Preventing Cancer with Vaccines: Status in 2017

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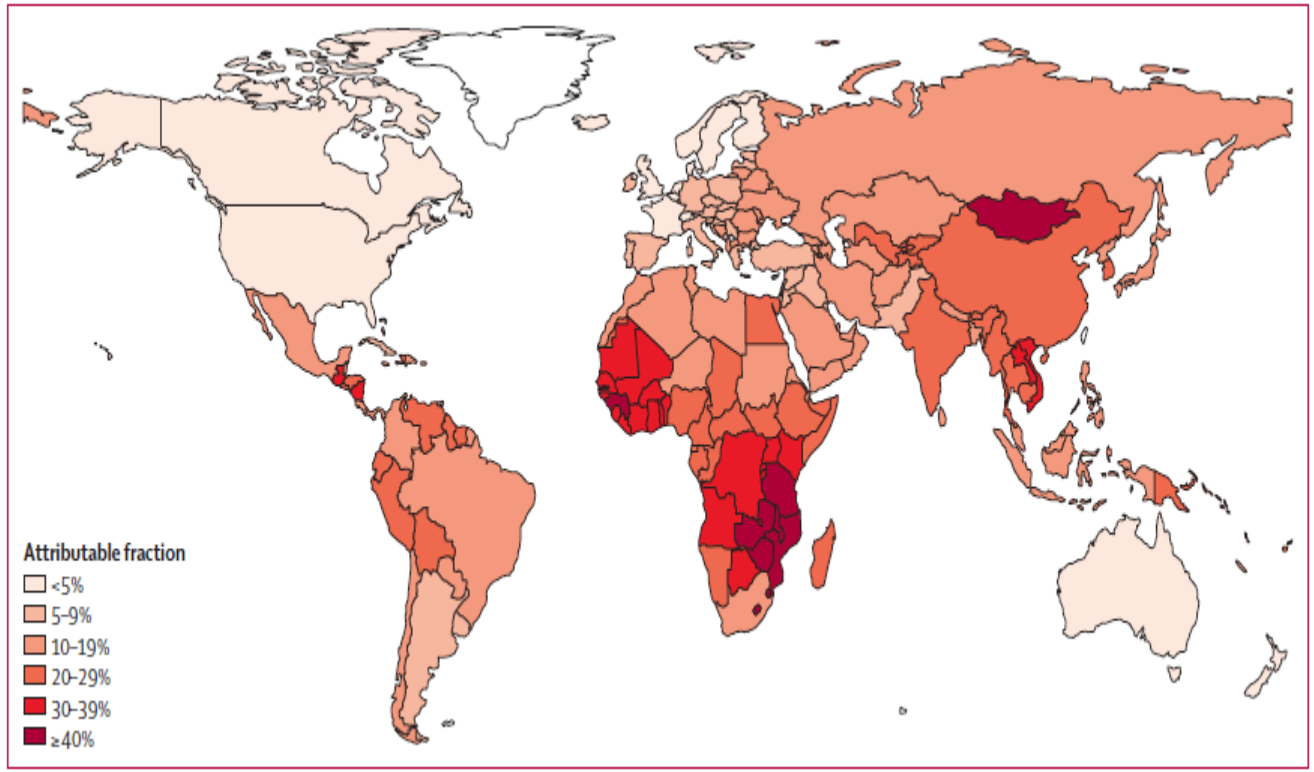
Large potential for reducing burden of cancer caused by infections

Attributable fraction of cancer related to infection, 2012



14 million new cancer cases in 2012

2.2 million (15·4%) carcinogenic infections

- *H. pylori* (770 000)
- HPV (640 000)
- HBV (420 000)
- HCV (170 000)
- EBV (120 000)

Source: Plummer M et al. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Global Health 2016; 4:e609-16
Shin HR et al. Jpn J Clin Oncol; 2016 46:13-22.

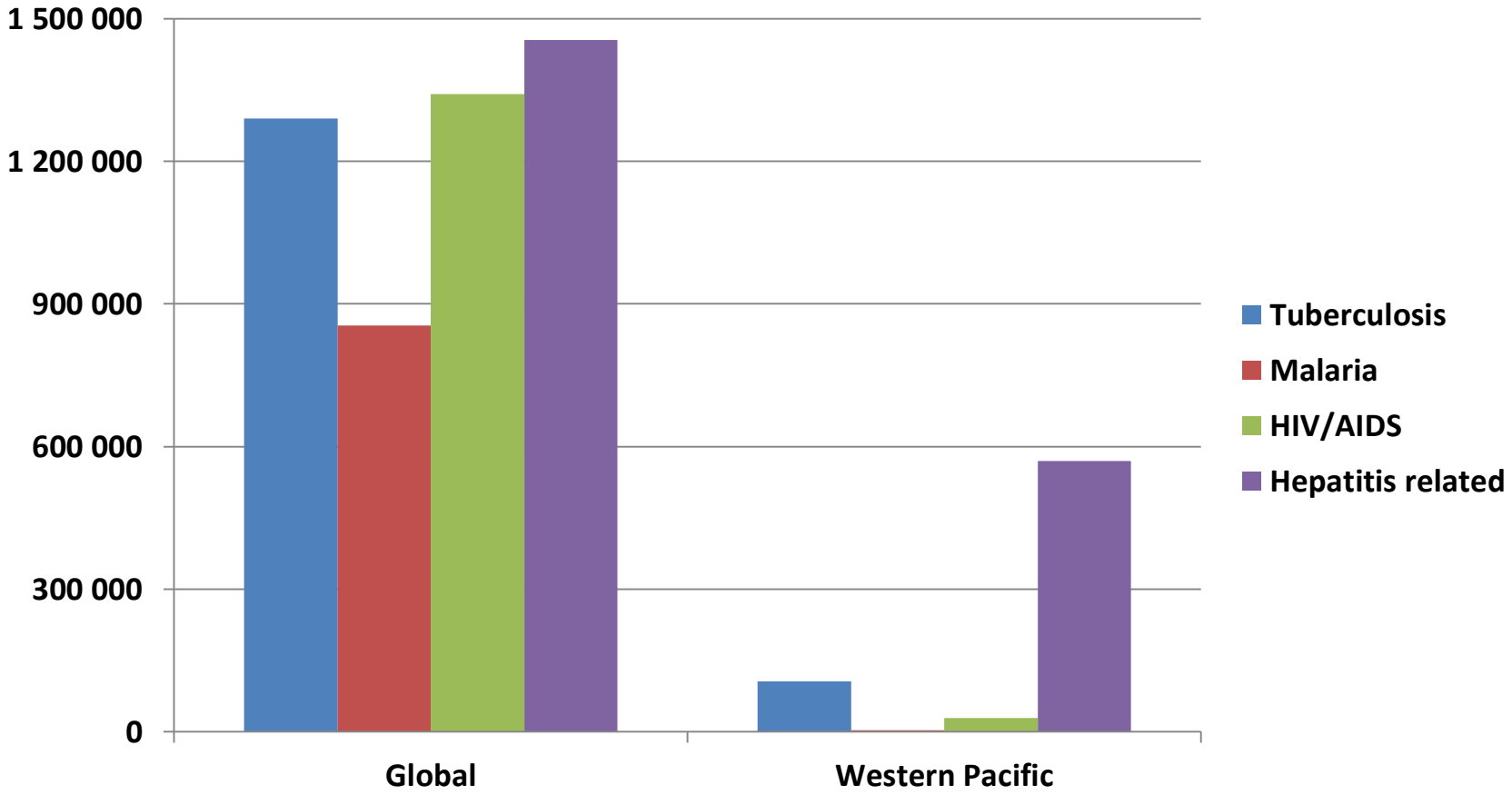
Infectious agents and cancer

- About 16% of human cancers are caused by infectious agents
  - Lower in high income countries, greater in low income
  - underestimate since less developed countries have poor cancer registries
  - Data from good registries suggests that >30-50% of cancers in Africa may be due to infectious agents
- Public, media, and even parts of the cancer control community largely unaware
- Oncogenic viruses with interesting similarities: HPV, HBV, HCV, EBV, HTLV1,HHV8,Merkle cell polyomavirus (MCV)
  - Cancer not a primary feature of the disease process
  - Cancers occur in chronically infected individuals
  - The tumors do not contain replicative virus
  - Immunosupression and co-factors exacerbate oncogenesis (HIV mechanism)

Un homme enceinte s’accouche dans son tombeau*

*A pregnant man delivers in his grave

Comparison of global and Western Pacific mortality by major communicable diseases, 2013



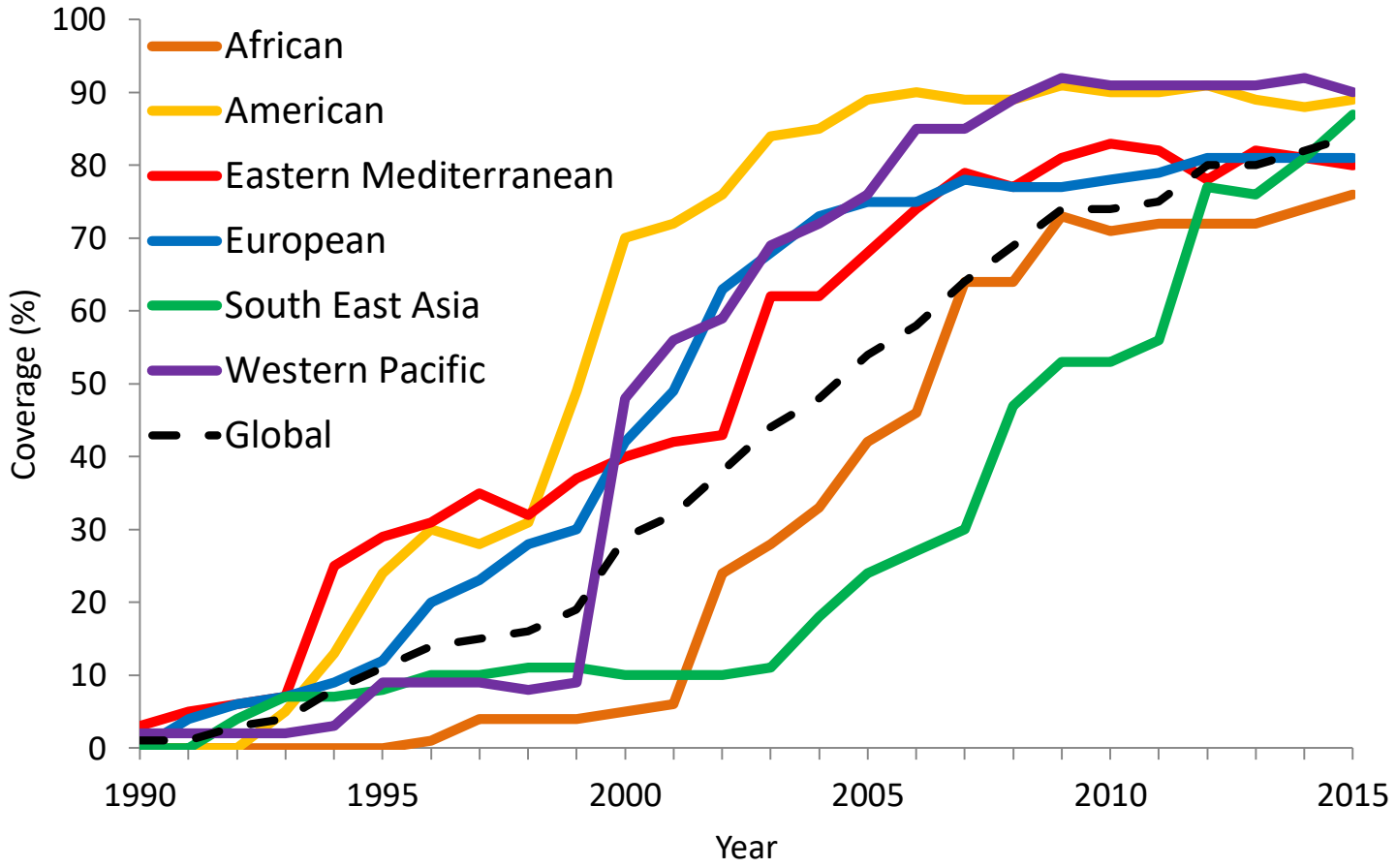
* Source: GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015 Jan 10;385(9963):117-71.

Hepatitis B and Hepatocellular Cancer

- Hepatitis B (Hep B) Vaccine prevents development of chronic carrier state, a precursor to cirrhosis and liver cancer. There are two paths to oncogenicity, one through cirrhosis and also a direct oncogenic effect. A direct reduction in HCC in immunized cohorts has been observed in Taiwan
- 880,000 deaths from HCC and cirrhosis in 2015.
- number one or two cause of male cancer deaths in much of Asia, Sub-Saharan Africa, and the Pacific Basin
- Most infections leading to the chronic carrier state occur asymptomatically in the first few years of life from perinatal or “horizontal” transmission from family, contacts, other children, and unsafe medical procedures
- Perinatal infection leads to the carrier state about 90% and is responsible for about half of carriers in Asia but less in Africa. Disproportionate impact on cancer
- In lower endemicity settings infections occur later in life due to occupational and “lifestyle” exposures and are likely to be symptomatic, but lead to the chronic carrier state only about 3-5%

3-DOSE HEPATITIS B VACCINE: 84% COVERAGE: IMPACT ON INCIDENCE

HBV



Source: WHO AND UNICEF

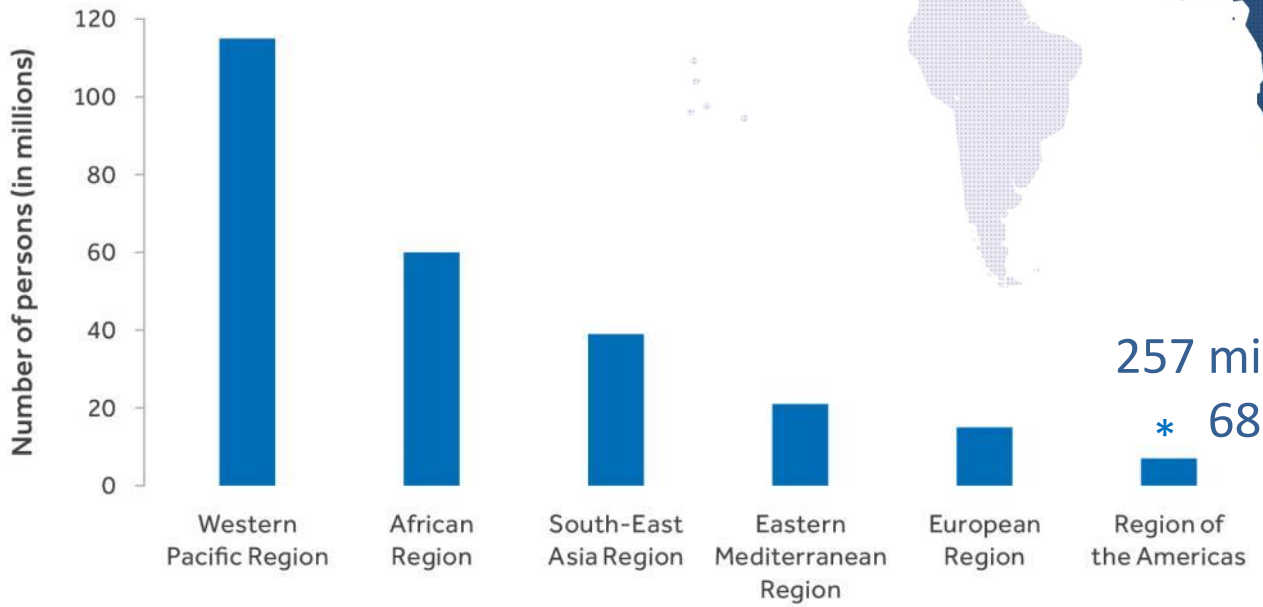
World Health Organization

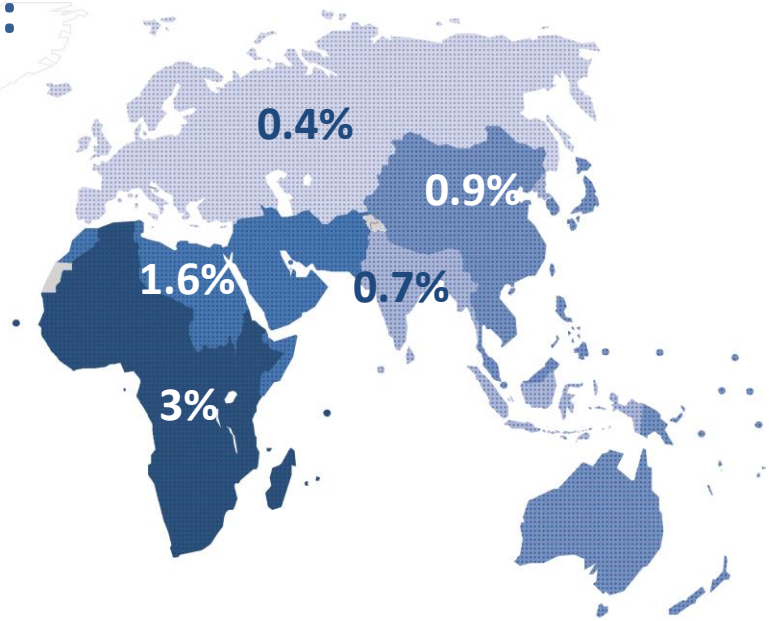
STATUS OF HEPATITIS B, 2015

HBV

Cumulated incidence of chronic infection:

Prevalence of HBV infection in children under 5 reduced from 4.7% to 1.3% (immunization)





Prevalence:

257 million people living with HBV

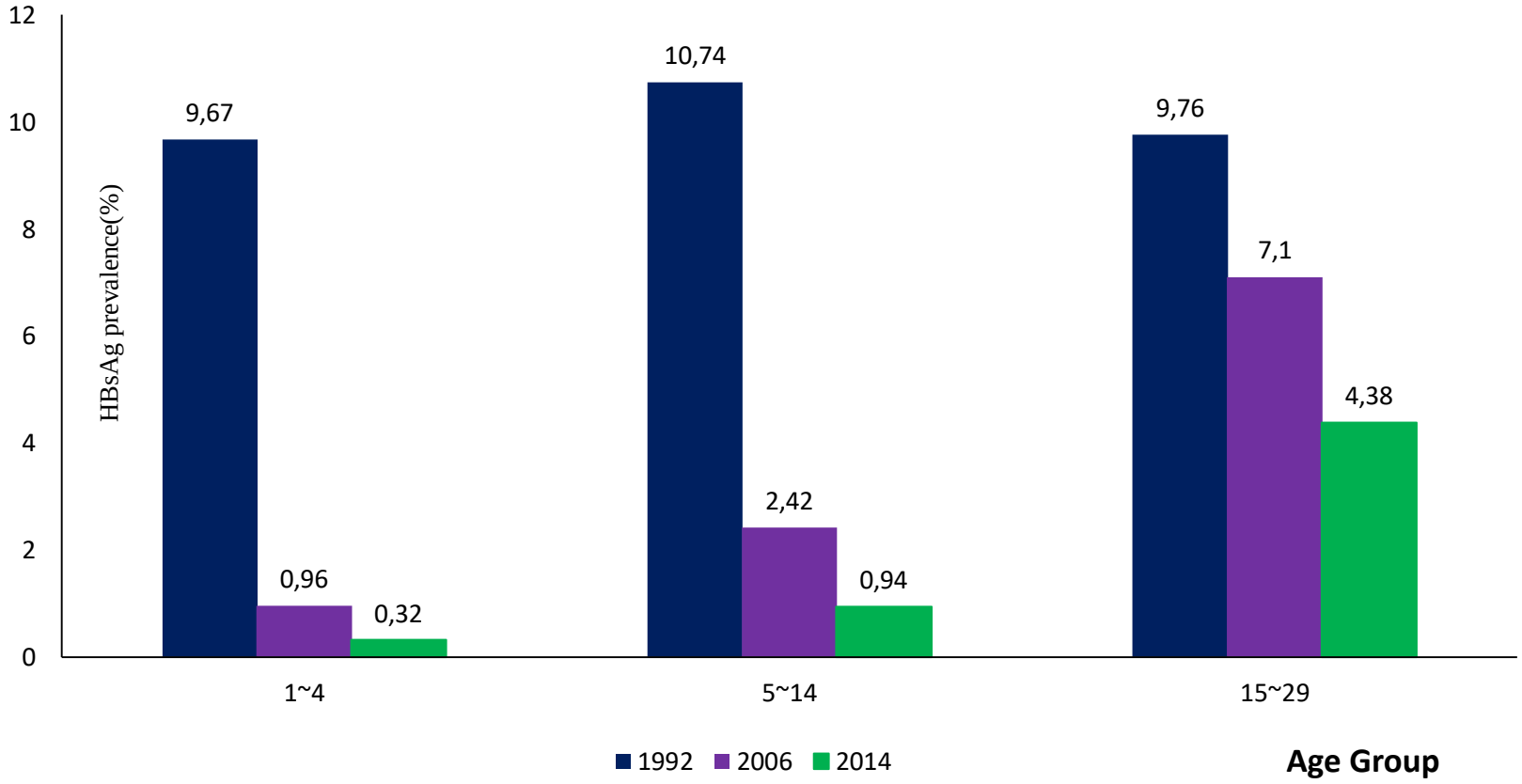
* 68% in Africa /Western Pacific

* Work in progress to understand differences between PAHO and WHO estimates

Source – WHO (LSHTM)

World Health Organization

HBsAg Prevalence by Age Group, China, 1992, 2006, and 2014

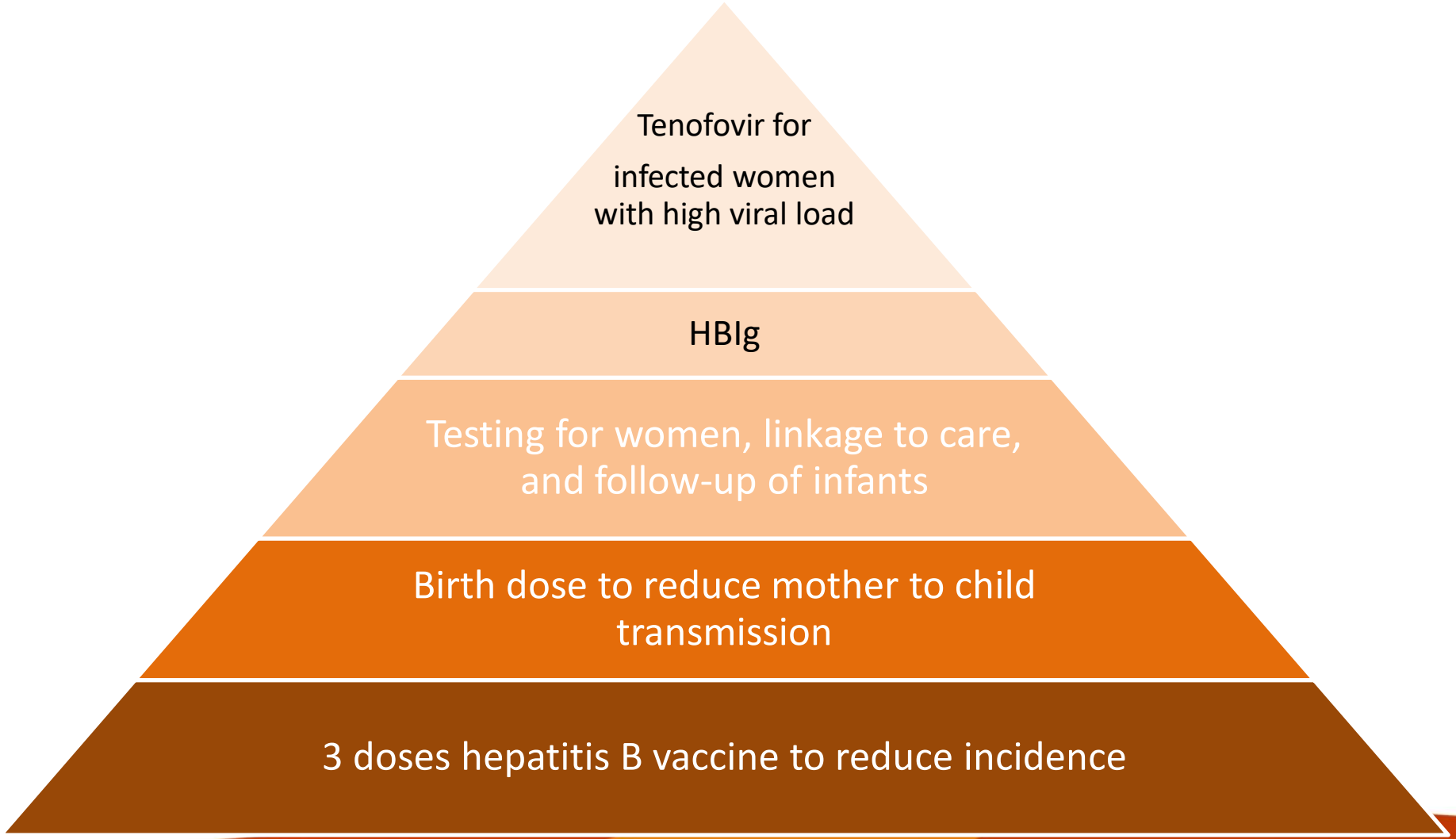


Source: Fuqiang Cui, National Immunization Programme, Chinese Center for Disease Control and Prevention. January 25, 2016

Universal Immunization and prevention of perinatal transmission

- Universal infant immunization strategy developed in 1990
- Every country in the world but 4 in Northern Europe (control group ;-)). Most given as quadrivalent to hexavalent DTP based combo vaccine.
- The trick was putting the vaccine in the same bottle as DTP making coverage HepB=coverage DTP
- Giving vaccine with DTP prevents horizontal but not perinatal transmission which is responsible for almost half of carriers worldwide. Need birth dose of monovalent HB vaccine given within 24 hours of birth ~90% efficacy. Addition of HBIg gives ~95% efficacy

INCREMENTAL APPROACH FOR PMTCT OF HBV



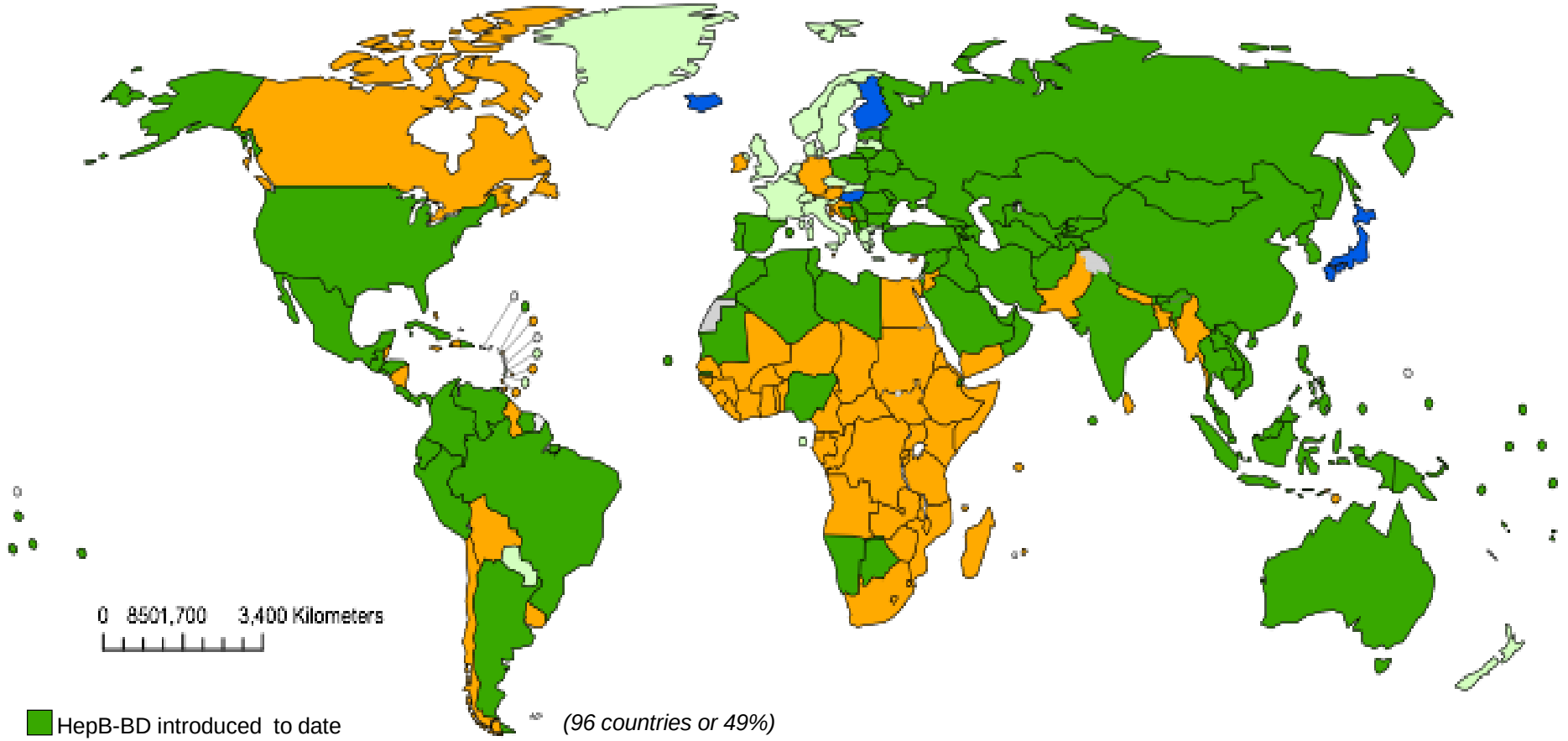
PMTCT: Prevention of mother to child transmission (universal birth dose or other approaches)

World Health Organization

Current issues in control of hepatitis B

- WHO has declared a target of “elimination of hepatitis B as a public health problem” by 2030 with a global target of 0.1% prevalence in immunized cohorts of children, 90% vaccine coverage and 90% prevention of perinatal transmission
- Various WHO regions developing their own targets for WHO elimination
- WHO repeated it’s call for routine birth dose of HB vaccine. EURO allows countries to do maternal screening and Tx of infants of carrier mothers or birth dose or both.
- Anti-viral drugs given prenatally to mothers with high viral loads can further reduce perinatal transmission (not yet WHO guideline) to very low levels
- Anti-viral drugs (tenofovir) highly effective in suppressing viral replication, progression of disease and infectivity if given to HBV carriers daily. Screen for carriage in high endemicity countries?
- Perception of vaccine safety and anti-vaccine activity continue to be a serious issue

Countries with hepatitis B vaccine birth dose (HepB-BD) in the national immunization programme



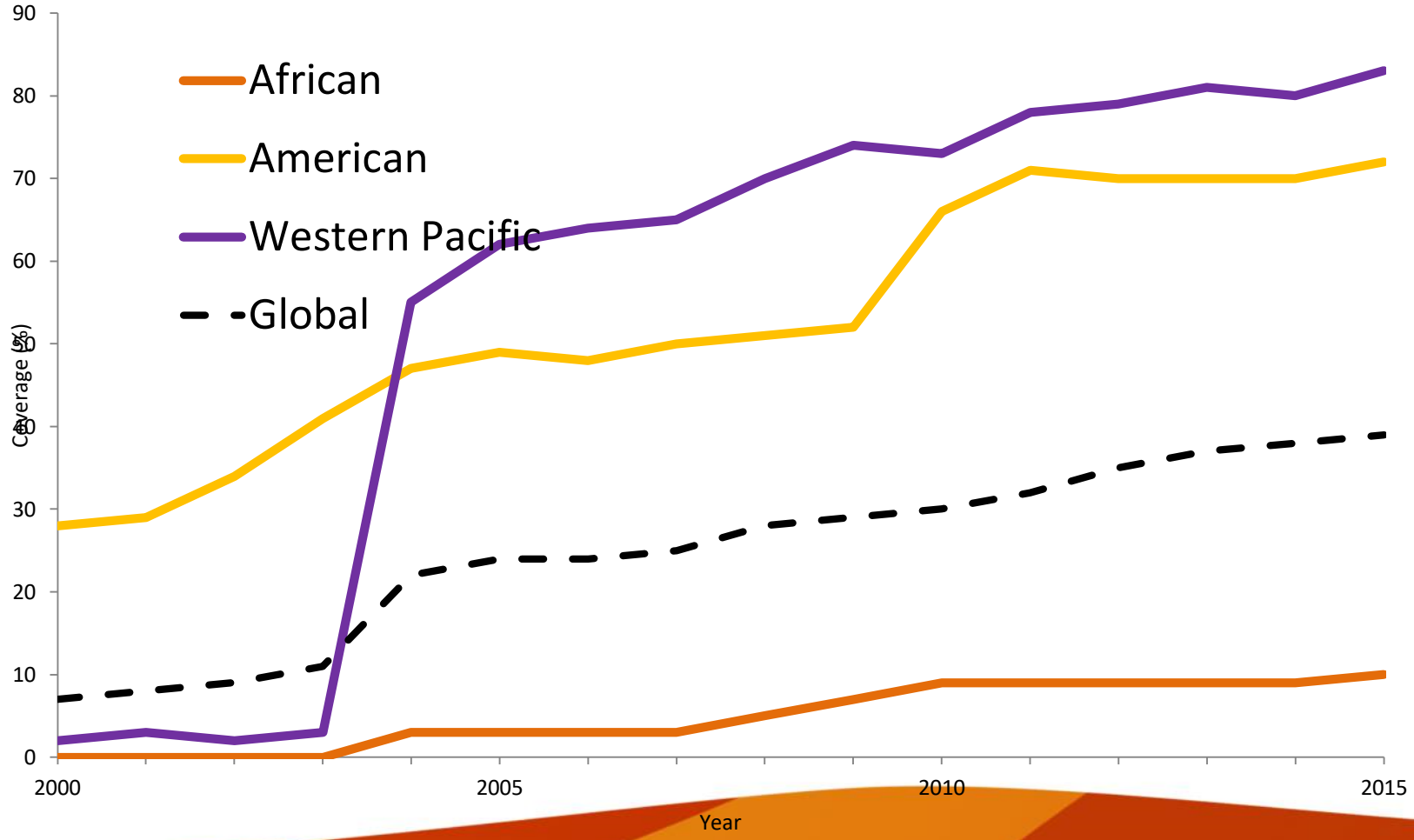
HepB-BD introduced to date	*(96 countries or 49%)*
HepB-BD only for infants born to HBsAG-positive mothers	*(22 countries or 11%)*
HepB in schedule but no HepB-BD	*(72 countries or 37%)*
HepB given only for risk groups or adolescents	*(4 countries or 2%)*
Not available	
Not applicable	

Data source: WHO/IVB Databse as at 30 June 2016 and ECDC published data at http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx
194 WHO Member States
Map production Immunization Vaccines and Biologicals (IVB),
World Health Organization
Date of slide: 30 June 2016

World Health Organization

HEPATITIS B BIRTH DOSE: 39% COVERAGE: IMPACT ON CHRONIC LIVER DISEASES

HBV



Source: WHO AND UNICEF

World Health Organization

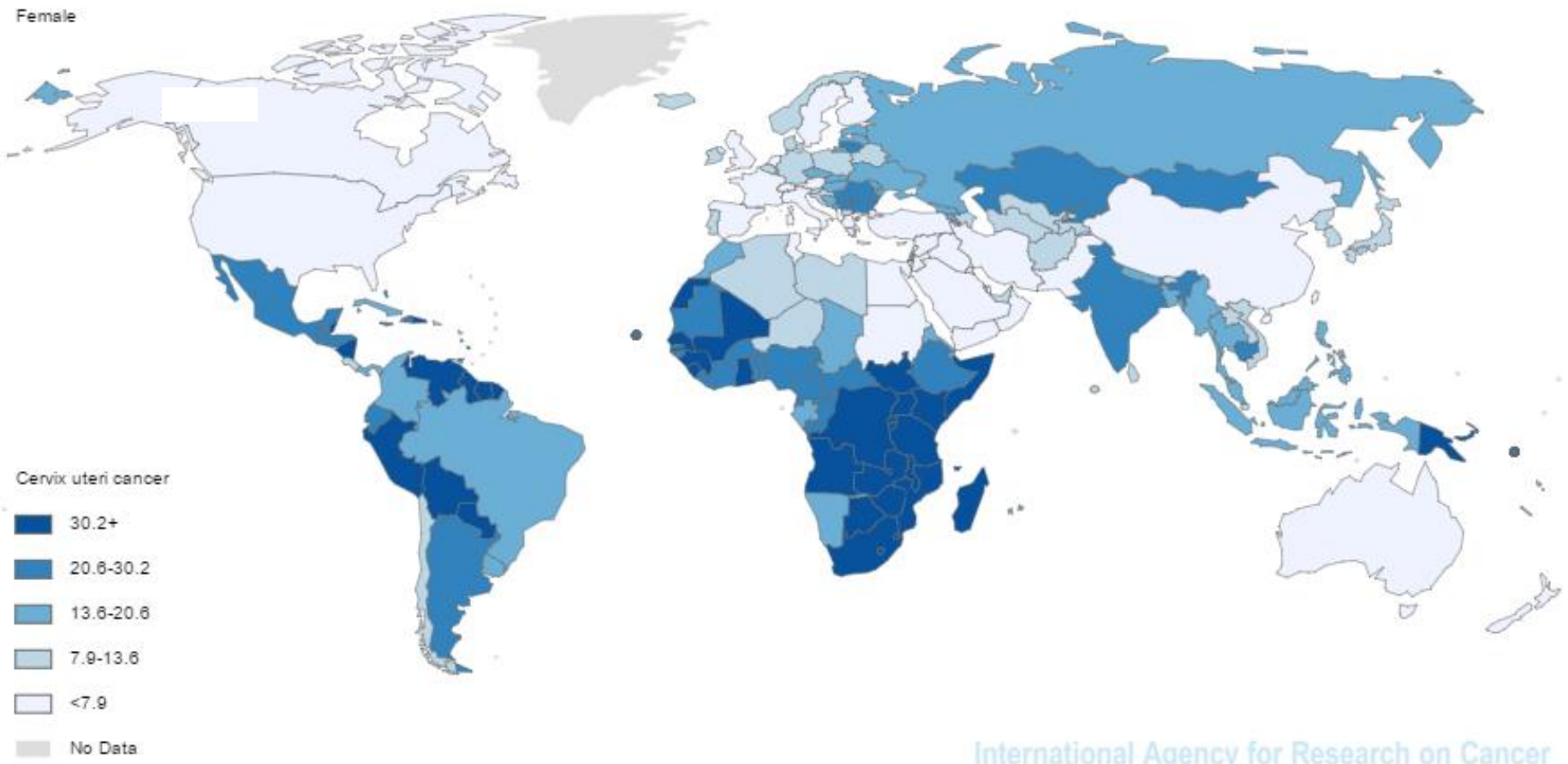
Duration of Protection

- The vaccine is almost completely effective in preventing acute hepatitis B and the carrier state in “horizontal” infection. Seroconversion is excellent in childhood through early adulthood. After 40 seroconversion levels decrease somewhat. New vaccines with enhanced adjuvants can overcome this.
- Although vaccine induced anti-HBs wanes over decades, long term protection against acute hep B and the carrier state persists for at least 25-30 years due to immune memory. The paradigm Antibody=Protection is wrong!
- However, sub-clinical breakthrough infections with anti-HBc and or anti-HBs are now seen. Most vaccines still boost anamnestically with a dose of HB vaccine but some do not. Worry?

HPV Issues

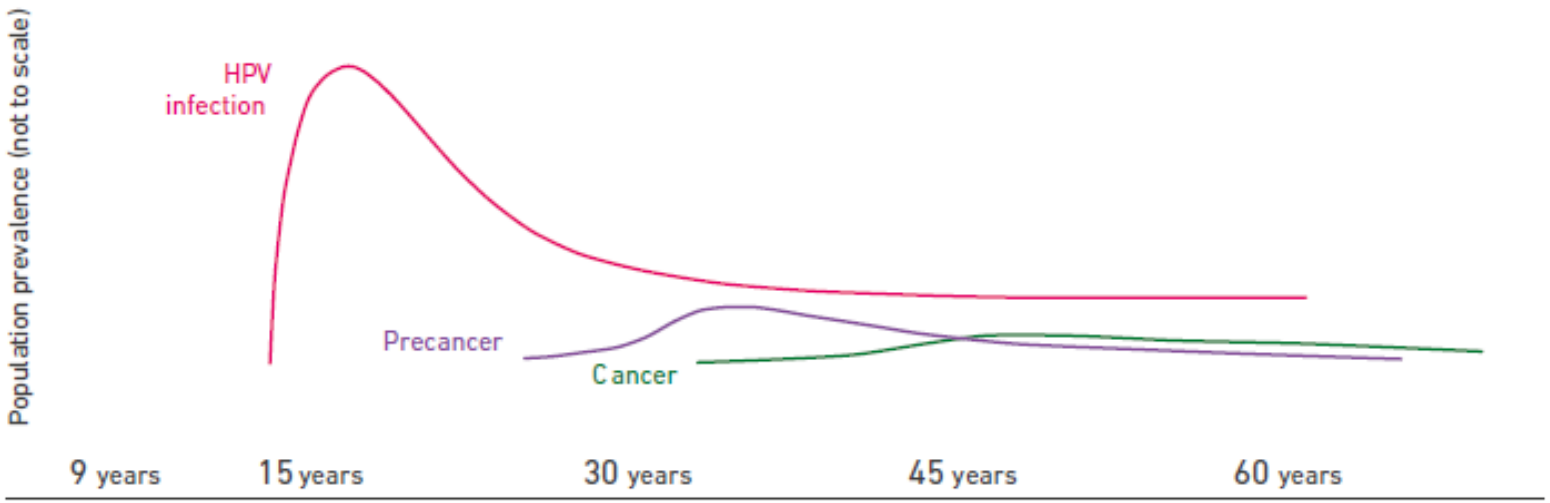
- HPV responsible for almost 100% of cervical cancer (CC) and varying proportions of many other cancers (vulvar, vaginal, anal, penile, oropharyngeal) plus ~90% of genital warts. CC is the number 3 cause of cancer deaths in women (266,000) deaths/yr
- Prior to vaccine availability screening tests for abnormal cells (PAP smear) and tests for HPV DNA available but screening largely occurs in high income countries that continue to have significant numbers of CC deaths.
- Few developing countries screen more than 10% of women
- Safe and highly effective vaccines were developed containing 2, 4, and 9 VLP's. ~100% seroconversion, long duration of antibody, and almost complete protection against infection and development of pre-cancerous lesions due to vaccine subtypes. Population based studies show herd immunity and impressive reductions in CIN2/3 cervical lesions and genital warts.
- Vaccine seroconversion and immunogenicity is so high that two dose schedules for pre-adolescents are recommended. Studies using a single dose are underway. Vaccine has no therapeutic efficacy.

Age-Standardized Incidence Rates of Cervical Cancer in Females, 2012



Source: GLOBOCAN 2012 (IARC)

Programmatic Interventions to Prevent HPV Infection, Cervical Cancer, and Mortality



PRIMARY PREVENTION

Girls and Boys 9-14 years

- HPV vaccination

Girls and boys, as appropriate

- Health information and warnings about tobacco use*
- Sexuality education tailored to age & culture
- Condom promotion/provision for those engaged in sexual activity
- Male circumcision

SECONDARY PREVENTION

Women >30 years of age

Screening and treatment as needed

- "Screen and treat" with low cost technology VIA followed by cryotherapy
- HPV testing for high risk HPV types (e.g. types 16, 18 and others)

TERTIARY PREVENTION

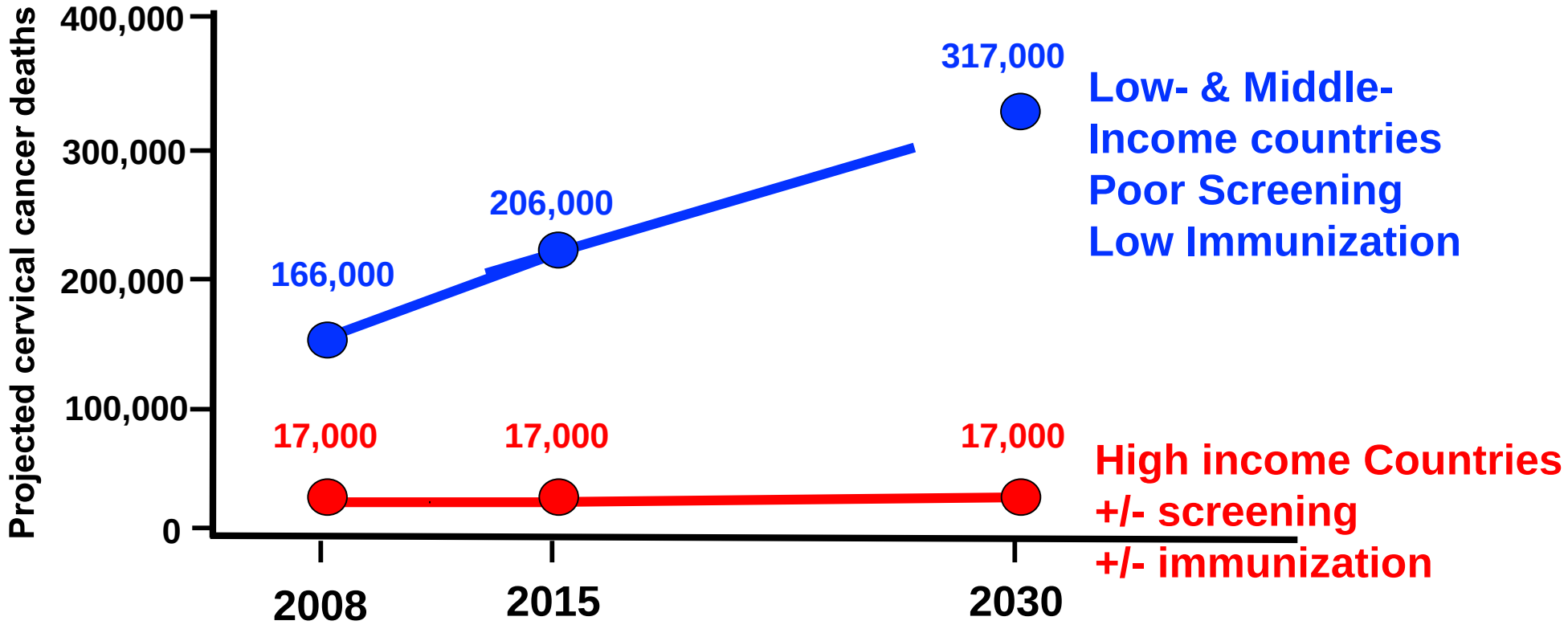
All women as needed

Treatment of invasive cancer at any age

- Ablative surgery
- Radiotherapy
- Chemotherapy

WHO Guide to Introducing HPV Vaccine into National Immunization Programmes, 2016

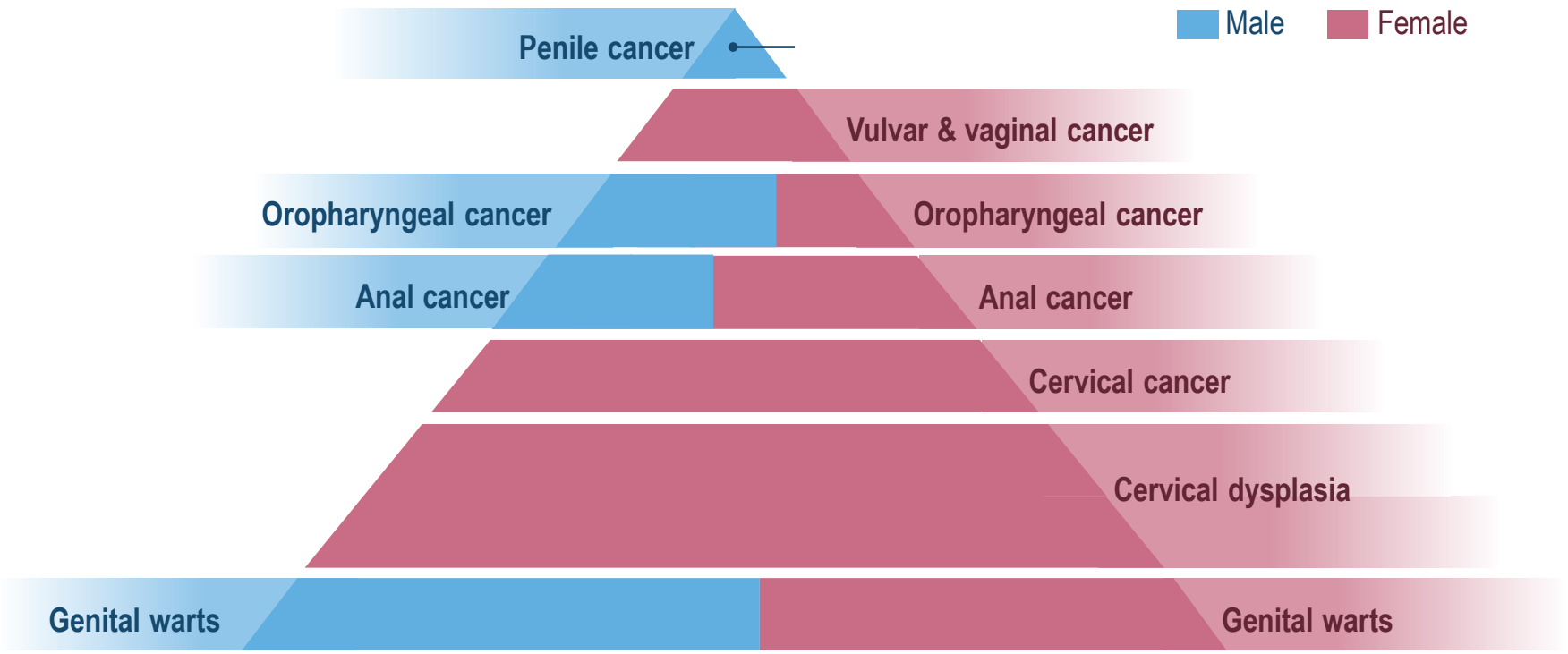
IARC's Globocan 2012 projection: Cervical cancer mortality rates continue to increase in Low- & Middle-income countries (LMIC's)



- In LMIC's, cervical cancer represents ~90% of HPV-associated cancer

Projections developed from Globocan 2012

High and Costly HPV Disease Burden Among Males and Females Worldwide



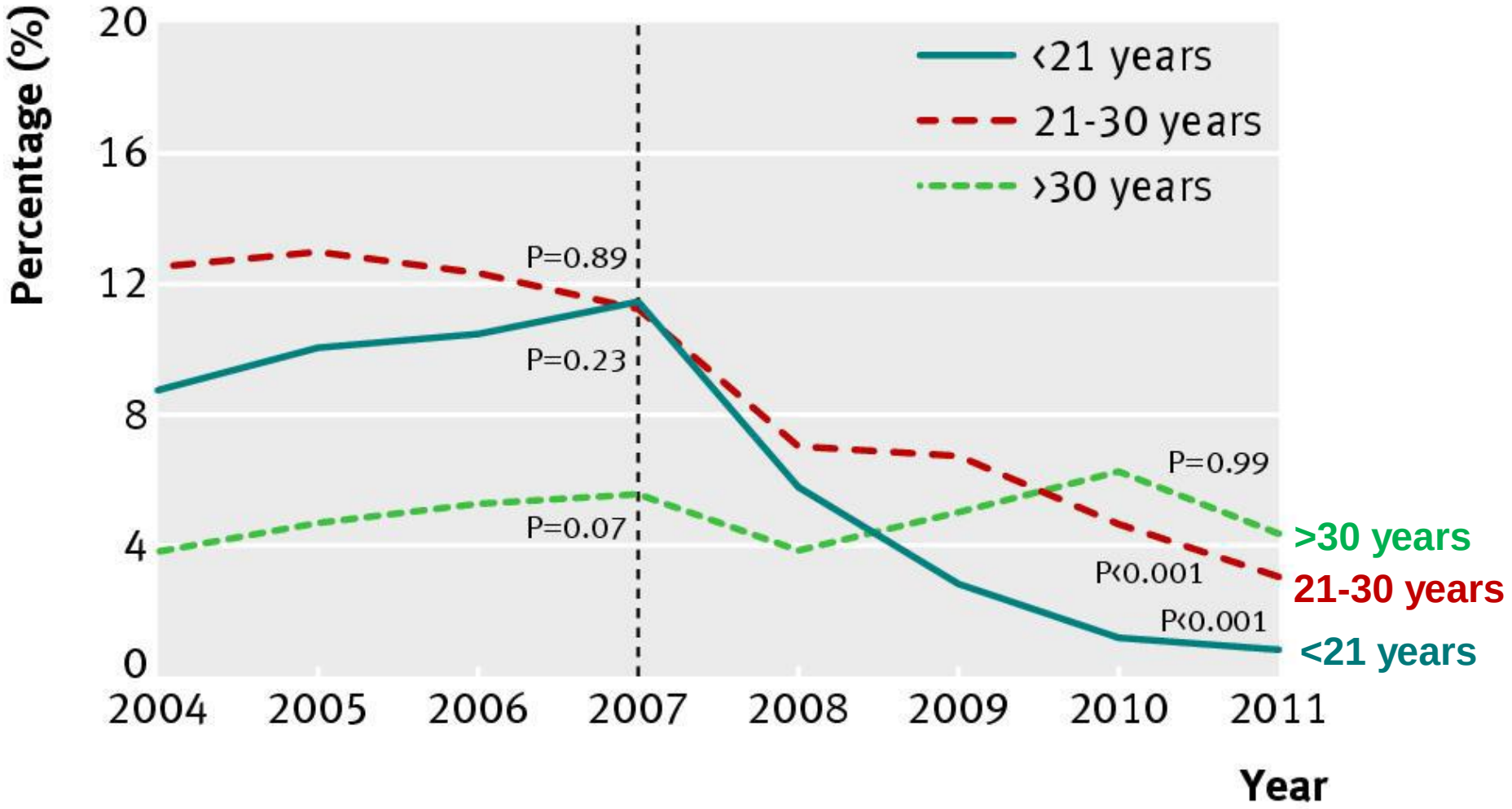
While CC predominates globally, in countries with effective screening, deaths from CC and non-cervical cancers are equal. Oropharyngeal cancers are increasing, occur mostly in males, and change the consideration concerning gender neutral immunization.

In the US male OP=CC

Impact on Clinical Disease

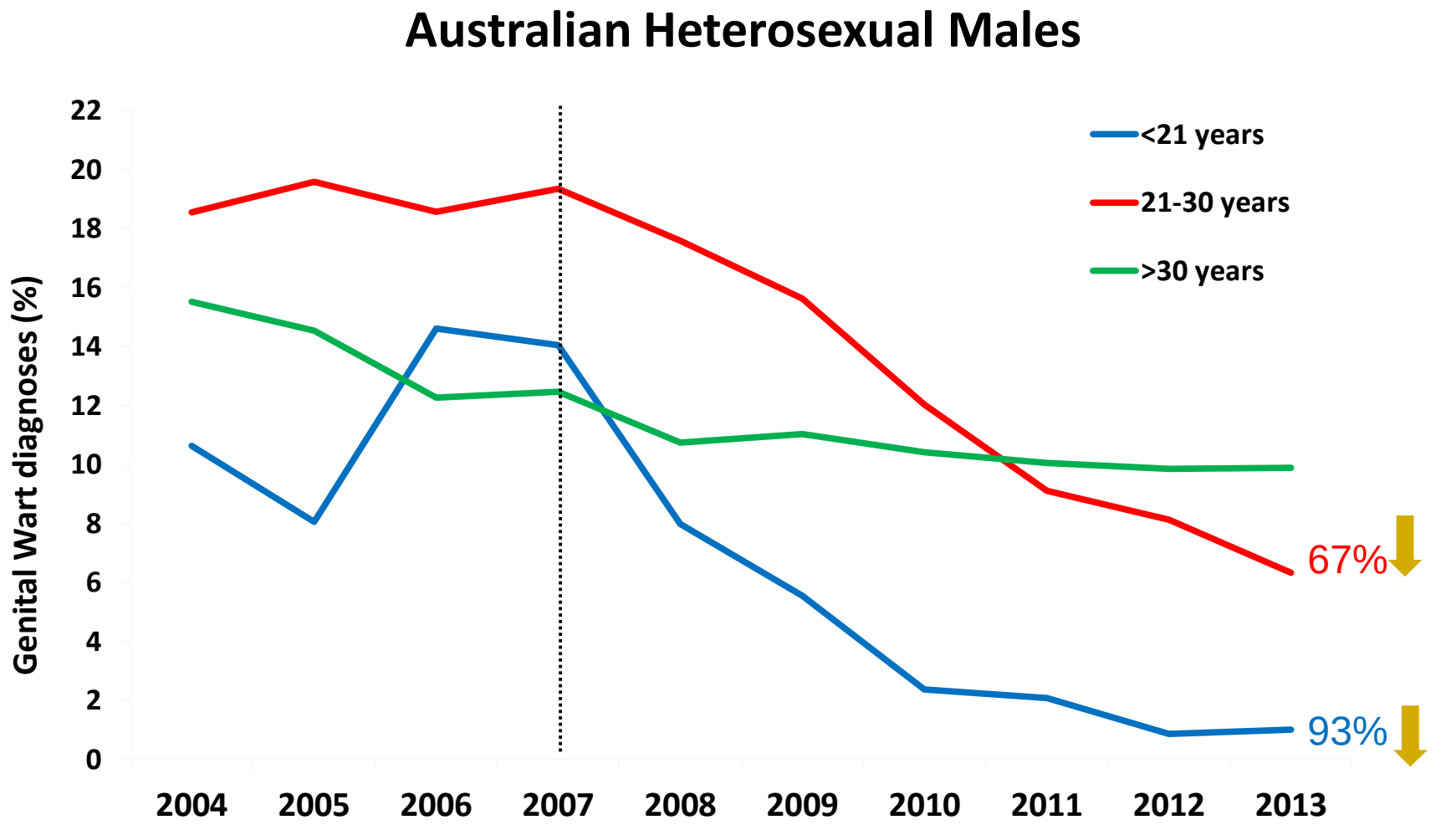
- The Australian National Vaccination Programme 2007, 4vHPV
- school-based 12-13 y/o girls + catch-up for 13–26 year old
- achieved 70% coverage in the school cohort.
- Four years after implementation, high-grade cervical abnormalities (CIN2/3, AIS) in the vaccinated cohorts (age 12–26 years) decreased by 48%
- Similar reductions in several other countries
- Evidence of herd immunity

Age-dependent decrease in genital warts in Australian women after HPV Vaccine Implementation in 2007



Ali et al, BMJ 2013

HPV Vaccination of Females Interrupts Transmission



Ali H et al. *BMJ* 2013 (extended data)

Global HPV Vaccine Dissemination

2007-2016

2007

2010

2013

October 2016

>100 countries

National | Demonstration | National-projected | Demo-projected | Demonstration stopped/on hold

LaMontagne et al Int J Gynecol Obstet, 2017
http://onlinelibrary.wiley.com/doi/10.1002/ijgo.12186/full#ijgo12186-fig-0001

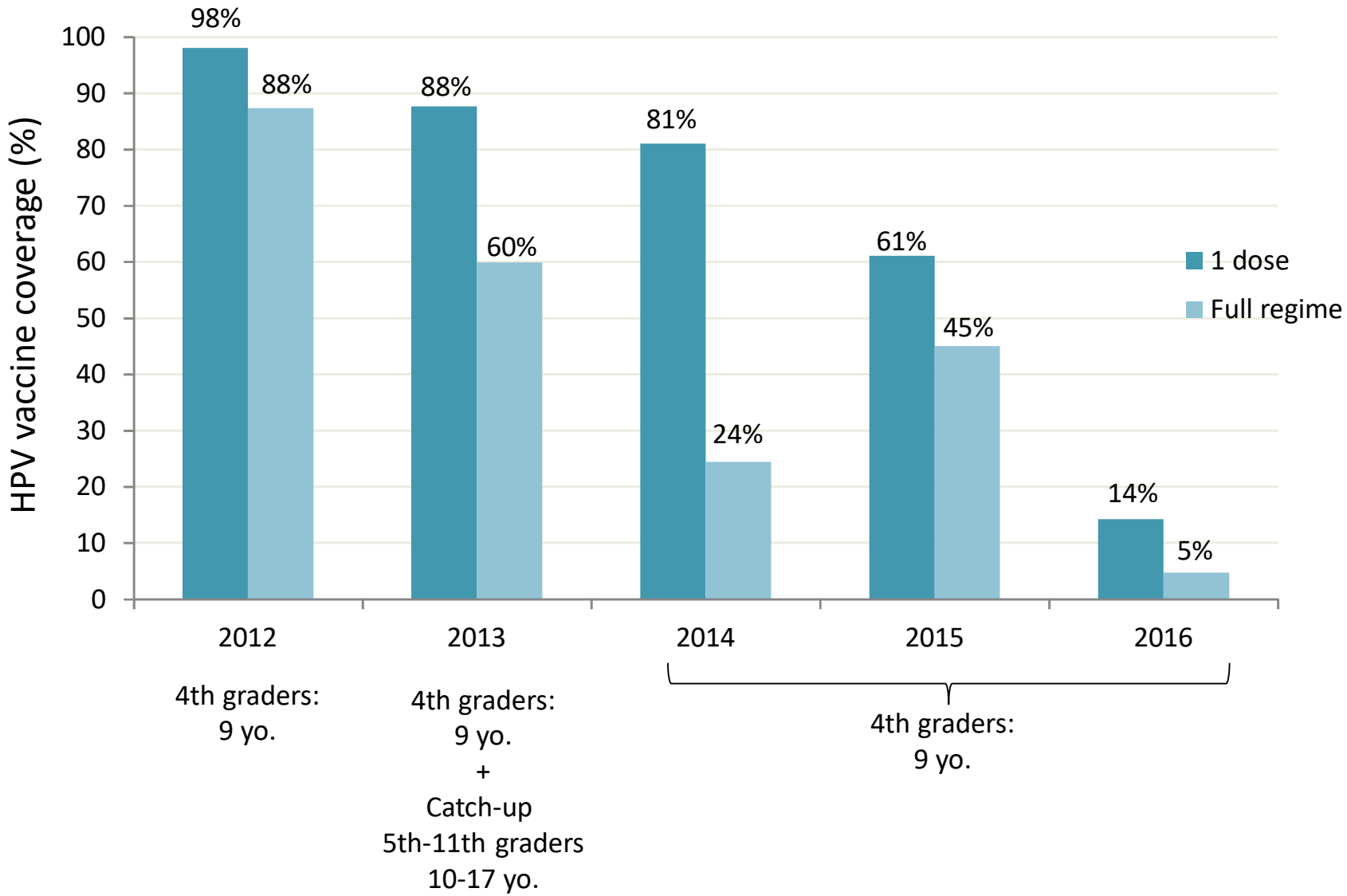
HPV Vaccine Issues

- HPV vaccines are expensive ~$ 120/dose in US. Most high income countries have been able to afford the vaccine but few middle income countries have it in their national immunization programs.
- GAVI pays for the vaccine for eligible countries but until this year has required countries to undertake a demonstration program. A number of successful demonstration projects are ending and National Programs should begin to adopt the vaccine soon.
- Most successful programs are school based, not the usual target group for National Immunization Programs.
- Gavi obtains the vaccine for ~ USD 4.5/dose and PAHO Revolving Fund gets an affordable price ~USD 9/dose. The Global Immunization Community needs to develop agreements that allow middle income countries to afford vaccine.

HPV Issues: Gender Neutral Immunization

- Early developers of the vaccine came from OBGYN community (researchers, clinicians, pathologists, academics, etc) and envisioned the vaccine as primarily for girls and women to control CC.
- Earlier economic modeling on CE of immunizing boys was done with the endpoint of reducing CC. Models predicted male protection with high female coverage. This led WHO and most countries to recommend vaccine only for girls.
- MSM not protected and high coverage often not achieved
- Several countries such as USA and Australia recommend the vaccine for both girls and boys.

HPV vaccine coverage in COLOMBIA



HPV vaccine safety

- Great body of evidence supports the safety of the vaccine
- Powerful “big data” techniques and large databases in Scandanavian countries and with large health insurers and delivery organizations like Kaiser give great statistical power to examine AEFI hypotheses
- Giving vaccine to pre-adolescents probably caused more vaccine safety concerns (fainting, POTS, chronic fatigue, autoimmune disease, regional pain syndrome and has damaged programs in Denmark, Japan, Columbia, Ireland and several countries in Eastern and Central Europe

Thank You