Human papillomavirus vaccine

Frequently Asked Questions for Health Professionals

What is HPV?
Human papillomavirus (HPV) is a double stranded DNA virus that infects squamous epithelia including the skin and mucous membranes of the upper respiratory and anogenital tracts. There are more than 100 different types of HPV, most of which are responsible for verrucae. Around 40 types can infect the genital tract. Some of these are low-risk types (e.g. HPV 6 and 11,) which cause genital warts, while others are high-risk (oncogenic) types.

Thirteen oncogenic HPV types have been identified. Although most HPV infections are asymptomatic and self-limiting, persistent infection with oncogenic HPV subtypes HPV 16, 18, 31, 33, 35, 45, 51, 52, and 56, may cause cancers of the cervix, oropharynx, anus, vagina, vulva and penis.

The majority of HPV infections do not cause any symptoms and infection is usually cleared by the body’s own immune system without the need for other treatment, 90% of new infections clear within 2 years. Persistent infection by such high-risk oncogenic HPV types is detectable in almost all cervical cancers.

Of these high-risk oncogenic types, HPV16, 18, 31, 33, 35, 45, 51, 52, and 56 are causative for 90% of all cervical cancers

How is HPV spread?
Transmission of HPV can occur by skin to skin contact during vaginal, oral or anal sexual intercourse or genital contact with an infected person. Anyone who is sexually active can contract it. Condom use reduces, but does not eliminate the risk of transmission of HPV

What is the burden of HPV disease in Ireland?
HPV is reported to be responsible for approximately 1 in every 20 cases of cancer across the world. In Ireland, an average of 406 cancers is attributable to HPV infection in both women and men every year. Of these cases, 307 are attributable to HPV 16 and 18 (targeted by Gardasil) and a further 53 cases are attributable to HPV 31, 33, 45, 52 and 58 (additionally targeted by Gardasil 9). The majority of these cancers are diagnosed in the cervix, oropharynx and anus. HPV is also causative for many cancers of the vulva, vagina and penis.

Of the 292 cervical cancers diagnosed annually, 260 (89%) are attributable to HPV strains targeted by Gardasil 9 vaccine.
Of 131 oropharyngeal squamous cell carcinomas, fifty one (38%) are attributable to HPV strains targeted by Gardasil 9, 75% of these cancers are seen in men.

Thirty one squamous cell carcinomas of the anus are diagnosed each year, 20 of these cancers (65%) are diagnosed in women. Twenty five (90%) of these cancers are attributable to HPV strains targeted by Gardasil 9.

See Table 1 for more information.

Average annual number of HPV-associated cancer cases, 2010-2014 (Ireland) showing number of these cancers attributable to strains targeted by 9-valent vaccine

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>HPV **associated Cancers</th>
<th>Percentage of Total</th>
<th>Cancers **attributable to HPV strains targeted by Gardasil 9 vaccine</th>
<th>Percentage of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>292</td>
<td>54%</td>
<td>260</td>
<td>72%</td>
</tr>
<tr>
<td>Oropharyngeal *SCC</td>
<td>133</td>
<td>25%</td>
<td>51</td>
<td>14%</td>
</tr>
<tr>
<td>Vulva SCC</td>
<td>38</td>
<td>7%</td>
<td>6</td>
<td>1.5%</td>
</tr>
<tr>
<td>Anus/Rectum SCC</td>
<td>36</td>
<td>7%</td>
<td>28</td>
<td>8%</td>
</tr>
<tr>
<td>Penis SCC</td>
<td>32</td>
<td>6%</td>
<td>9</td>
<td>3%</td>
</tr>
<tr>
<td>Vagina SCC</td>
<td>10</td>
<td>2%</td>
<td>6</td>
<td>1.5%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>538</td>
<td></td>
<td>360</td>
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</tr>
</tbody>
</table>

*SCC = squamous cell carcinoma

** An HPV-associated cancer is a specific cellular type of cancer that is diagnosed in a part of the body where HPV is often found. Three out of four of these cancers are diagnosed in women and one out of four in men. A HPV-attributable cancer is a cancer where there is direct evidence the cancer is caused by HPV.

Data courtesy of Health Information and Quality Authority Health Technology Assessment (HTA) of extending the national immunisation schedule to include HPV vaccination of boys 2018.

Oncogenic HPV is also responsible for a range of other precancerous lesions of the cervix, vagina and vulva.
in women and HPV types 6 and 11 for anogenital warts in both women and me as well as cancers of the cervix.

In Ireland, ano-genital warts account for approximately 30% of all sexually transmitted infection notifications annually. Furthermore, 6,500 women require treatment for precancerous lesions of cervix annually.

**HPV Vaccine**

**What is HPV vaccine?**

HPV vaccines contain virus-like particles (VLPs) produced from the major capsid protein L1 of each HPV type using recombinant DNA technology.

These vaccines:
- contain no viral DNA and are not infectious or oncogenic
- are not live vaccines
- cannot cause HPV infection
- cannot cause cancer.

**What HPV vaccines are licensed?**

Three HPV vaccines are licensed for use in Ireland.

- Cervarix, (manufactured by GSK) a bivalent vaccine containing VLPs for two HPV types (16 and 18)
- Gardasil (manufactured by MSD), a quadrivalent vaccine containing VLPs for four HPV types (6, 11, 16 and 18)
- Gardasil 9 (manufactured by MSD), a nonavalent vaccine containing VLPs for nine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58).

**What HPV vaccine is being used in the school programme in Ireland?**

Following recommendations from the National Immunisation Advisory Committee (NIAC), the Minister for Health and Children announced that Gardasil 9 vaccine would be introduced into the national immunisation programme from September 2019 for all students as part of the national strategy to prevent cancers attributable to HPV. Gardasil 9 vaccine replaces Gardasil vaccine (HPV4) in the schools programme which was given to girls only.
Gardasil 9 is licensed for use from the age of 9 years for the prevention of pre-cancerous lesions and cancers of the female genitals (cervix, vulva, and vagina), pre-cancerous lesions and cancers of the anus and genital warts in males and females causally related to HPV types 6, 11, 16 and 18, 31, 33, 45, 52 and 58.

**Why is Gardasil 9 being used?**

Gardasil 9 protects against the HPV types causative in 90% of cervical cancer.

The replacement of Gardasil with Gardasil 9 vaccine should prevent a further 50 women developing cervical cancer each year and also offer more protection against premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by vaccine HPV types.

More than 80 countries have now established HPV vaccine programmes, and more than 20 countries, including the US, Canada, and Australia have introduced universal HPV vaccination programmes.

**Why is Gardasil 9 being offered to boys?**

1. **HPV vaccination of boys provides direct protection against HPV-related disease to boys**
   Every year, a quarter of the 406 HPV attributable cancers are diagnosed in men
   More than 75% of oropharyngeal cancers attributed to HPV are diagnosed in men.

   Unlike cervical precancers there is no screening test available for oropharyngeal, anal or penile cancers in men. Though licensed for prevention of cancers of the female genital tract, anus and genital warts, with time it is expected that the Gardasil 9 vaccine will also be effective in reducing the incidence of other cancers attributable to HPV.

2. **Vaccinating boys also provides greater protection to women.**
   A gender neutral programme reduces spread of HPV and is likely to reduce the overall burden of HPV related malignancy sooner than would a girls only programme.

3. **A gender neutral programme ensures that the vaccine programme is more robust**
   A gender neutral programme ensures that the vaccine programme is more robust in relation to potential short-term fluctuations in uptake.

4. **Protection of vulnerable groups**
   Extension of the HPV vaccine programme to include boys will likely greatly improve protection against HPV
infection and associated HPV-attributable disease in vulnerable groups e.g. The MSM and migrant groups.

It is estimated that changing from a HPV 4 vaccine girls only programme to a gender neutral HPV 9 vaccine programme could prevent 113 deaths from cancers attributable to HPV annually.

**How does Gardasil 9 work?**

Gardasil 9 vaccination causes the mounting of the humoral immune response to develop antibodies to the antigens in the VLPs.

**What are the constituents of Gardasil 9?**

Virus like particles (VLPs) for HPV types

Other constituents

- Sodium chloride
- L-histidine
- Polysorbate 80
- Sodium borate
- Water for injection
- Adjuvant (substance that enhances an immune response)
- Amorphous aluminium hydroxyphosphate sulphate (0.5mg Al)

**How commonly are these constituents found in other products?**

These constituents outlined above are commonly found in some other vaccines and in other medicinal compounds.

Examples are outlined below:

- L-histidine is an essential amino acid available in food. A small amount is required in the vaccine. L-histidine is also a component of some hepatitis vaccines
- Polysorbate 80 is used as an emulsifier in foods e.g. ice cream. It is a component of several of the childhood vaccines and other medication e.g. mycostatin used for oral thrush and Feldene gel used as an anti-inflammatory medication. Sodium borate is a component of some vaccines and medicinal compounds such as Optrex eye drops
- Aluminium hydroxyphosphate sulphate is a component of several of the childhood vaccines. Aluminium
Salts have been used in many vaccines for 70 years. The quantity of aluminium in the vaccine is very small (most adults will get approximately 35x more aluminium in their diet each day, than is contained in the vaccine).

**Are aluminium containing vaccines safe?**

The World Health Organization’s Global Advisory Committee on Vaccine Safety stated that at present there is no evidence of a health risk from aluminium-containing vaccines.

**Is latex used in either the manufacturing or packaging process for Gardasil?** No. Latex is not used in the manufacturing or packaging process for Gardasil.

**Are there any reasons not to give the vaccine?**

**Contraindications**

- Known hypersensitivity to the active substances, the adjuvant, or any of the vaccine constituents.
- Pregnancy.

**Precautions**

- Acute severe febrile illness; defer until recovery.
- Vaccine should be administered with caution to individuals with coagulation defects. When vaccines are given intramuscularly to persons with bleeding disorders or on anticoagulants, it is prudent to use a 23 gauge or wider needle to reduce the pressure gradient and cause less trauma to the tissues, and to apply gentle pressure to the vaccine site for 1-2 minutes after the injections. If using a 25 gauge needle, the vaccine should be injected into the muscle over 5 seconds to reduce the risk of tissue damage. In those with a severe bleeding tendency vaccination can be scheduled shortly after administration of clotting factor replacement or similar therapy. There is no recommendation on the subcutaneous administration of the HPV vaccine. The patient or parent should be advised of this.

When there are doubts as to whether or not to give a vaccine contact a Pediatrician or Consultant in Public Health Medicine.

**How safe is the vaccine?**

Gardasil is safe and well tolerated.

The only serious adverse event is Anaphylaxis which has been reported after 1 per million vaccinations.
See adverse reactions listed below.

**Table 2: Adverse reactions following administration of Gardasil 9 occurring with a frequency of at least 1.0% from clinical trials**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorder</td>
<td>Very common</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Nausea</td>
</tr>
<tr>
<td>General disorders and administration site</td>
<td>Very Common</td>
<td>At the injection site: pain, swelling, erythema</td>
</tr>
<tr>
<td>conditions</td>
<td>Common</td>
<td>Pyrexia, fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At the injection site: pruritus, bruising</td>
</tr>
</tbody>
</table>


Post marketing adverse events have also been reported, e.g.; syncope (fainting); fatigue; chills; malaise; vomiting; injection site cellulitis.

Post-vaccination fainting has been reported with most vaccines. Based on data from the USA, syncope is most common after three adolescent vaccines HPV, MCV4 (4th dose Meningococcal vaccine given in the USA), and Tdap. The onset of syncope is usually within 15 minutes of vaccination.

An EMA and a UK MHRA review found no evidence that HPV vaccines cause POTS.

**Postural Orthostatic Tachycardia Syndrome (POTS)** is 4 times more common in females and onset peaks in adolescence. It is likely therefore to develop spontaneously in girls who are at the age when they have received HPV vaccine.

Worldwide independent health authorities have reviewed HPV vaccine safety and all have concluded that evidence does not support a link between HPV vaccine and the development of any chronic illness.
In January 2016 the EMA issued a final report on the review of HPV vaccines. This report found no evidence the vaccine was linked to chronic fatigue like conditions. Please see link for full details at http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/European_Commission_final_decision/WC500196773.pdf

The European Commission endorsed the conclusion of the EMA.


WHO reported in July 2017 that HPV vaccines are considered to be extremely safe.

Further information can be found at http://www.who.int/vaccine_safety/committee/topics/hpv/en/

**Why is Gardasil 9 recommended in 1st year of second level school?**

NIAC recommended that HPV vaccine be given to 12 year old students (equivalent to First year of second level school) because

- The vaccine is most effective if given before sexual activity occurs
- A superior immune response has been demonstrated at this age.

**What is the vaccine dose and schedule?**

For those aged less than 15 years at the first dose, two doses (0.5ml) are recommended at 0 and 6 months.

For students aged 15 years and older at the first dose, three doses (0.5ml) are recommended at 0, 2 and 6 months as there is no evidence to support a two dose schedule in those aged 15 and older. The vaccine is given by intramuscular injection in the deltoid region.

**What is the minimum interval between the first and second dose of Gardasil 9 vaccine?**

While every effort should be made to comply with the recommended interval of six months,

*The minimum interval between the 2 doses Gardasil 9 is 5 months*

This means the second dose of HPV vaccine can be considered valid if given at an interval of 5 calendar months after the first dose.
Can other vaccines be given at or around the same time?

Gardasil 9 vaccine can be administered the same time as or at any interval before or after any other vaccines such as Tdap (tetanus, low dose diphtheria and low dose acellular pertussis vaccine) and MenACWY vaccine (meningococcal vaccine).

What happens if a student is absent from school and misses a dose?

The student should be given an appointment for a mop-up clinic to be held at the end of the period of school vaccination clinics.

When is the latest time for a student to start their 1st dose of HPV vaccine in 2019/2020?

Only students who are clinically unwell and unable to have the vaccine in September/October and students who are new to the school when the team visits the schools in 2019 should be given their 1st dose of HPV in March/April. This means a very small number should start the programme in March/April 2020.

What about older girls who wish to be vaccinated?

If a parent/legal guardian makes contact with the vaccination team and now requests that their unvaccinated daughter receives HPV vaccine, Gardasil may be given at a mop up clinic. Gardasil 9 will be given when stock of Gardasil is depleted.

What about girls who started but did not complete their vaccination schedule?

Girls who started vaccination with Gardasil in school should be facilitated to complete the schedule in mop-up clinics. They should complete the schedule with Gardasil.

If stocks of Gardasil are no longer available, they can complete the schedule with Gardasil 9, they do not need to start the schedule again.

Girls who have completed the schedule with Gardasil do not need to be revaccinated with Gardasil 9.

What consent form should I use for older girls outside First year?

Please use the “outside cohort” 3 dose HPV vaccine yellow consent form.
What should a vaccinator check before giving the second or third dose of Gardasil 9?

I. Vaccine scheduling in relation to the 2nd dose:
The minimum interval of 5 calendar months should have passed since the 1st dose.

If a student presents for the 2nd dose less than the minimum interval after the 1st dose, vaccination should be deferred and they should be given an appointment to attend at a later date.

In relation to the 3rd dose for those students aged 15 years and older at time of first dose:
Students aged 15 years and older at time of first HPV vaccine (Gardasil 9) require 3 doses of HPV vaccine.
The recommended interval between the between the first and second doses is 2 months. The minimum interval between the first and second doses is 4 weeks. The minimum interval between the second and third doses is 12 weeks. The minimum interval between the first and third doses is 5 calendar months.
If a dose is administered at less than the recommended minimum interval then the dose should be repeated at or after the recommended minimum interval and at least one month after the discarded dose.

See Table NIAC advice below

### Table 10.1 Optimal age and intervals and minimum intervals for HPV vaccines

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of doses</th>
<th>Dose 1 to Dose 2</th>
<th>Dose 2 to Dose 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Optimal interval</td>
<td>Minimum interval</td>
<td>Optimal interval</td>
</tr>
<tr>
<td>HPV4 &lt;15</td>
<td>2</td>
<td>6 months</td>
<td>5 months</td>
</tr>
<tr>
<td>≥15</td>
<td>3</td>
<td>2 months</td>
<td>4 weeks</td>
</tr>
<tr>
<td>≥15</td>
<td>6 months</td>
<td>5 months</td>
<td></td>
</tr>
<tr>
<td>HPV9 &lt;15</td>
<td>2</td>
<td>6 months</td>
<td>5 months</td>
</tr>
<tr>
<td>≥15</td>
<td>3</td>
<td>2 months</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

II. Clinical Issues

- Did the student have any reaction/adverse effects to the first/second dose of Gardasil 9 (or Gardasil)?
- Has the student developed any new medical condition or are they on any new medication?
- Is there any possibility that a girl may be pregnant?
- Is the student feeling well today?

These clinical issues are dealt with in the “Supporting Information: Schools Immunisation Programme 2019/2020” and it is essential that all clinical staff involved in the programme are familiar with this document.
What should happen if a student receives a dose of HPV (Gardasil 9) vaccine before the recommended minimum time interval?
Those aged under 15 years at the first dose require two doses of Gardasil 9 vaccine. The minimum interval between dose 1 and dose 2 is 5 months.

If the second vaccine dose is administered earlier than 5 months after the first dose, a third dose should be administered at least 12 weeks after the second dose.

Those aged 15 years and older at the first dose require three doses of HPV vaccine. The minimum interval between dose 1 and dose 2 is 1 month.

The minimum interval between dose 2 and dose 3 is three months.

The 4 day rule applies.

If the HPV vaccine schedule is interrupted, does the vaccine series need to be restarted?
No. If the vaccine schedule is interrupted the vaccine series does not need to be restarted even if this means that it will take more than 12 months to complete the vaccine course.

What about a student who received the 1st dose of HPV vaccine in 2018/2019 but missed subsequent doses?
If a student was less than 15 year of age at the 1st dose of vaccine the student only needs one further dose at least 6 months after the first dose to complete the course.

If the student was 15 or older at the 1st dose they needs two further doses with at least 3 months between the 2nd and 3rd doses.

How effective is Gardasil 9?
- Gardasil 9 is as effective as Gardasil for the prevention of diseases caused by the four shared HPV types (6, 11, 16, and 18), based on similar antibody responses in participants in clinical studies.
- The trials that led to approval of Gardasil 9 found it to be nearly 100% effective in preventing cervical, vulvar, vaginal and anal disease caused by the five additional HPV types (31, 33, 45, 52, and 58) that it targets.
- HPV vaccine is associated with an 88% reduction in CIN2 and 89% reduction in CIN3+ in Scotland.
**How long does protection last?**

Efficacy studies have shown the Gardasil vaccine to be effective for more than 12 years, with no evidence of waning immunity. It is expected that the Gardasil 9 will provide long term protection.

**What protection is provided by one dose?**

Data are not available on the efficacy of one dose. Efficacy studies to date are based on a 2 or 3 dose vaccination course.

**How do I report an adverse event following vaccination?**

All adverse events should be reported to the HPRA. More information at [http://www.hpra.ie/homepage/about-us/report-an-issue](http://www.hpra.ie/homepage/about-us/report-an-issue)

**What should happen with a student who has a non anaphylactic allergic reaction post vaccination?**

The Immunisation Guidelines for Ireland state that those who have had a non-anaphylactic allergy may be given a subsequent dose of that vaccine if indicated. [http://www.hse.ie/eng/health/immunisation/hcpinfo/guidelines/chapter10.pdf](http://www.hse.ie/eng/health/immunisation/hcpinfo/guidelines/chapter10.pdf)

NIAC wishes to draw attention to the following:

1. There are degrees of severity of hypersensitivity reactions.
2. The only absolute contraindication to most vaccines is previous anaphylaxis to the vaccine or any of its constituents.
3. Cases of hypersensitivity need to be considered on a case by case basis.
4. Mild hypersensitivity reactions are not contraindications to a subsequent dose of a vaccine.
5. More severe non anaphylactic reactions should be discussed with a Consultant in Public Health Medicine and/or Pediatrician. In these cases vaccination in a hospital setting may be appropriate.
6. Recommendations from NIAC, including those in the Immunisation Guidelines for Ireland, may differ from those of the SmPC and the Health Products Regulatory Authority (HPRA).

To assist in the assessment of reactions it is important that the HPRA adverse reaction report form is completed in full for all cases. A medication error does not need to be routinely reported to the HPRA unless the student experiences harm (i.e. an adverse reaction) associated with it. In any such cases involving adverse reactions, an adverse reaction report should be submitted to the HPRA, including information on the nature of the error involved.
Is Gardasil 9 contraindicated in immunosuppressed students?

No. Gardasil 9 is NOT contraindicated in students who are immunosuppressed as long as they are well and do not have a high fever. Again there is no risk to receiving HPV vaccine if their immune system is lowered – however the vaccine manufacturer has stated that those with reduced immune responses may not respond to HPV vaccine as well as those with healthy immune systems (this is the same as with most other vaccines) but there is no long term data about this yet. If the immunosuppression is temporary vaccination may be deferred until the immune system is functioning normally.

What should happen to a student who receives the first or second dose of HPV and then becomes immunosuppressed?

As above, there is no contraindication to a student receiving a further dose of HPV vaccine (if indicated) as long as they are well and do not have a high fever. However, they may not respond to HPV vaccine as well as those with healthy immune systems. If the immunosuppression is expected to be temporary, vaccination may be deferred until the immune system is functioning normally.

Can Gardasil be administered during pregnancy?

No. Gardasil is not currently recommended during pregnancy, although there is no known risk associated with using recombinant viral vaccines during pregnancy.

What should happen if a girl finds out she is pregnant and has received the vaccine?

If a girl who was vaccinated subsequently finds out that she was pregnant at or conceived around the time of vaccination, any further HPV vaccination should be postponed. There is no evidence to date that the vaccine will have caused any harm to her, the pregnancy, or the foetus. She should be advised to discuss the matter with her GP. The course of Gardasil9 HPV vaccination may be finished when the pregnancy is completed.

Can Gardasil 9 affect a girl's/boy's fertility?

No. Gardasil 9 does not affect future fertility.


Do fully vaccinated girls need cervical screening?

Yes. Currently HPV vaccines only protect against HPV types which cause approximately 90% of cervical cancers. Girls who have been fully vaccinated still need to be screened for cervical cancer caused by the remaining HPV types which the vaccine does not protect against. In addition a small number of girls (<1%) may not develop an adequate immune response post vaccination and a small number of girls may be already
infected. Thus it is essential that girls participate in the National Cervical Screening Programme when they are of an appropriate age.

**Is information available in other languages?**

The HPV Leaflet is available in the following languages:

English, Irish, Arabic, Simplified Chinese, German, French, Polish, Portuguese, Romanian and Russian.

These are available for download at [www.immunisation.ie](http://www.immunisation.ie)
Where to look for further information

Further information regarding HPV, cervical cancer and HPV vaccine can be found on the following websites.

- Health Protection Surveillance Centre available at [www.hpsc.ie](http://www.hpsc.ie)
- Health Products Regulatory Authority available at [www.hpra.ie](http://www.hpra.ie)
- Irish Cancer Society available at [www.cancer.ie](http://www.cancer.ie)
- Medicines Information online available at [www.medicines.ie](http://www.medicines.ie)
- National Cancer Screening Service available at [http://www.screeningservice.ie/](http://www.screeningservice.ie/)
- National Cancer Registry Ireland available at [http://www.ncri.ie](http://www.ncri.ie)
- National Immunisation Office available at [www.immunisation.ie](http://www.immunisation.ie) and [www.hpv.ie](http://www.hpv.ie)
- Centers for Disease Control and Prevention – HPV information available at [www.cdc.gov/hpv/](http://www.cdc.gov/hpv/)
- World Health Organization HPV information available at [www.who.int/immunization/topics/hpv/en/](http://www.who.int/immunization/topics/hpv/en/)