NCI DCP Early Phase Cancer Prevention Clinical Trials Consortia

Webinar Series: “Immunoprevention - Studying a Promising New Approach to Cancer Prevention”

Vaccines for Infectious Agents and Cancer Prevention and Control

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Outline

• Burden of infection-associated Cancers

• Overview of vaccination principles

• Vaccination against infectious agents causing cancer
  • Hepatitis B vaccines
  • Human papillomavirus vaccines

• Issues in scaling up implementation of vaccination globally
<table>
<thead>
<tr>
<th>Infectious agent</th>
<th>Associated Cancer(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helicobacter pylori (H. pylori)</td>
<td>Stomach cancer</td>
</tr>
<tr>
<td>Human papillomavirus (HPV)</td>
<td>Cervical cancer, Anal, vaginal, vulvar, penile, oropharyngeal cancers</td>
</tr>
<tr>
<td>Hepatitis B virus (HBV)</td>
<td>Liver Cancer</td>
</tr>
<tr>
<td>Hepatitis C virus (HCV)</td>
<td>Liver Cancer, non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Epstein-Barr virus (EBV)</td>
<td>Hodgkin's lymphoma, Burkitt's lymphoma, Nasopharyngeal carcinoma</td>
</tr>
<tr>
<td>Human herpesvirus type 8 (HHV-8)</td>
<td>Kaposi's sarcoma</td>
</tr>
<tr>
<td>Schistosoma haematobium (Parasitic flatworm)</td>
<td>Bladder cancer</td>
</tr>
<tr>
<td>Human T-cell lymphotropic virus, type 1 (HTLV-I)</td>
<td>Adult T-cell leukaemia and lymphoma</td>
</tr>
<tr>
<td>Opisthorchis viverrini/Clonorchis sinensis (Liver fluke)</td>
<td>Bile duct cancer</td>
</tr>
<tr>
<td>Region</td>
<td>Number of all new Cancer cases (2012)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Worldwide</td>
<td>14 million</td>
</tr>
<tr>
<td>More developed regions</td>
<td>7.9 million</td>
</tr>
<tr>
<td>Less developed regions</td>
<td>6.2 million</td>
</tr>
</tbody>
</table>

Plummer et al 2016
## Burden of Infection-Associated Cancer

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Number of new cases*</th>
<th>Attributable proportion of all new cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helicobacter pylori (H. pylori)</td>
<td>770,000</td>
<td>35.4%</td>
</tr>
<tr>
<td>Human papillomavirus (HPV)</td>
<td>640,000</td>
<td>29.5%</td>
</tr>
<tr>
<td>Hepatitis B virus (HBV)</td>
<td>420,000</td>
<td>19.2%</td>
</tr>
<tr>
<td>Hepatitis C virus (HCV)</td>
<td>170,000</td>
<td>7.8%</td>
</tr>
<tr>
<td>Epstein-Barr virus (EBV)</td>
<td>120,000</td>
<td>5.5%</td>
</tr>
<tr>
<td>Human herpesvirus type 8 (HHV-8)</td>
<td>44,000</td>
<td>2.0%</td>
</tr>
<tr>
<td>Schistosoma haematobium (Parasitic flatworm)</td>
<td>7,000</td>
<td>0.3%</td>
</tr>
<tr>
<td>Human T-cell lymphotropic virus, type 1 (HTLV-I)</td>
<td>3,000</td>
<td>0.1%</td>
</tr>
<tr>
<td>Opisthorchis viverrini/Clonorchis sinensis (Liver fluke)</td>
<td>1,300</td>
<td>0.1%</td>
</tr>
<tr>
<td><strong>All infectious agents</strong></td>
<td><strong>2.2 million</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

*Cancer cases associated with HIV are presumed to be with coinfection with other agents

Preventable by available vaccines

Plummer et al 2016
Vaccines: historical context

• “The impact of vaccination on the health of the world's people is hard to exaggerate. With the exception of safe water, no other modality has had such a major effect on mortality reduction and population growth”

- Stanley Plotkin
“...the annihilation of the Small Pox, the most dreadful scourge of the human species, must be the final result of this practice” (Edward Jenner, 1801)
“How preventive vaccines work 101”

- Vaccines stimulate the immune system to develop long-lasting immunity against antigens from specific pathogens.
- Vaccines elicit an immune response against an antigen so that when the individual is again exposed to the antigen, a much stronger secondary immune response will result.
- Vaccines contain the same/similar antigens that are found on pathogens that cause the associated disease, but exposure to the antigens in vaccines is controlled.
- By priming the immune system through vaccination, when the vaccinated individual is later exposed to the live pathogens in the environment, the immune system can destroy them before they can cause disease.
The image illustrates the immune response to an antigen, focusing on the roles of T helper cells, B cells, and macrophages in the immune system. It shows the interaction of APCs (Antigen Presenting Cells) with T helper cells and B cells, leading to the production of antibodies against the virus.

- **Antigen** binds to the APCs, which present the antigen to T helper cells.
- T helper cells activate B cells and macrophages.
- Activated B cells differentiate into memory B cells and produce antibodies specific to the virus.
- Antibodies neutralize the virus, leading to a secondary immune response.

The graph below the diagram shows the antibody levels over time, with a primary and secondary response. The primary response is characterized by a lag time followed by an increase, while the secondary response shows a quicker and more robust response.

**WHO**
Classification of Vaccines

Live attenuated vaccines
• Viral: measles, mumps, rubella, vaccinia, varicella, zoster, yellow fever, rotavirus, intranasal influenza, oral polio*
• Bacterial: BCG*, oral typhoid

Inactivated vaccines
• Whole
  • Viruses: polio, hepatitis A, rabies, influenza*
  • Bacteria: pertussis*, typhoid*, cholera*, plague*
• Fractional
  • protein-based
    • Toxoid: diphtheria, tetanus
    • Subunit: hepatitis B, influenza, acellular pertussis, human papillomavirus, anthrax
  • polysaccharide-based
    • Pure: pneumococcal, meningococcal, Salmonella Typhi (Vi)
    • Conjugate: Haemophilus influenzae type b (Hib), pneumococcal, meningococcal

Recombinant vaccines
• Viral: hepatitis B, human papillomavirus, influenza (one brand), live attenuated influenza
• Bacterial: Salmonella Typhi (Ty21a)

* not available in the US
Conceptual models for natural history of infectious diseases and pathogenesis of cancers of infectious origin - I

Anderson, 2016
Conceptual models for natural history of infectious diseases and pathogenesis of cancers of infectious origin - II

SIS model

Susceptible \( \rightarrow \) Infectious

SIR model

Susceptible \( \rightarrow \) Infectious \( \rightarrow \) Recovered

SIS/SIR model

Susceptible \( \rightarrow \) Infectious \( \rightarrow \) Recovered

SEIR model

Susceptible \( \rightarrow \) Latent \((E)\) \( \rightarrow \) Infectious \( \rightarrow \) Recovered

SEICR model

Susceptible \( \rightarrow \) Latent \((E)\) \( \rightarrow \) Infectious \( \rightarrow \) Recovered

\( \downarrow \) Carrier

SIS/SIR and cancer model

Susceptible \( \rightarrow \) Infectious \( \rightarrow \) Pre-cancer \( \rightarrow \) Invasive cancer

Transition between compartments

Source of infection for susceptible individuals

Baussano et al 2014
Conceptual models for natural history of infectious diseases and pathogenesis of cancers of infectious origin - III

Flora and Bonanni, 2011
Determinants of vaccination impact

• Ro = Basic Reproduction Rate = Avg. number of secondary cases of infections generated by one primary case in a wholly susceptible population.

• Ro dependent upon per capita transmission probability, population size or density and average duration of infectiousness

• Crudely, the critical level of effective immunization required to block transmission should be \( > [1 - \frac{1}{Ro}] \)

<table>
<thead>
<tr>
<th>Infection/ infectious agent</th>
<th>Average age at infection in years</th>
<th>Interepidemic period in years</th>
<th>( R_0 )</th>
<th>Critical level of effective immunization required to block transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>4–5</td>
<td>2</td>
<td>15–17</td>
<td>92–95</td>
</tr>
<tr>
<td>Pertussis</td>
<td>4–5</td>
<td>3–4</td>
<td>15–17</td>
<td>92–95</td>
</tr>
<tr>
<td>Mumps</td>
<td>6–7</td>
<td>3</td>
<td>10–12</td>
<td>90–92</td>
</tr>
<tr>
<td>Rubella</td>
<td>9–10</td>
<td>3–5</td>
<td>7–8</td>
<td>85–87</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>11–14</td>
<td>4–6</td>
<td>5–6</td>
<td>80–85</td>
</tr>
<tr>
<td>Polio virus</td>
<td>12–15</td>
<td>3–5</td>
<td>5–6</td>
<td>80–85</td>
</tr>
</tbody>
</table>

Anderson, 2016
Vaccine effectiveness examples:
Impact on cases of Measles in the United States

Anderson, 2016
Vaccine effectiveness examples:
Impact on cases of Measles globally

World Health Organization
Vaccine effectiveness examples: Impact on cases of Poliomyelitis globally
Vaccines for cancers caused by infectious agents

• Hepatitis B virus (HBV) vaccines

• Human papillomavirus (HPV) vaccines

• Vaccines in development for prevention and treatment of precancers/cancers caused by infectious agents
  • HCV
  • HIV
  • HHV-8
  • EBV
  • Others at various stages of preclinical development
Hepatitis B Virus (HBV)

- Established cause of chronic hepatitis, cirrhosis and up to 50% of hepatocellular carcinomas
- >350 million chronically infected worldwide; >1 million in US
- Hepadnaviridae family (DNA)
- Numerous antigenic components
- Humans are only known host
- May retain infectivity for more than 7 days at room temperature
- Transmitted by parenteral or mucosal exposure to HBsAg-positive body fluids from persons who have acute or chronic HBV infection.
Global Age-Standardized Mortality Rates of Liver Cancer

Source: GLOBOCAN 2012 (IARC)
Hepatitis B Vaccine

Composition
• recombinant HBsAg

Efficacy
• 95% (Range, 80%-100%)

Duration of Immunity
• 20 years or more

Schedule
• 3 Doses
• Booster doses not routinely recommended

Adults at Risk for HBV Infection
• sex partners of HBsAg-positive persons
• sexually active persons not in a long-term, mutually monogamous relationship (>1 partner in last 6 months)
• persons seeking evaluation or treatment for a sexually transmitted disease
• men who have sex with men
• percutaneous or mucosal exposure to blood
• current or recent IDU
• household contacts of HBsAg-positive persons
• residents and staff of facilities for developmentally disabled persons
• healthcare and public safety workers with risk for exposure to blood or blood-contaminated body fluids
• persons with end-stage renal disease
• persons with diabetes mellitus
• international travelers to regions with high or intermediate levels (HBsAg prevalence of 2% or higher) of endemic HBV infection
• persons with HIV infection
Coordinated prevention strategies for Hepatocellular Carcinoma

Flora and Bonanni, 2011
Risk for becoming chronic HBV carriers by age

Van Damme 2016
Three major strategies of universal HBV immunization

Chang et al 2016
Impact of HBV vaccination in the United States

FIGURE. Rate* of reported acute hepatitis B among children aged 1–9 years and percentage of children aged 19–35 months who received hepatitis B vaccine, by year — United States, 1986–2000

* Per 100,000 children aged 1–9 years.
Thirty-Year Outcomes of the National Hepatitis B Immunization Program in Taiwan

Chiang et al, JAMA, 2013
Human papillomavirus (HPV)

• Small double-stranded DNA virus
• More than 120 types identified based on the genetic sequence of the outer capsid protein L1
• 40 types infect the genital mucosa; 13 ‘high-risk’ or carcinogetic types
• Reservoir: human; strictly epithelialotropic
• Transmission: direct contact, predominantly sexual
• Necessary (although not sufficient) cause of cervical cancer and high proportions of anal, vaginal, vulvar, penile & oropharyngeal cancers
Global Age-Standardized Incidence Rates of Cervical Cancer

Source: GLOBOCAN 2012 (IARC)

IARC/WHO
Global Age-Standardized Mortality Rates of Cervical Cancer

Source: GLOBOCAN 2012 (IARC)

IARC/WHO
Impact of cervical cytology screening on the incidence of invasive cervical cancer in the United States


Denny, L, Wright, T, Glob. libr. women's med., (ISSN: 1756-2228) 2009;
Cervical Cancer Incidence and Mortality rates in the US

A. Incidence rates
- 5.5 – 8.2
- 8.3 – 9.2
- 9.3 – 10.2
- 10.3 – 11.5
- 11.6 – 16.2

B. Mortality rates
- 0.0 – 1.9
- 2.0 – 2.5
- 2.6 – 2.9
- 3.0 – 3.6
- 3.7 – 8.1

## Licensed Prophylactic Virus-like Particle (VLP)-based HPV vaccines

<table>
<thead>
<tr>
<th></th>
<th>HPV4 Gardasil</th>
<th>HPV9 Gardasil 9</th>
<th>HPV2 Cervarix</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HPV types covered</strong></td>
<td>6, 11, 16, 18</td>
<td>6, 11, 16, 18, 31, 33, 45, 52, and 58</td>
<td>16, 18</td>
</tr>
<tr>
<td><strong>Manufacturing</strong></td>
<td>Saccharomyces cerevisiae (Baker’s yeast) - expressing L1</td>
<td>Saccharomyces cerevisiae (Baker’s yeast) - expressing L1</td>
<td>Trichoplusia ni insect cell line infected with L1 encoding recombinant baculovirus</td>
</tr>
<tr>
<td><strong>Adjuvant</strong></td>
<td>AAHS: 225 µg amorphous aluminum hydroxyphosphate sulfate  AS04: 500 µg</td>
<td>AAHS: 225 µg amorphous aluminum hydroxyphosphate sulfate  AS04: 500 µg</td>
<td>aluminum hydroxide 50 µg 3-O-desacyl-4’ monophosphoryl lipid A</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>Store refrigerated at 2°C to 8°C (35°C to 46°F). Do not freeze.</td>
<td>Store refrigerated at 2°C to 8°C (35°C to 46°F). Do not freeze.</td>
<td>Store refrigerated at 2°C to 8°C (35°C to 46°F). Do not freeze.</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Intramuscular</td>
<td>Intramuscular</td>
<td>Intramuscular</td>
</tr>
</tbody>
</table>
HPV vaccination is the best way to protect your children from cancers caused by HPV

Percentage of adolescent boys and girls who have received one or more doses of HPV vaccine

NATIONWIDE 6 OUT OF 10 parents are choosing to get the human papillomavirus vaccine for their children.

National coverage is 60%

Coverage by state:
- 49% or less
- 50-59%
- 60-69%
- 70% or greater

CDC RECOMMENDS THE HPV VACCINE AT AGES 11-12
Talk to your child’s doctor about HPV cancer prevention


www.cdc.gov/hpv
HPV vaccination is the best way to protect your children from cancers caused by HPV.

2006: HPV vaccine routinely recommended for girls
2011: HPV vaccine routinely recommended for boys
2016: 2-dose HPV vaccination schedule introduced.

Infections with HPV types that cause most HPV cancers and genital warts have dropped 71 percent among teen girls.

6 out of 10 parents are choosing to get the human papillomavirus vaccine for their children.

CDC recommends the HPV vaccine at ages 11-12. Talk to your child’s doctor about HPV cancer prevention.

www.cdc.gov/hpv
Talking to Parents about HPV Vaccine

Recommend HPV vaccination in the same way and on the same day as all adolescent vaccines. You can say, “Now that your son is 11, he is due for vaccinations today to help protect him from meningitis, HPV cancers, and pertussis.” Remind parents of the follow-up shots their child will need and ask them to make appointments before they leave.

Why does my child need HPV vaccine?
HPV vaccine is important because it prevents infections that can cause cancer. That’s why we need to start the shot series today.

Is my child really at risk for HPV?
HPV is a very common infection in women and men that can cause cancer. Starting the vaccine series today will help protect your child from the cancers and diseases caused by HPV.

What diseases are caused by HPV?
Some HPV infections can cause cancer—like cancer of the cervix or in the back of the throat—but we can protect your child from these cancers in the future by getting the first HPV shot today.

How do you know the vaccine works?
Studies continue to prove HPV vaccination works extremely well, decreasing cancer risk.

HPV Vaccine
Is Cancer Prevention Champion
HPV vaccines are very safe. CDC has carefully studied the risks of HPV vaccination. The benefits of HPV vaccination, such as prevention of cancer, far outweigh the risks of possible side effects.

HPV vaccines are safe and recommended for girls and boys at age 11 or 12.

Human papillomavirus (HPV) is a common virus that affects men and women. HPV can cause cancers of the cervix, vagina, and vulva in women, cancer of the penis in men, and cancers of the anus and throat in men and women.

HPV vaccination is recommended for girls and boys at age 11 or 12. There are three HPV vaccines approved by the Food and Drug Administration (FDA) and recommended by the Centers for Disease Control and Prevention (CDC) to protect against HPV and the cancers it can cause.

Like all vaccines used in the United States, HPV vaccines are required to go through years of safety testing before they are approved by the FDA. CDC and FDA closely monitor vaccines to make sure they are safe even after they are available to the public.

HPV vaccines have good safety records. Studies have shown that each HPV vaccine is very safe, and careful safety monitoring has not shown any problems.

The safety of HPV vaccines was tested in thousands of volunteers before the vaccines were approved.

<table>
<thead>
<tr>
<th>HPV Vaccine</th>
<th>Number of Volunteers</th>
<th>Year Approved</th>
<th>Age Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gardasil 4</td>
<td>More than 30,000</td>
<td>2006</td>
<td>Girls age 11 or 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gardasil 9</td>
<td>More than 50,000</td>
<td>2006</td>
<td>Girls age 11 or 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gardasil 9</td>
<td>More than 15,000</td>
<td>2014</td>
<td>Girls age 11 or 12</td>
</tr>
</tbody>
</table>

Like any vaccine or medicine, HPV vaccines can cause side effects.

Some people have mild side effects after getting the HPV vaccine. Common side effects include:

- Pain, swelling, or redness in the arm where the shot was given
- Fever
- Headache or feeling tired
- Nausea, vomiting, diarrhea, or stomach pain
- Muscle or joint pain

Talk with your doctor about any health concerns before vaccination.

If your child is scheduled for HPV vaccination, tell your doctor about any severe allergies. Some children should not get some HPV vaccines, including:

- Children who have ever had a life-threatening allergic reaction to any ingredient of an HPV vaccine, or to a previous dose of HPV vaccine
- Children who have an allergy to yeast (Gardasil and Gardasil 9)
- Children who have an allergy to latex (Cervarix)

HPV vaccines are safe for children who are mildly ill—but, for example, with a low-grade fever of less than 101 degrees, a cold, runny nose, or cough. Children with a moderate or severe illness should wait until they are better.
HPV vaccine protects against cancers and other diseases caused by human papillomavirus (HPV). Follow the chart below to determine whether your patient needs two or three doses of HPV vaccine.

**IS THE PATIENT AGE 11–12?**

- **NO**
  - See FAQs on reverse side for patients outside this age range.

- **YES**
  - **Has the patient received any doses of HPV vaccine?**
    - **NO**
      - **VACCINATE**
        - CDC recommends 11- to 12-year-olds receive two doses of HPV vaccine 6–12 months apart.
    - **YES**
      - **More than one?**
        - **NO**
          - **VACCINATE**
            - The patient should receive the second dose of HPV vaccine 6–12 months after the first dose to complete the series.
        - **YES**
          - **Two doses or three doses?**
            - **NO**
              - **VACCINATE**
                - The patient should receive a third dose of HPV vaccine 6–12 months after the first dose to complete the series.*
            - **YES**
              - **Three doses**
                - **Administered at least 5 months apart?**
                  - **YES**
                    - **THE SERIES IS COMPLETE**
                  - **NO**
                    - **VACCINATE**
                      - The patient should receive a third dose of HPV vaccine 6–12 months after the first dose to complete the series.*

*All minimum intervals must be met second dose at least 4 weeks after first dose; third dose at least 12 weeks after second dose and at least 5 months after first dose.
Published data on one dose vaccine efficacy (VE) after 4-yrs follow-up

Cohort: Costa Rica Vaccine Trial, women aged 18-25 years who were HPV16/18 DNA naïve at 1st vaccination

Endpoint: Incident HPV16/18 infections that persist for 6+ mo

<table>
<thead>
<tr>
<th># of Doses</th>
<th>Vaccine Arm</th>
<th># Women</th>
<th># (%) with endpoint</th>
<th>HPV16/18 VE (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Control</td>
<td>3010</td>
<td>229 (7.6%)</td>
<td>84% (77% to 89%)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>2957</td>
<td>37 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Control</td>
<td>380</td>
<td>24 (6.3%)</td>
<td>81% (53% to 94%)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>422</td>
<td>5 (1.2%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Control</td>
<td>188</td>
<td>15 (8.0%)</td>
<td>100% (79% to 100%)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>196</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

Kreimer AR et al JNCI, 2011
Published data on one-dose immunogenicity after 4-yrs follow-up

Cohort: Costa Rica Vaccine Trial, women ages 18-25 years

* There was a 4-fold difference between 1 dose and 3 dose plateau titers
** There was a 9-fold difference between 1 dose and natural infection plateau titers

Safaeian M et al Cancer Prevention Research, 2013
Clinical equipoise: will one dose of HPV vaccines be enough?

- Results from CVT, and other studies, challenge the prevailing dogma that subunit vaccines require a prime/boost regimen
- Dense repetitive display of epitopes by the HPV VLP may be the exact structural characteristic needed for B cells to recognize (via their B-cell receptors) antigen as foreign or dangerous, leading to exceptionally strong B-cell activation and survival signal
- HPV vaccine may be the first subunit vaccine with true virus-like display of surface epitopes to be stringently evaluated
- Importance of an immune stimulating adjuvant currently unknown- does it augment the B-cell receptor signals?

- NCI (with Gates Foundation) is conducting a large randomized clinical trial to evaluate non-inferiority of 1 vs. 2 doses of the bivalent and nonavalent HPV vaccines in Costa Rica (NCT03180034) and ancillary studies

Schiller JT and Lowy DR J Infect Dis 2014;
FIGURE 1: OVERVIEW OF PROGRAMMATIC INTERVENTIONS OVER THE LIFE COURSE TO PREVENT HPV INFECTION AND CERVICAL CANCER

**PRIMARY PREVENTION**
Girls 9-13 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

* Tobacco use is an additional risk factor for cervical cancer.

World Health Organisation
Guidance Note 2013
GAVI ALLIANCE TACKLES CERVICAL CANCER
EVERY YEAR, 266,000 WOMEN DIE OF CERVICAL CANCER. OVER 85% OF THOSE DEATHS ARE IN DEVELOPING COUNTRIES.

CHANGING THE BALANCE
GAVI's support for HPV vaccines will help redress the inequity, delivering vaccines to countries with the highest burden.

ABOUT HPV VACCINE
Safe and effective, human papillomavirus (HPV) vaccines protect against 70% of cervical cancer.

LOWERING THE PRICE
The new low price of US $4.50 per dose marks a two-thirds reduction on the current lowest public sector price.

DRAMATIC ACCELERATION
By 2020, over 30 million girls in more than 40 countries will be vaccinated against HPV.

Since 2013, over 20 countries have been approved to introduce HPV vaccines with GAVI support.
National programs
American Samoa  Czech Republic  Lesotho  Portugal
Argentina     Denmark          Libya      Romania
Aruba            Dominican Republic  Luxembourg  Rwanda
Australia        Ecuador           Macedonia  San Marino
Austria           Fiji            Luxembourg  Seychelles
Bahamas          Finland           Malaysia  Singapore
Barbados          France           Malta      Slovenia
Belgium            French Polynesia  Marshall Islands  South Africa
Bermuda          Germany           Mexico      Spain
Bhutan            Guam            Micronesia  St. Eustatius
Belize            Guayana        Niue       Suriname
Bermuda            Hungary        Northern Marianas  Trinidad and Tobago
Bhutan              Iceland       Norway       Uganda
Brunei            Ireland          Palau       United Kingdom
Bulgaria            Israel        Palau       United States
Canada           Italy            Panama       Uruguay
Cayman Islands    Japan            Paraguay     Uzbekistan
Chile                Kiribati     Peru        Vanuatu
Colombia            Latvia
Issues in global implementation of HPV vaccination for prevention and control of HPV-associated cancers

- HPV vaccine delivery strategies
  - Health facility
  - School-based
  - Community outreach
  - Campaign-based
- Integration with other public health programs
- Forecasting and calculating need for vaccine supply and cold chain requirements
- Communication planning and crisis management
- Training, Service delivery and Supervision
# Adverse Events Following Immunization (AEFI)

<table>
<thead>
<tr>
<th>AEFI type</th>
<th>Description</th>
</tr>
</thead>
</table>
| Vaccine product-related reaction | An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.  
  *Example:* Extensive limb swelling following DTP vaccination                                                                                   |
| Vaccine quality defect-related reaction | An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer.  
  *Example:* Failure by the manufacturer to completely inactivate a lot of inactivated polio vaccine leads to cases of paralytic polio. |
| Immunization error-related reaction | An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.  
  *Example:* Transmission of infection by contaminated multidose vial.                                                                                |
| Immunization anxiety-related reaction | An AEFI arising from anxiety about the immunization.  
  *Example:* Vasovagal syncope in an adolescent during/following vaccination.                                                                         |
| Coincidental event            | An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.  
  *Example:* A fever occurs at the time of malaria vaccination (temporal association) but is in fact caused by malaria. |
General public has low tolerance to adverse events as vaccines are usually given to healthy persons.

Expectation to safety standard is higher with vaccines compared to medicines for sick people.

National regulatory authorities (NRAs) rigorously ensure the quality, safety, & effectiveness of vaccines and pharmaceutical products.

Once introduced, vaccines are thoroughly and continuously reviewed.

NRAs monitor and investigate AEFIs to ensure safety for population.

Before being introduced, vaccines are assessed in clinical trials.
### Extreme Rarity of Serious Adverse Events following Childhood Vaccination

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Rate of Serious Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>1 in 1,000 to 1 in 50,000 doses</td>
</tr>
<tr>
<td>OPV (oral polio vaccine)</td>
<td>1 in 2 – 3 million doses (or 1 in 750,000 doses for the first dose)</td>
</tr>
<tr>
<td>Measles</td>
<td>1 in 1 million doses</td>
</tr>
<tr>
<td>DTP</td>
<td>1 in 750,000 doses</td>
</tr>
</tbody>
</table>

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Vaccine reaction rate (related to vaccine)
\[
( = \text{Observed rate} - \text{Background rate})
\]
Detected in placebo controlled Randomized Clinical Trials or passive surveillance/postlicensure studies.

Background rate (not related to vaccine)
\[
\text{occur per 1,000 unvaccinated children.}
\]
Recorded prior or simultaneously to vaccination.
Understanding and addressing critical barriers for improving health care and immunization

Too many people are “…uninsured, underinsured, underrepresented, underserved, uninformed, untrusting, uninspired..”

-Dr. David Satcher, former US Surgeon General
Thank you!

• Questions/comments?

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