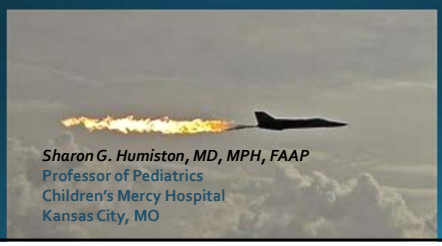
Refueling your personal conviction:

HPV Disease & Vaccine Update



Sharon G. Humiston, MD, MPH, FAAP
Professor of Pediatrics
Children's Mercy Hospital
Kansas City, MO

DISCLOSURE:

Dr. Humiston's institution (CMH) receives funding from "Pfizer Independent Grants for Learning & Change" for her work to develop and test a curriculum to teach residents about how to manage vaccine hesitancy.

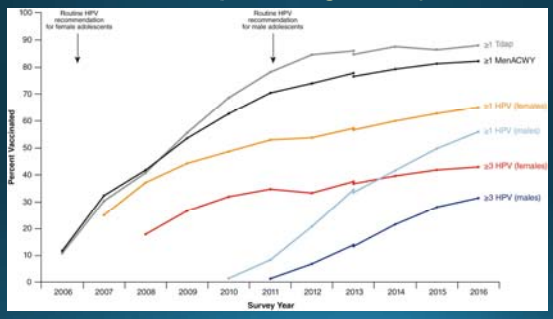
This relationship is not relevant to this presentation.

Dr. Humiston's presentation today was funded by a grant from CDC to APA.

ACADEMIC PEDIATRIC ASSOCIATION

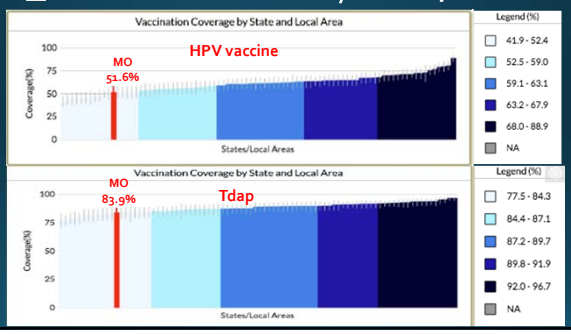
Topic #1

Vaccination Coverage, **Teens Ages 13-17 years**, U.S.

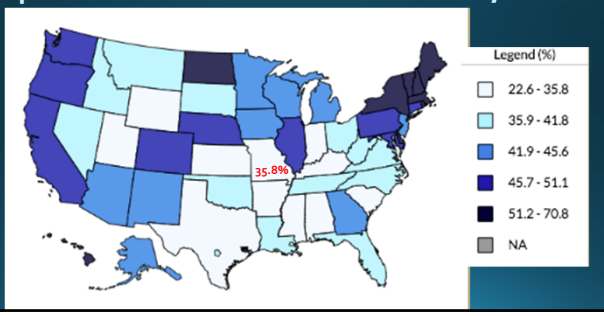


Markowitz et al. Academic Pediatrics 2018 18, S3-S10DOI:

≥1 dose of vaccine by state, 2016



Up-to-date HPV Vaccination Rates, 2016



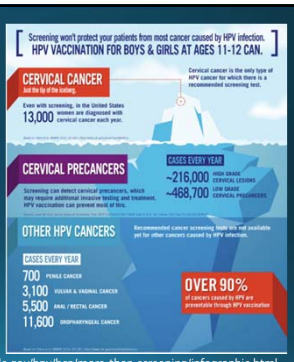
"Here's the bottom line:
nothing goes further than having
a **deep knowledge** of the issues;
a sincere, meaningful and trustworthy
connection with the family; and
a strongly held **personal conviction** that
vaccines save lives and prevent misery."

The Vaccine Handbook

Topic #2

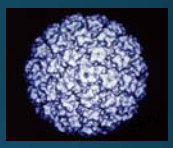
HPV disease causes loss of lives and plenty of misery.

HPV vaccine prevents this.



https://www.cdc.gov/hpv/hcp/more-than-screening/infographic.html

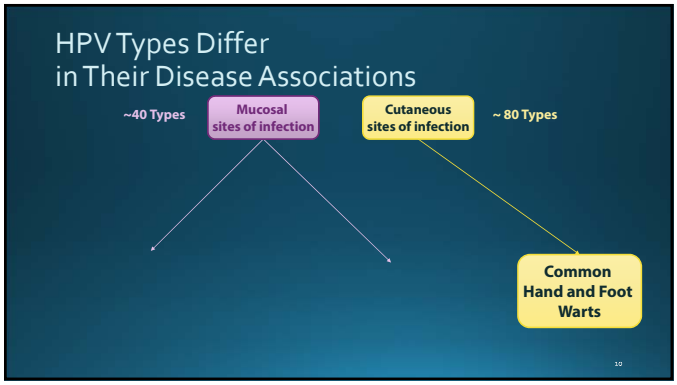
Human Papillomavirus



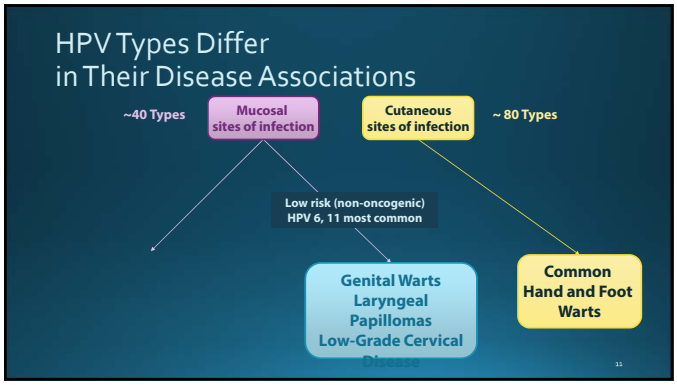
- A virus that infects human skin and mucosal surfaces
- Transmitted easily
  - >90% of men and
  - >80% of women

  will be infected with ≥1 type of genital HPV at some time
- Some strains cause cancers

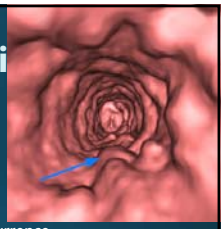
HPV Types Differ in Their Disease Associations



HPV Types Differ in Their Disease Associations



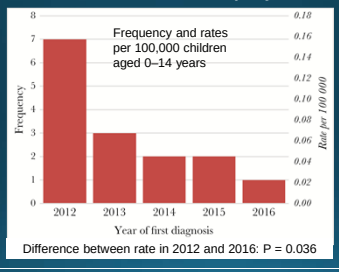
Laryngeal Papillomatosi



- Annual cases per 100,000:~4.3 children, 1.8 adults
- Benign tumors along the aerodigestive tract
- Caused by HPV infection of the throat
- Lead to narrowing of the airway
- Treatment
  - Aims to remove the papillomas and limit their recurrence
  - Repeated treatments usually are needed
  - Primarily treated surgically (laser microsurgery)
- Though total recovery may be observed, it is often persistent despite treatment

Incident cases of juvenile onset recurrent respiratory papillomatosis notified in Australia per year 2012–2016

Among incident cases no mothers were vaccinated pre-pregnancy



Difference between rate in 2012 and 2016: P = 0.036

Australia has had extensive 4-valent HPV vaccination program (females 12–26 years old, started in 2007)

From: A Prospective Study of the Incidence of Juvenile-Onset Recurrent Respiratory Papillomatosis After Implementation of a National HPV Vaccination Program
J Infect Dis. 2017;217(2):208-212. doi:10.1093/infdis/jix498
Available at https://academic.oup.com/jid/article/217/2/208/4596529

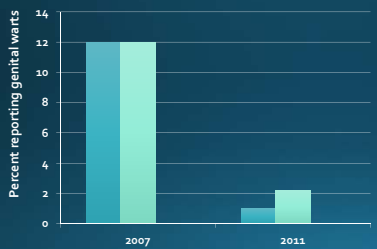
Genital warts

- > 3 million US cases per year
- Highly transmissible
  - May be transmitted during birth
  - Auto-inoculation
  - Non-penetrative sexual activity
  - Penetrative sex
- Treatment can help, but there is no cure

Photo credit: https://en.wikipedia.org/wiki/Genital_wart

Near-disappearance of genital warts in Australia following introduction of HPV vaccination

70% 4-valent HPV vaccination rate for females 12-26 only, started in 2007



Australia has had extensive 4-valent HPV vaccination program (females 12–26 years old, started in 2007)

93% reduction in girls <21

82% reduction in boys <21

Ali H et al. BMJ 2013;346:bmj.f2032

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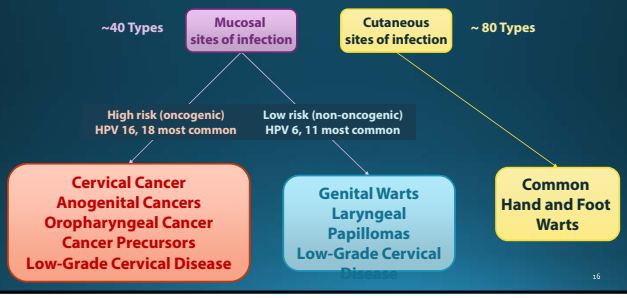
HPV Types Differ in Their Disease Associations



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Cancers Caused by HPV per Year, U.S., 2010–2014

Cancer site	Percentage probably caused by any HPV type	Number probably caused by any HPV type		
		Female	Male	Both Sexes
Cervix	91%	10,600	0	10,600
Vagina	75%	600	0	600
Vulva	69%	2,600	0	2,600
Penis	63%	0	800	800
Anus*	91%	3,800	1,900	5,700
Oropharynx	70%	2,100	10,100	12,200
TOTAL		19,700	12,800	32,500

*Includes **anal and rectal** squamous cell carcinomas
Sources: https://www.cdc.gov/cancer/hpv/statistics and Saraiya M et al. J Natl Cancer Inst. 2015;107:djv086

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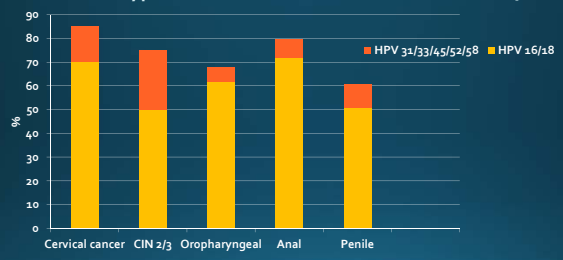
%of HPV types found in common HPV related cancers, US



9-valent vaccine is estimated to prevent:
85% of cervical, 70% of oropharyngeal,
80% of anal, and 60% of penile cancers

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Do women still actually get cervical cancer & does anyone die of it?

Isn't early detection enough?

(Do we really need to prevent infection?)

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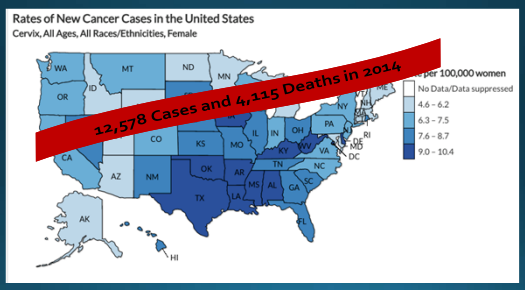
HPV-Associated Cervical Cancer Incidence Rates, 2014



Source: https://nccd.cdc.gov/USCSDataViz/rdPage.aspx

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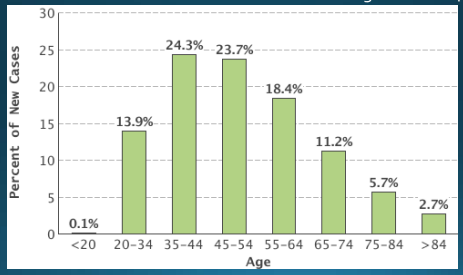
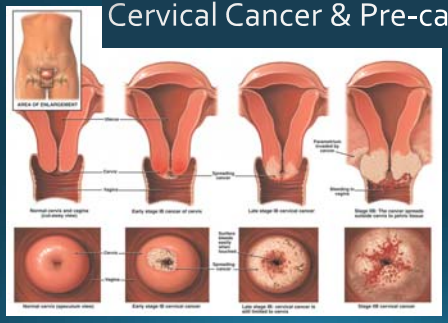
Cervical Cancer During Child-bearing Years

38% of cervical cancers occur in women between the ages of 20 & 44 years.



http://seer.cancer.gov/statfacts/html/cervix.html

Cervical Cancer & Pre-cancers



Drawing from http://www.womeningovernment.org/oncology/hpv

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Cervical Dysplasia

- **Mild dysplasia (CIN1)**
  - aka Low-grade Squamous Intraepithelial Lesion (LSIL)
  - Regression is the norm
  - 1.4 million/ year in U.S.
  - Conservative follow-up
- **Moderate/severe dysplasia (CIN2/3)**
  - aka High-grade Squamous Intraepithelial Lesion (HSIL)
  - High risk for progression to cancer
  - 330,000/ year in U.S.
  - LEEP offers high cure rate

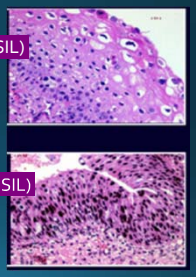
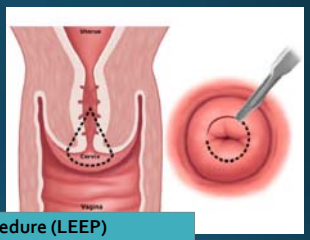


Photo Credit: Medscape (Available at https://www.medscape.org/viewarticle/508691)



Loop electrosurgical excision procedure (LEEP) or a cold-knife cone biopsy is used to treat high grade cervical dysplasia and even early cervical cancer

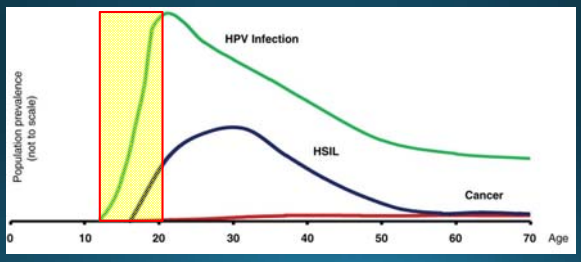
Even pre-cancerous lesions have implications for a woman & her offspring because LEEP is associated with:

- oPerinatal mortality
- oPreterm delivery
- oLow birth weight
- oLong term developmental outcomes
- oNeonatal intensive care costs

Bjorge, Obstet Gynecol, 2016; Sadler, JAMA, 2004, Insinga, Pharmacoeconomics, 2005,

25

We need HPV vaccination to eliminate first peak of HPV acquisition

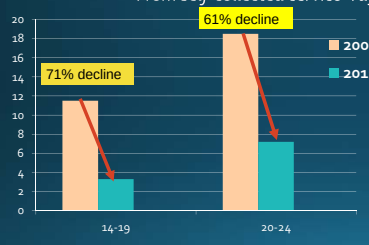


Schiffman M et al. CEBP 2013.

26

Within 8 years of U.S. vaccine introduction 4vHPV-type prevalence has decreased significantly

From self-collected cervico-vaginal specimens



Vaccine effectiveness: 83%

Compared to 2003-2006, 4vHPV prevalence in sexually active 14- to 24-year-olds in 2011-2014 decreased

- **89% among those vaccinated**
- **34% among those unvaccinated**

which suggests herd protection

Oliver , et al. J Infect Dis. 2017 Sep 1;216(5):594-603. doi: 10.1093/infdis/jix244. https://www.ncbi.nlm.nih.gov/pubmed/28931217

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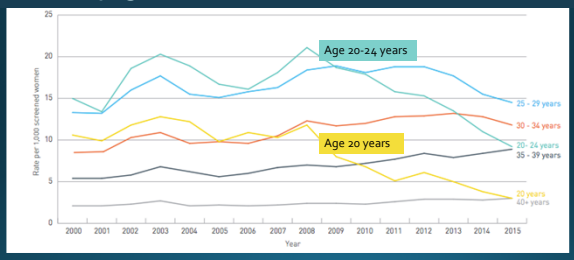
Trends in high-grade cervical abnormalities (histologically-confirmed) by age, 2000-2015, as recorded on the VCCR, Australia



From the Victorian Cervical Cytology Report, 2015

http://www.vccr.org/site/VCCR/filesystem/documents/dataandresearch/StatisticalReports/17030_VCS_StatsReport15_ART.3.pdfhttp://www.vccr.org/site/VCCR/filesystem/documents/dataandresearch/StatisticalReports/17030_VCS_StatsReport15_ART.3.pdf

Vaccination protects against invasive HPV-associated cancers

Data from the Finnish Cancer Registry, Helsinki, Finland

	Vaccinated	Women	Unvaccinated	Women
MALIGNANCIES	n	Rate	n	Rate
Cervix	0	--	8	6.4
Vulva	0	--	1	0.8
Oropharyngeal	0	--	1	0.8
Vaginal, anal	0	--	0	--
All HPV assoc CA	0	--	10	8.0
Breast	2	3.0	10	8.0
Thyroid	1	1.5	9	7.2
Melanoma	3	4.6	13	10.5
Other skin	2	3.0	3	2.4

Tapio Luostarinen, et al. Int J Cancer. 2017 Dec 26. doi: 10.1002/ijc.31231. https://www.ncbi.nlm.nih.gov/pubmed/29280138

4vHPV efficacy trial in women 16–23 years

Interim 10 year follow-up (14 years planned)

Base RCT included >12,000 women from 13 countries[1]
- Follow-up in Nordic Cancer Registries, ~3,800 participants[2]
- Registry searches every 2 years

Endpoint	N cases/ n subjects	Person-yrs at risk	Incidence / 100 person years at risk % (95% CI)
HPV 6/11/16/18- related CIN and vulvar/vaginal cancer	1/2171	10483	0 (0-0.1)
Time since day 1:			
< 4 years	0/2050	861	0 (0-0.4)
4-6 years	0/2168	4257	0 (0-0.1)
6-8 years	1/2059	3649	0 (0-0.2)
8-10 years	0/1439	1686	0 (0-0.2)

1 case of CIN1 with HPV types 16, 45, 52 concurrently detected

[1]Protocol 015. Future II, NEJM 2007 [2]Kjaer, EUROGIN 2015

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4vHPV immunogenicity trial in adolescents 9–15 years Final 10 year follow-up

- No cases of HPV 6,11,16,18 disease
- 10 persistent infections >6 months, 2 > 12 months
- This is a 90% reduction compared with placebo groups from older trials (No placebo group for this trial as considered unethical to withhold vaccine)

Gender	Cases/100 person-years 10 year follow up 9-15 year olds	Cases/100 person-years 3-4 year follow up of 16-26 year olds
Males	0.4-0.6	6
Females	0.3	4

Das and Saah Eurogin 2016

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Without vaccination, annual burden of genital HPV-associated disease in U.S. females

Data Sources: American Cancer Society. 2008, Schiffman, Mark, and Philip E. Castle., Koshiol *Sex Transm Dis.* 2004, Insinga, Ralph P., Erik J. Dasbach, and Elamin H. Elbasha, 2005

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Extrapolating the prior pyramid with projections of vaccine efficacy based on Australian data

Cervical cancer

46% reduction in CIN2/3 requiring LEEP
75% if vaccination by age 14

92% reduction in genital warts

35% reduction in CIN1

Data Sources: Gertig, 2013; Read, 2011; Smith, 2015

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Beyond the Statistics: What HPV Means to Women's Lives

Rebecca Perkins and Tamika Felder

The March issue of *Academic Pediatrics* (http://bit.ly/2sYPfFU) offers a CDC-sponsored supplement, "Raising Human Papillomavirus Vaccination Rates."

http://www.academicpedsjnl.net/article/S1876-2859(17)30169-9/fulltext

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Obviously, we want to prevent HPV infection in females.

Why do we want to protect males from HPV?

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Why vaccinate males?

- Non-oncogenic problems
- Prevent HPV infection of females
- Male only: Penile cancer
- Both sexes:
  - Anal cancer
  - Oropharyngeal cancer

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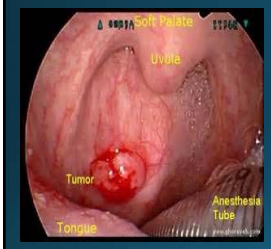
Oropharyngeal Cancer



- 11,000 cases annually, 9,000 in men
- Rise in incidence and changing patient demographics due to HPV
- Now more common than cervical cancer
- No screening test
- Good survival statistics

http://www.ghorayeb.com/OropharyngealCarcinoma.html
J Clin Oncol 29:4294-4301. © 2011 by American Society of Clinical Oncology

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Photo Credit: Dr Michael Moore

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Side effects of non-surgical therapy

Side Effect	Percent affected
Taste Disturbance	88%
Nausea/Vomiting	36%
Dry Mouth	29-38%
Esophageal Stricture	5%
Require G tube > 1 year	9%

Irune, et al, 2014; Kocak-Uzel, et al, 2014; Nutting, et al, 2011; McBride, et al, 2014
Photo credit: www.jpalliativecare.com

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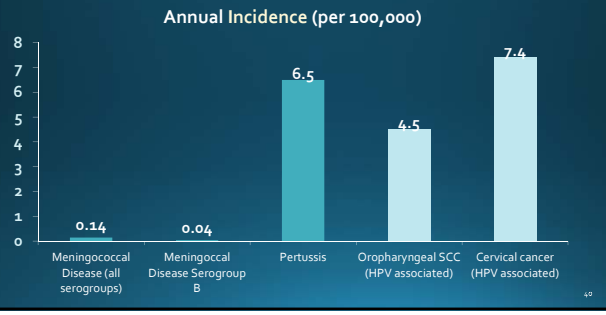
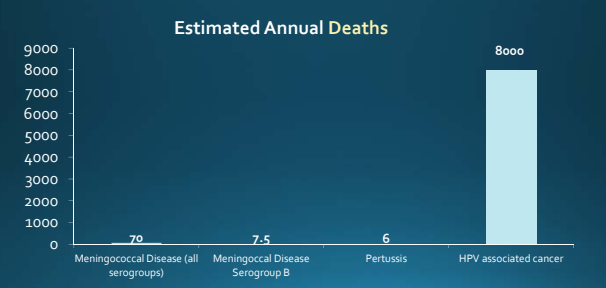
Incidence of Diseases covered in Adolescent Vaccine Series



Data Sources: CDC, 2016; CDC 2015; Viens 2016

40

Deaths from Diseases covered in Adolescent Vaccine Series



Data Sources: CDC, 2016; CDC 2015; American Cancer Society

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Annual Costs of HPV-associated Diseases, US

HPV-Associated Problem	U.S. Cost*
Genital warts treatment	$288 Million
Cervical cancer screening and follow-up of abnormal tests	$6.6 Billion
All HPV-associated diseases, including cancer	$8 Billion

*Based on 2010 dollars

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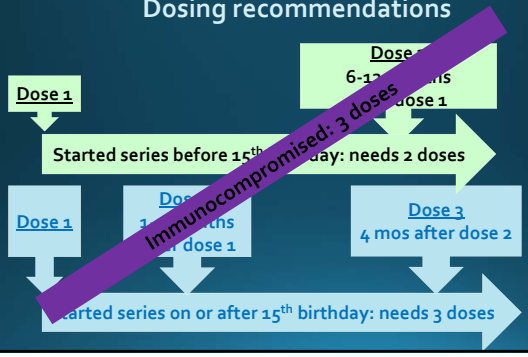
Topic #3

HPV prevention is easier than ever.

Dosing recommendations



What forms of "immunocompromise" necessitate a 3-dose HPV vaccine series?

Needs 3 doses irrespective of age:
Primary or secondary conditions that might reduce cell-mediated or humoral immunity
Examples:

- **B lymphocyte Ab deficiencies**
- **T lymphocyte complete or partial defects**
- **HIV infections**
- **Malignant neoplasm**
- **Transplantation**
- **Autoimmune disease**
- **Immunosuppressive therapy**

Can use 2 dose series for those initiating before 15th birthday:

- Asthma
- Asplenia
- Diabetes mellitus
- Sickle cell disease
- Chronic granulomatous disease
- Chronic disease of liver, lung, kidneys
- Heart disease
- CNS barrier defects (eg, cochlear implant)
- Complement deficiency, persistent complement component deficiency

Recommended # of Doses & Dosing Schedule

Population	Recommended # of Doses	Recommended Schedule	Minimum Intervals
Started series at age 9 through 14 years, except immuno-compromised persons	2	0, 6-12 months	5 months between doses
	Memory B cells require at least 4-6 months to mature and differentiate into high-affinity B cells ~6 month interval between first and last dose allows last dose to efficiently reactivate memory B cells		
Started series at age 15 through 26 years, and immunocompromised persons (any age)	3	0, 1-2, 6 months	4 weeks between doses 1-2 12 weeks between doses 2-3 5 months between doses 1-3

Case example - 1

A boy is starting the HPV vaccine series on his 15th birthday. *How many doses does he need in total?*

A. 0
B. 2
C. 3

This adolescent needs 3 doses (0, 1-2, 6 months schedule) because he is starting the series on (or after) the 15th birthday.

Case example - 2

A 13 year old has a history of 2 doses of HPV vaccine:
4vHPV given at age 12 years and
9vHPV given 6 months later.
How many more doses are needed?

A. 0
B. 1
C. 2

No further doses are recommended because she initiated vaccination before the 15th birthday and received 2 doses of vaccine 6 months apart.

Case example - 3

A 13 year old has a history of 2 doses of HPV vaccine:
4vHPV given at age 11 years
& 9vHPV given 2 months later.

How many <u>more</u> doses are needed?

A. 0
B. 1
C. 2

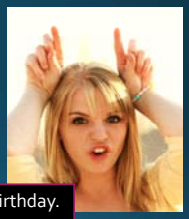
1 more dose…Although she initiated the vaccination series before her 15th birthday, she needs another dose because HPV vaccine doses #1 and #2 were administered <5 months apart.
Give a 3rd dose with
- a minimum of 12 weeks between doses 2-3 and
- a minimum of 5 months between doses 1-3

Case example - 4

A (spunky) 16 year old had
1 dose of HPV vaccine:
4vHPV given at age 11 years

How many <u>more</u> doses are needed?

A. 0
B. 1
C. 2



1 more dose… Her first dose was before her 15th birthday.
Complete her series today.

Topic #4

What are the HPV vaccine true contraindications and precautions?

Which of the following is a **contraindication** to HPV vaccine?

A. Pregnancy

B. Moderate or severe acute illness with or without fever

C. A severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component

D. All of the above

E. B and C

https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html

Which of the following is **contraindication** to HPV vaccine?

A. Pregnancy **(precaution)**

B. Moderate or severe acute illness with or without fever **(precaution)**

C. A severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component

https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html

None of these is a contraindication

COMMONLY MISUNDERSTOOD
- Lack of previous physical examination
- Current antibiotic use
- History of HPV
- Autoimmune disease

ILLNESS
- Mild acute illness, with or without fever
- Mild respiratory illness (including most cases of otitis media)
- Mild gastroenteritis
- Convalescent phase of illness
- Exposure to an infectious disease

REACTION TO PREVIOUS VACCINATION
- Low-grade or moderate fever and/or local reaction after a previous dose
- Fainting (syncope) after a previous dose

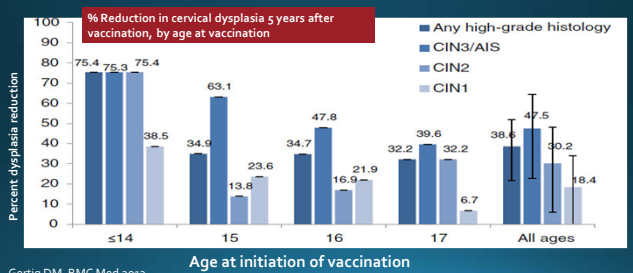
Topic 5: Deep knowledge of FAQs

1. Why give it so young?
2. Should we give it to 9 year olds?
3. Should I only give it to kids at "high risk?"
4. Will it cause infertility?
5. Is it safe?

Topic 5: Deep knowledge of FAQs

1. **Why give it so young?**
2. Should we give it to 9 year olds?
3. Should I only give it to kids at "high risk?"
4. Will it cause infertility?
5. Is it safe?

Higher effectiveness with vaccination at younger ages



Gertig DM, BMC Med 2013

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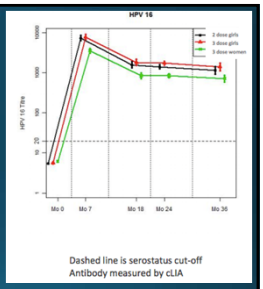
Antibody response at age 9-13 vs. 16-26 years

Follow-up through month 36

- 2 doses (0,6 months) in 9–13 yr olds (black)
- 3 doses 0,2,6 months in 9–13 yr olds (red)
- 3 doses (0,1,6 months) in 16–26 yr olds (green)

Antibody kinetics similar in 3 groups



Dashed line is serostatus cut-off
Antibody measured by cLIA

Dobson, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. JAMA2013 May 1;309(17):1793-802. doi: 10.1001/jama.2013.1625.
Slide presented by Dr. L.Markowitz, 10/2016

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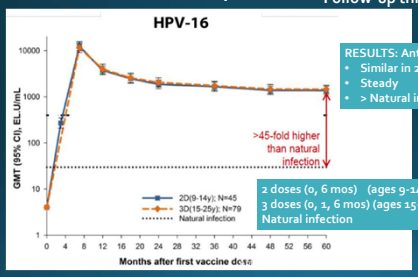
Will immunity last?

Follow-up through month 60



RESULTS: Antibody kinetics
- Similar in 2 groups
- Steady
- > Natural infection

2 doses (0, 6 mos) (ages 9-14 y)
3 doses (0, 1, 6 mos) (ages 15-25 y)
Natural infection

Source: Romanowski, Hum Vaccine 2016

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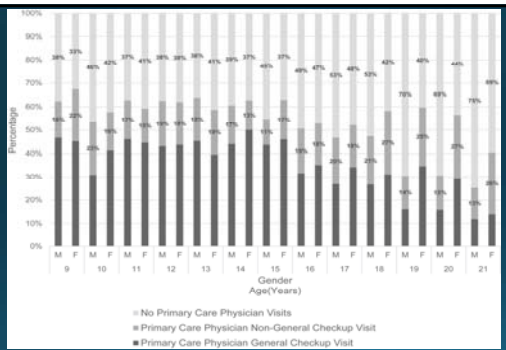

C. Rand, N. Goldstein. Academic Pediatrics 2018 18, S72-S78DOI: (10.1016/j.acap.2018.01.002)

When should the bike helmet go on?

A. Before they get on their bike
B. When they are riding their bike in the street
C. When they see the car heading directly at them
D. After the car hits them

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Topic 5: Deep knowledge of FAQs

1. **Why give it so young?**
2. **Should we give it to 9 year olds?**
3. Should I only give it to kids at "high risk?"
4. Will it cause infertility?
5. Is it safe?

Topic 5: Deep knowledge of FAQs

1. **Why give it so young?**
2. **Should we give it to 9 year olds?**
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Topic 5: Deep knowledge of FAQs

1. **Why give it so young?**
2. **Should we give it to 9 year olds?**
3. **Should I only give it to kids at "high risk?"**
4. **Will it cause infertility?**
5. Is it safe?

The effect of HPV vaccination on fecundability (the ability to get pregnant)

HPV vaccination:

- Had no effect on fecundability overall
- Was *positively* associated with fecundability among women with a history of STI

Paediatr Perinat Epidemiol. 2017 Nov;31(6):531-536. doi: 10.1111/ppe.12408. Epub 2017 Sep 7.
The Effect of Vaccination Against Human Papillomavirus on Fecundability.
McInerney KA[1], Hatch EE[1], Wesselink AK[1], Mikkelsen EM[2], Rothman KJ[1,3], Perkins RB[4], Wise LA[1].

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Do we have enough data to KNOW that the vaccine is safe?

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HPV vaccine long-term safety data

No increased risk of:

- ❑ 2011- allergic reactions, anaphylaxis, Guillain–Barré Syndrome, stroke, blood clots, appendicitis, or seizures (than unvaccinated or who received other vaccines)
- ❑ 2013 – (almost 1 million girls) blood clots or AEs related to the immune & CNS
- ❑ 2014 – (>1 million women) venous thromboembolism or blood clots
- ❑ 2012 and 2014 – (2 studies) autoimmune disorders
- ❑ 2015 – Multiple sclerosis or other demyelinating diseases
- ❑ 2016- over 60 conditions

2012 - vaccine may be associated with skin infections where the shot is given during the 2 weeks after vaccination and fainting on the day the shot is received

Gee, HV&A, 2016; Cameron Int Med Journal

9vHPV Vaccine Safety

- 7 pre-licensure studies including 15,000 males and females
- Generally well tolerated
  - Adverse event profile similar to that of 4vHPV across age, gender, race, and ethnicity
  - More injection-site reactions expected among those who receive 9vHPV

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More HPV Vaccine Safety FAQ

- **Can HPV vaccines damage women's ovaries?**
  No evidence that HPV vaccination causes reproductive problems in women, including premature ovarian failure
- **Can HPV vaccines cause Postural Orthostatic Tachycardia Syndrome (POTS)?**
  - There are no unusual or unexpected patterns detected among these cases of POTS following Gardasil vaccination
  - CDC monitoring through VAERS has not detected any safety concern of POTS following HPV vaccination

https://www.cdc.gov/vaccinesafety/vaccines/hpv/hpv-safety-faqs.html

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Putting it all together…

HPV is very common and causes bad disease

HPV vaccine is
- effective,
- long-lasting, and
- safe

You and your office team can prevent cancer by vaccinating all everyone!

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Questions