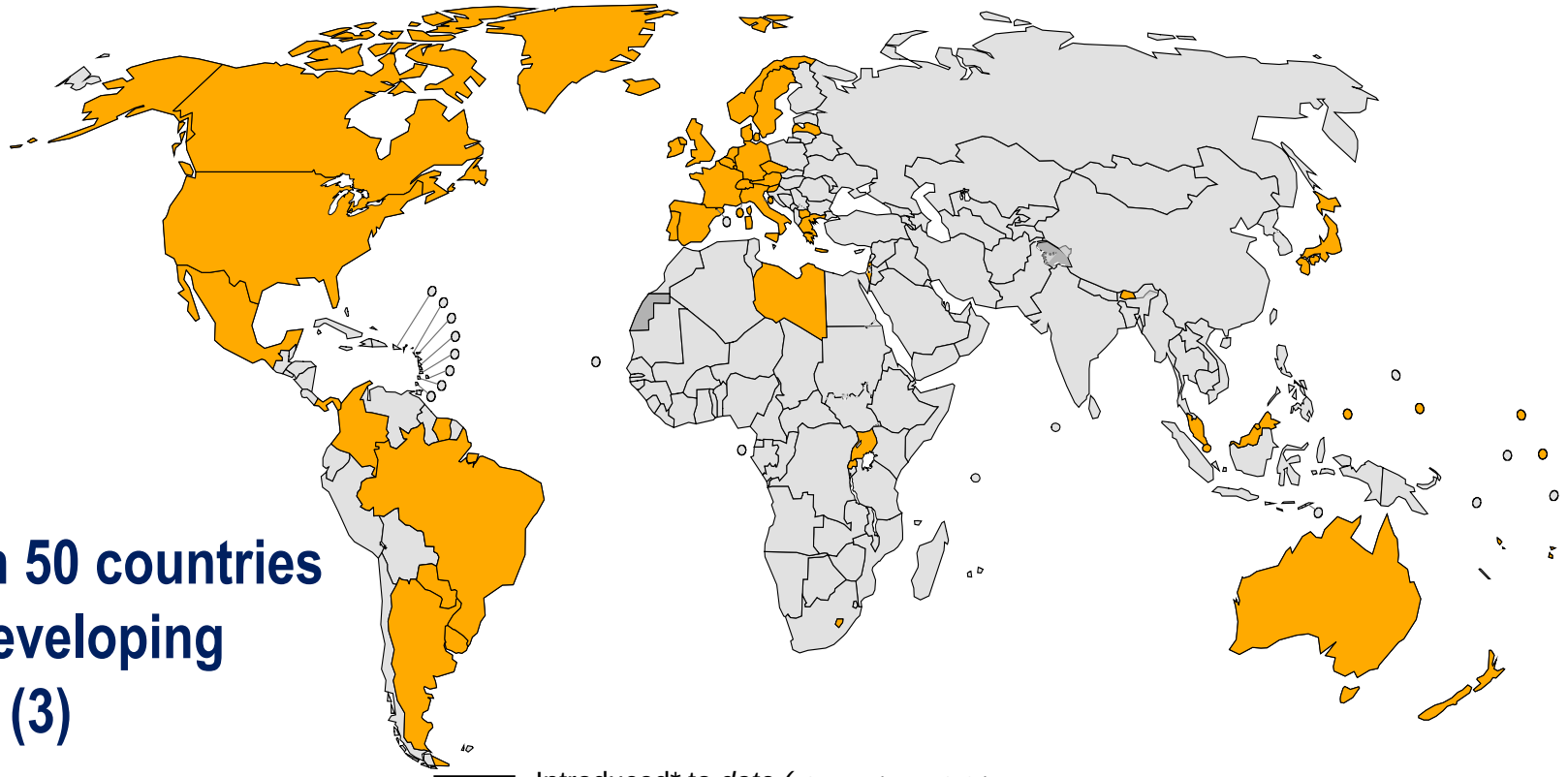
Bases for the introduction of HPV vaccines

- **Phase III immunogenicity study (qHPV) in male and female adolescents and young adult women** *(Block SL, Pediatrics 2006)*
- **Non-inferiority of antibody titers ↔ 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)

Introduced* to *date* (*52 countries or 27%*)

Not Available, Not Introduced /No Plans *(142 countries or 73%)*

Not applicable

Data Source: WHO/IVB Database, as at 23 January 2014

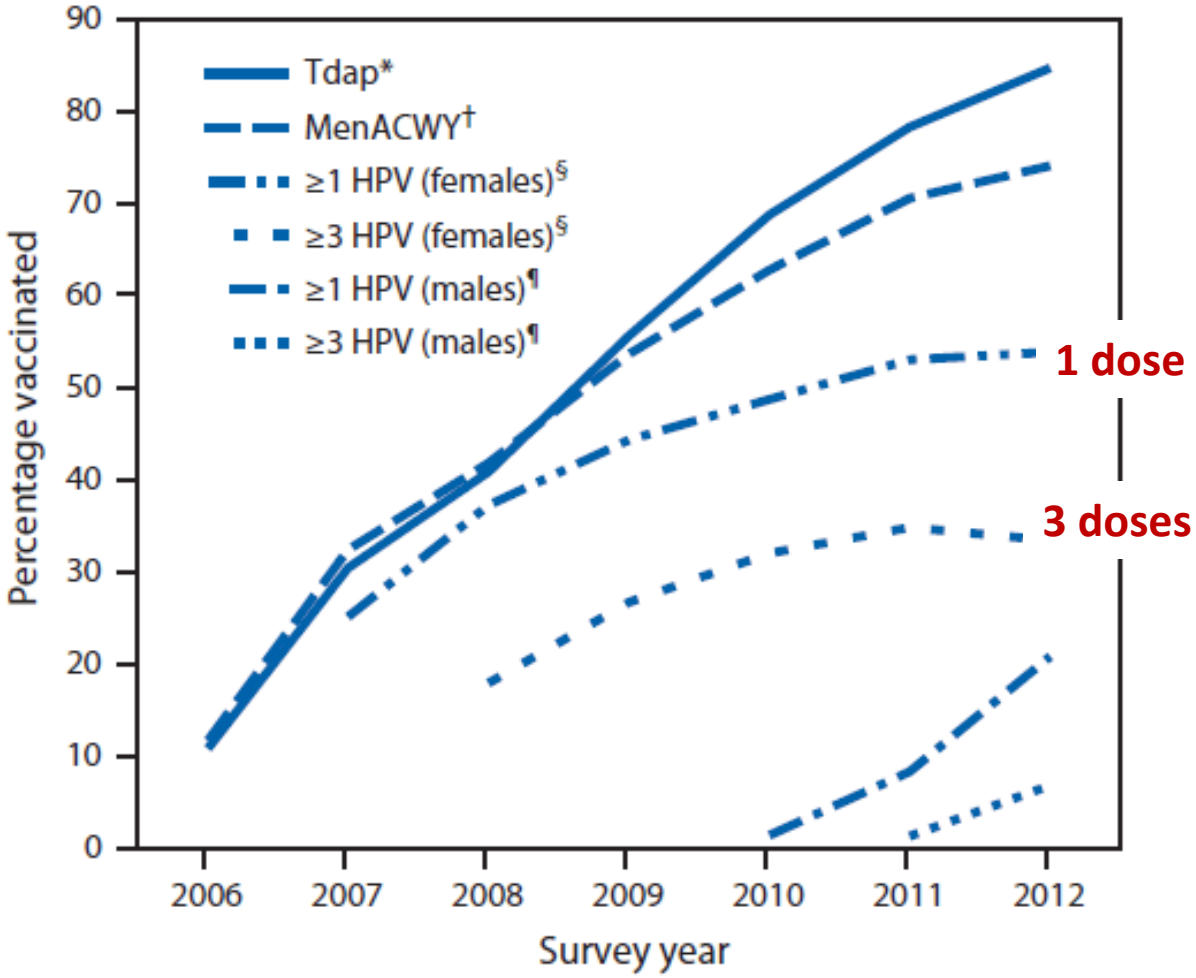
Map production: Immunization Vaccines and Biologicals, (IVB), World Health Organization

Date of slide: 24 January 2014

* Includes partial introduction

World Health Organization

Main challenge for HPV immunization



WANTED: increased implementation and increased coverage !

FIGURE. Estimated vaccination coverage with selected vaccines and doses among adolescents aged 13–17 years, by survey year — National Immunization Survey–Teen, United States, 2006–2012 *MMWR August 30, 2013 / 62(34);685-693*

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

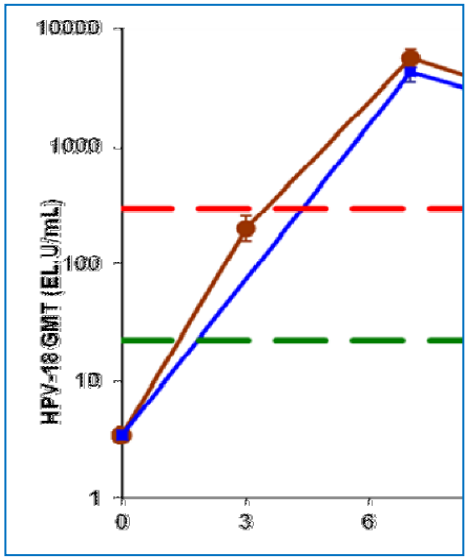
Protection: assumed as only antibody-mediated

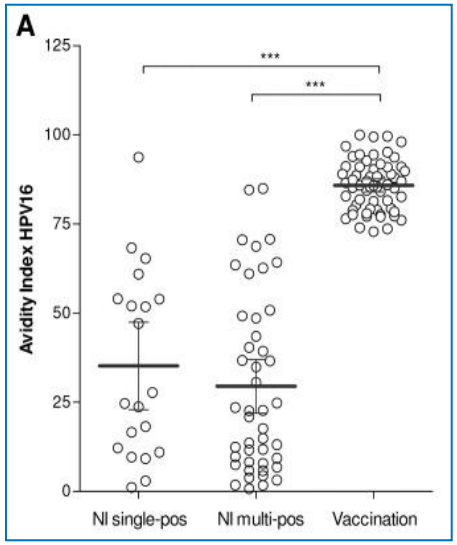
Protective threshold undefined - markedly below (100x ?) detection levels of current assays (no failure despite apparent “Ab loss”)

Correlates of protection against HPV

Vaccine-induced antibodies

- **much higher (10 – 100x)**
- **of higher "potency" than infection-induced antibodies**





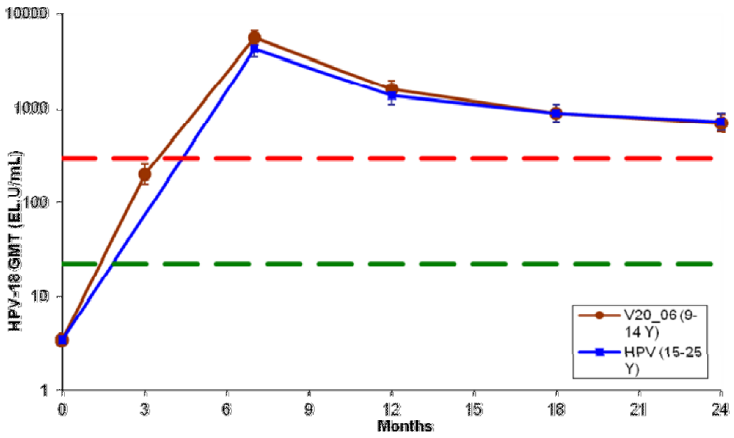
(Scherpenisse M, Plos One 2013)

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

Duration of protection against HPV

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

Prime affinity maturation

Boost **Last dose (≥ 6 mo):** reactivate memory cells to differentiate into plasma cells

Duration of protection against HPV

Duration of protection ↔ duration of antibody persistence

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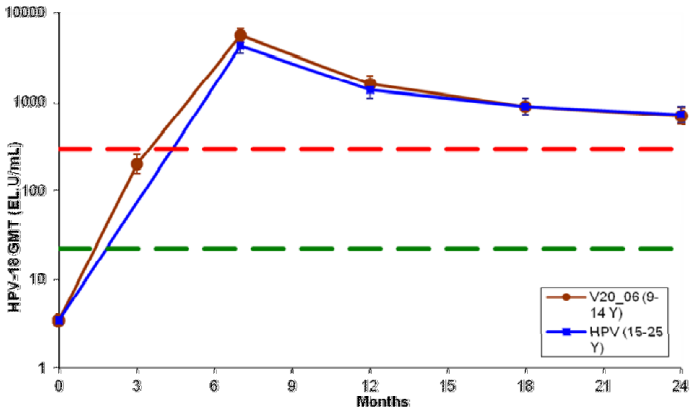
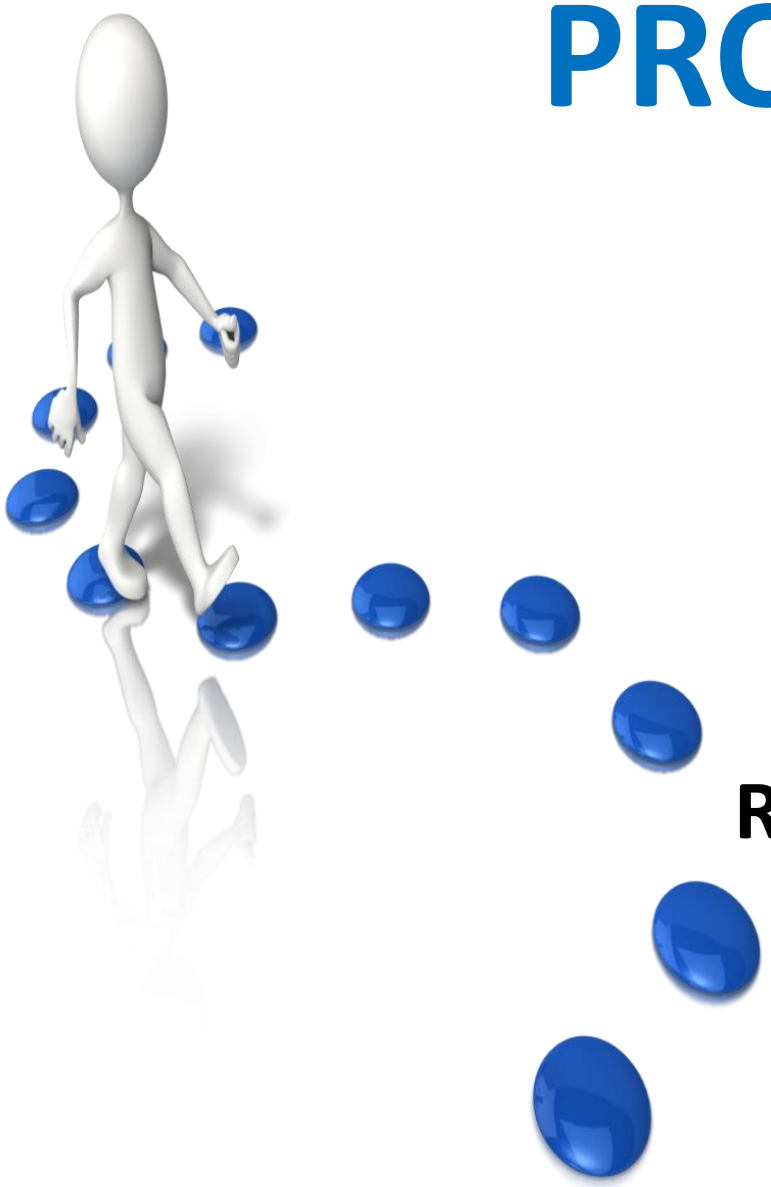


Immunological correlates of long term protection:

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

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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- Maddalena D'Addario, Swizterland
- Simon Dobson, Canada
- Dorota Gertig, Australia
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- Amy Leval, Sweden
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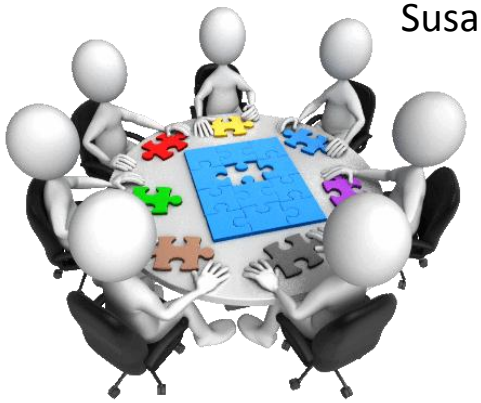

Today's Questions

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 – bost (0 - ≥ 6 months)

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