The HPV Vaccine &
Other New Approaches for Fighting Oral Cancers

Dr. Iain Morgan, Director, VCU Philips Institute for Oral Health Research

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Concerns or complaints about a CE provider may be directed to the provider or to ADA CERP at www.ada.org/cerp.
Who am I?

- Did an undergraduate degree in Biochemistry and a PhD in Molecular Oncology at the Beatson Institute for Cancer Research, Glasgow, Scotland
- Did post-doctoral work at USC and Scripps Research Institute with Dr. Peter Vogt, a world leading cancer expert
- Worked in industry for a while but started working on human papillomaviruses in the mid 90s.
- Have had several leadership roles at the University of Glasgow and now at VCU
- Expert on HPV life cycle studies
- Arrived at VCU March 2013
THE PHILIPS INSTITUTE FOR ORAL HEALTH RESEARCH
Philips Institute Today

• Re-launched as VCU Philips Institute for Oral Health Research in October 2014
• Several original Faculty have now left and several new ones have arrived
• The recruitment drive has been in cancer and we recruited excellent Faculty from Harvard, Johns Hopkins and Madison, Wisconsin
• There are 16 Principal Investigators and around 70 total staff
• We have increased by 10-fold our external funding since 2013
• The 5 year plan was to be a top 20 Public Dental School for research and we might make this
Philips Institute History

- Originally started as the Philips Institute for Oral and Craniofacial Molecular Biology in 1999
- A donation was made by an alumnus Dr. John Philips
- Original Director, Dr. Frank Macrina, left in 2005 to become VCU VP for Research
- The Institute was then mothballed until Dean David Sarrett took over in 2011
- National search for new Director followed and here I am, from 2013
Philips Institute Focus

- [http://www.philipsinstitute.vcu.edu/](http://www.philipsinstitute.vcu.edu/)
- Cancer
- Infection and inflammation
- Bioengineering of the oral cavity
- Oral health services
- Bringing together these disciplines
- As the only Dental School in Virginia the aim is to provide a research focus for the State
VCU Philips Institute for Oral Health Research

Ph.D. in Oral Health Research

with a focus on

CANCER, INFECTION & STEM CELL ENGINEERING

Students will be based at the Philips Institute for Oral Health Research in the School of Dentistry. The Philips Institute is a center of educational and research excellence at Virginia Commonwealth University, focused on:

- Cancer and developmental biology
- Infection, immunology, and inflammation of the host-microbe interaction
- Tissue engineering, stem cells, and new materials

The Institute has strong links with the VCU Massey Cancer Center, an NCI designated cancer center, the VCU School of Medicine, the VCU Center for Clinical and Translational Research, and VCU School of Engineering.

We encourage applications from candidates with bachelors, masters, or dental degrees.

The curriculum consists of graduate core basic sciences courses, oral health sciences core course and advanced elective courses. The specific curriculum for each student is determined, with the student’s academic advisor, in consultation with the Oral Health Research Program Committee.

VCU Health – VCU School of Dentistry

APPLICATIONS PROCESS

Applicants are encouraged to submit complete applications as early as possible. For all info visit http://dentistry.vcu.edu/gradschool.

Well-qualified Ph.D. applicants will receive an offer of financial support which typically includes a stipend and the payment of all applicable tuition and fees on behalf of the student.

For more information, visit www.dentistry.vcu.edu/graduateprogram/phd or contact Dr. Conagh Hingman, Program Director, at shingman@vcu.edu

RICHMOND

Richmond today is a thriving hub for culture, shopping and outdoor fun. Its location on the James River leads to access to tubing, kayaking, paddle boarding, swimming and fishing within minutes for the university campus making it one of the best river towns in the country. It’s commonly referred to as an up and coming foodie spot with a dozen craft breweries downtown and plenty of breweries in the region. There is an active local music scene and a host of art museums and galleries. Whether your tastes include nature paintings, sculptures, avant-garde works or "street art" you’re sure to find something amazing.
Oral Cancer

• Is one of the few diseases that dental professionals will encounter that can be fatal
• It is important therefore that the dental professional has an understanding of the epidemiology and history of this disease
• Only in this way can the dental professional competently discuss options for treatment and prevention with patients
Today

• Discussion about tobacco and cancer
• Point out the tools we have to combat cancer
• Talk about the HPV vaccine
• Consider the options for preventing cancer, this is by far the best tool we have
Tobacco

The war between the people (government) and “big business”
Tobacco still a huge killer

- **Cigarette smoking** is responsible for more than 480,000 **deaths** per year in the United States, including more than 41,000 **deaths** resulting from secondhand smoke exposure. This is about one in five **deaths** annually, or 1,300 **deaths** every day. On average, smokers **die** 10 years earlier than nonsmokers.
SMOKING AND CARCINOMA OF THE LUNG
PRELIMINARY REPORT
BY
RICHARD DOLL, M.D., M.R.C.P.
Member of the Statistical Research Unit of the Medical Research Council
AND
A. BRADFORD HILL, Ph.D., D.Sc.
Professor of Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Director of the Statistical Research Unit of the Medical Research Council

In England and Wales the phenomenal increase in the number of deaths attributed to cancer of the lung provides one of the most striking changes in the pattern of mortality recorded by the Registrar-General. For example, in the quarter of a century between 1922 and 1947 the annual number of deaths recorded increased from 612 to 9,287, or roughly fifteenfold. This remarkable increase is of course, out of all proportion to the increase of population—both in total and, particularly, in its older age groups. Stocks (1947), using standardized death rates to allow for these population changes, shows the following trend: rate per 100,000 in 1901–20, males 1.1, females 0.7; rate per 100,000 in 1936–9, males 10.6, females 2.5. The rise seems to have been particularly rapid since the end of the first world war; between 1921–30 and 1940–4 the death rate of men at ages 45 and over increased sixfold and of women of the same ages approximately threefold. This increase is still continuing. It has occurred, too, in Switzerland, Denmark, the U.S.A., Canada, and Australia, and has been reported from Turkey and Japan.

Many writers have studied these changes, considering whole explanation, although no one would deny that it may well have been contributory. As a corollary, it is right and proper to seek for other causes.

Possible Causes of the Increase
Two main causes have from time to time been put forward: (1) a general atmospheric pollution from the exhaust fumes of cars, from the surface dust of tarred roads, and from gas-works, industrial plants, and coal fires; and (2) the smoking of tobacco. Some characteristics of the former have certainly become more prevalent in the last 30 years, and there is also no doubt that the smoking of cigarettes has greatly increased. Such associated changes in time can, however, be no more than suggestive, and until recently there has been singularly little more direct evidence. That evidence, based upon clinical experience and records, relates mainly to the use of tobacco. For instance, in Germany, Müller (1939) found that only 3 out of 86 male patients with cancer of the lung were non-smokers, while 55 were heavy smokers, and, in contrast, among 85 "healthy men of the same age group" there were 14 non-
1930
1949

Viceroy
Filter Tip
Cigarettes

As your Dentist,
I would recommend
Viceroy
1970 Congress passes the Public Health Cigarette Smoking Act, which bans cigarette ads on TV and radio, and strengthens the Surgeon General’s warning label on cigarette packs.
Today – sports
Today - movies
Today – electronic cigarettes

blu eCigs owned by Imperial Tobacco
Australia today
UK today
Smoking rates in UK

42% of US adults smoked in 1964. 18% in 1964.

1962 – smoking kills

Note: The gap indicates that data is unavailable for the years between the two sources
Stopping smoking at any age is beneficial!
What health practitioners can do

The 5A’s framework

• Ask
• Advise to quit
• Assessing the willingness to quit
• Assisting with the attempt to quit
• Arrange follow-up
# Tobacco Smoking Cessation in Adults, Including Pregnant Women: Behavioral and Pharmacotherapy Interventions

**Release Date:** September 2015

## Recommendation Summary

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade (What's This?)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults who are not pregnant</td>
<td>The USPSTF recommends that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and U.S. Food and Drug Administration (FDA)--approved pharmacotherapy for cessation to adults who use tobacco.</td>
<td>A</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>The USPSTF recommends that clinicians ask all pregnant women about tobacco use, advise them to stop using tobacco, and provide behavioral interventions for cessation to pregnant women who use tobacco.</td>
<td>A</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of pharmacotherapy interventions for tobacco cessation in pregnant women.</td>
<td>I</td>
</tr>
<tr>
<td>All adults, including pregnant women</td>
<td>The USPSTF concludes that the current evidence is insufficient to recommend electronic nicotine delivery systems (ENDS) for tobacco cessation in adults, including pregnant women. The USPSTF recommends that clinicians direct patients who smoke tobacco to other cessation interventions with established effectiveness and safety (previously stated).</td>
<td>I</td>
</tr>
</tbody>
</table>

See the Clinical Considerations section for suggestions for practice regarding the I statements.
### Screening for Oral Cancer

#### Clinical Summary of U.S. Preventive Services Task Force Recommendation

<table>
<thead>
<tr>
<th><strong>Population</strong></th>
<th>Asymptomatic adults aged 18 years or older</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
<td>No recommendation. Grade: I statement</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Risk Assessment</strong></th>
<th>The primary risk factors for oral cancer are tobacco and alcohol use. Additional risk factors include male sex, older age, use of betel quid, ultraviolet light exposure, infection with <em>Candida</em> or bacterial flora, and a compromised immune system. Recently, sexually transmitted oral human papillomavirus infection has been recognized as a risk factor for oropharyngeal cancer, another subset of head and neck cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening Tests</strong></td>
<td>The primary screening test for oral cancer is a systematic clinical examination, including inspection and palpation of the oral cavity.</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Suspected oral cancer or its precursors detected on examination require confirmation by tissue biopsy. Treatment for screen-detected oral cancer includes surgery, radiotherapy, and chemotherapy.</td>
</tr>
<tr>
<td><strong>Balance of Benefits and Harms</strong></td>
<td>The USPSTF found inadequate evidence on the diagnostic accuracy, benefits, and harms of screening for oral cancer. Therefore, the USPSTF cannot determine the balance of benefits and harms of screening for oral cancer in asymptomatic adults.</td>
</tr>
<tr>
<td><strong>Other Relevant USPSTF Recommendations</strong></td>
<td>The USPSTF has made recommendations on counseling to prevent tobacco use and screening for and counseling to reduce alcohol misuse. These recommendations are available at <a href="http://www.uspreventiveservicestaskforce.org">www.uspreventiveservicestaskforce.org</a>.</td>
</tr>
</tbody>
</table>

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to www.uspreventiveservicestaskforce.org.
New approaches to cancer therapy
MORE OPTIONS FOR CANCER CARE

CANCER CARE

SURGERY
RADIONUCLIDE
TRADITIONAL CHEMOTHERAPY
PRECISION THERAPY
IMMUNOTHERAPY

ancient times-present 1890s-present 1940s-present 1998-present 1997-present

Physicians often refer to the “pillars” of cancer treatment. For thousands of years, there was one treatment pillar: surgery. In 1896, a second pillar, radiotherapy, was added. The foundations for the third treatment pillar, traditional chemotherapy, were laid in the early 1940s when a derivative of nitrogen mustard was explored as a treatment for lymphoma. These three pillars—surgery, radiotherapy, and traditional chemotherapy—continue to be mainstays of cancer care. In the late 1990s, the first precision therapeutics were introduced, leading to the fourth pillar, precision therapy, which continues to grow. Likewise, the late 1990s laid the groundwork for the fifth pillar, immunotherapy. The number of anticancer therapeutics that form the most recent pillars of cancer care has increased dramatically in the past five years.
Precision Medicine

Sometimes called personalized medicine, sometimes called stratified medicine
Cancer is a genetic disease
Gain of function: oncogene
Loss of function: tumor suppressor gene
Technology advancement has created therapeutic opportunities

<table>
<thead>
<tr>
<th>Time</th>
<th>Human Genome Project vs genome sequencing now</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 years</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Money</td>
<td>$2.7 billion</td>
</tr>
<tr>
<td>Man Power</td>
<td>$1000</td>
</tr>
</tbody>
</table>
Precision medicine is based on genomics, not anatomy
Melanoma

- Over half contain mutations/alterations in the enzyme BRAF turning it into an oncogene
- This mutant BRAF sends uncontrolled growth signals
- Specific inhibitors were developed to block BRAF
Inhibition of BRAF signalling
The promise of precision medicine - melanoma

PLX4032. Developed by Plexxikon and Genentech.

Named vemurafenib; \textbf{V600E} mutated \textbf{BRAF inhibition}.
Marketed as Zelboraf.

FDA approval 2011.
And the problem with precision medicine - resistance

<table>
<thead>
<tr>
<th>Before Rx</th>
<th>PLX4032—15 wks</th>
<th>PLX4032—23 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
</tbody>
</table>

Despite this “failure”, 6 additional months of life
Resistance is the result of further mutations that retain activation of pathway.
Cancer immunotherapy

A type of biological therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases. Some types of immunotherapy only target certain cells of the immune system.
TRADITIONAL CANCER THERAPIES

Kills Cancerous Cells
Kills Healthy Cells

DRUGS OR RADIATION

CANCER IMMUNOTHERAPIES

Selectively Kills Cancerous Cells

Unleash Patient’s Immune System

Healthy Cells

IMMUNOTHERAPY

VCU Philips Institute for Oral Health Research
“Checkpoint inhibition”

This is how the new immunotherapy for cancer works

1. Normal work of the immune system
   T lymphocytes are the cells of the immune system that identify tumour cells and destroy them.

2. Camouflage of tumour cells
   Some tumour cells arm themselves with a shield of molecules called PD-L1. Lymphocytes possess PD-1 receptors which, by bonding to these traps, destroy their capacity to attack.

3. Action of the new inhibitor drugs
   The new drugs based on antibodies block PD-1 from the cells of the immune system and PD-L1 from tumour cells to prevent their fatal action.

4. Result of immunotherapy
   Lymphocytes, once freed from their blindness by the drug, regain their defence potential. They recognise cancer and reduce it.

This treatment, although still in its experimental stage, has had preliminary results on lung, kidney and skin cancers.

JOSE ANTONIO PENA
THE CAMOUFLAGED CANCER CELL EVADES THE EFFECTOR CELL

CTLA-4

STOp

Cancer cell death

THE CANCER CELL IS UNMASKED AND KILLED BY THE EFFECTOR CELL

Yervoy

GO

Cancer cell death
President Carter benefitted!

- **Jimmy Carter**, 91, just announced that scans show no cancer in his body, an amazing diagnosis after having a melanoma that had metastasized to his brain and liver. A key part of his treatment was the new drug **Pembrolizumab**, also known by the Merck brand name **Keytruda** (targets PD-L1).

December 2015
The promise of Keytruda

FDA News Release

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

For Immediate Release

May 23, 2017

The U.S. Food and Drug Administration today granted accelerated approval to a treatment for patients whose cancers have a specific genetic feature (biomarker). This is the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated.
So far..

• Realize tobacco is still the number one problem and consider cessation advocacy
• Understand the principal of precision medicine and its limitations
• Understand the hope of cancer immunotherapy, particularly checkpoint inhibition
Next

• Discuss the role of HPV in oropharyngeal cancers
• Discuss the vaccine and how it works
• Discuss the problems around vaccination implementation and how dental practitioners can contribute to solutions
• Finish by considering therapeutic options for head and neck cancer: PREVENTION IS A MUCH MORE SUCCESSFUL APPROACH THAN THE CURE
The course will resume after a short break
THE VACCINE AGAINST HPV THAT WILL SAVE LIVES
WHO SHOULD GET IT AND WHEN AND WHY THAT IS THE CASE
THE PROBLEM
HPV and Cancer

- **Cervical cancer**: The most common HPV-associated cancer. Over 90% are caused by HPV.
- **Vulvar cancer**: About 70% are linked to HPV.
- **Vaginal cancer**: About 75% are linked to HPV.
- **Penile cancer**: About 60% are linked to HPV.
- **Anal cancer**: About 90% are linked to HPV.
- **Oropharyngeal cancers (cancers of the back of the throat, including the base of the tongue and tonsils)**: About 70% are linked to HPV. [Note: Many of these cancers may be related to tobacco and alcohol use]
HPV associated Cancers in Women

- Nearly all cervical cancer cases are caused by HPV
  - 70% of cervical cancer cases are caused by two types of HPV: 16 & 18
  - 500,000+ new cases and 275,000 attributable deaths world-wide in 2008
- 25% cervical cancers occur in women who are between the ages of 20 and 39

New Cancers Related to HPV for Women, VA 2008-2012

- Cervix (n=1,281) 49%
- Vulva (n=434) 17%
- Oropharynx (n=352) 13%
- Anus (n=405) 15%
- Rectum (n=61) 2%
- Vagina (n=94) 4%

Women (n=2,627)
HPV associated Cancers in Men

- Oropharyngeal is the most common HPV associated cancer in men.
  - It’s estimated 70% of all oropharyngeal cancers are caused by HPV. In the United States over half of oropharyngeal cancers are caused by one strain of HPV:16.
New Cancers Caused by HPV per Year
United States 2008-2012 – 5% of ALL CANCER CASES

Women (n = 19,200)
- Cervix: n=10,700 (56%)
- Oropharynx: n=2,000 (10%)
- Vagina: n=2,400 (13%)
- Vulva: n=600 (3%)
- Anus: n=3,000 (16%)
- Rectum: n=500 (3%)

Men (n = 11,600)
- Cervix: n=9,100 (78%)
- Oropharynx: n=200 (2%)
- Penis: n=700 (6%)
- Anus: n=1,600 (14%)
- Rectum: n=200 (2%)
HPV infection

• HPV is the most common STI; most females and males will be infected with at least one type of HPV at some point in their lives
  – Estimated 79 million Americans currently infected
  – 14 million new infections/year in the US

• Most people will never know that they have been infected

• HPV causes 5% of ALL CANCERS!
Number of new Sexually Transmitted Infections per annum in US (2008): Center for Disease Control Estimate

Infectious agent
- HPV accounts for almost half of new STIs
- New STIs cost around $15.6 billion in future years

Total: 19,738,800
Number of existing Sexually Transmitted Infections in US (2008):
Center for Disease Control Estimate

- Total: 110,197,000

HPV accounts for 72% of existing STIs

No exact figure for cost per annum of managing HPV induced disease but runs to billions
The HPV life cycle

By age 50 80% of sexually active women will have acquired HPV infection
There are two different classes of HPV

• High risk HPV (HR-HPV): these cause cancer, types 16 and 18 are typical examples
• Low risk HPV (LR-HPV): these cause genital warts, types 6 and 11 are typical examples
• Other HPV are relatively harmless, cause common warts on hands and verrucas on feet etc., different types for different anatomical sites. We don’t understand why
Keratin filled sacs – capsid synthesis. L1 and L2 expressed

Amplification
No cellular replication; genome copy number increases to around 1000 per cell

Maintenance:
viral genome copy number per cell maintained at steady state (~50)

Establishment
Infection of stem cells; multi-copy, extrachromosomal genomes

Cervical cancer

- HPV “high risk” types (e.g. 16 and 18) now detected in over 99% of cervical cancer
- WHO designated causative agent for cervical cancer
- Around 550,000 new cases per annum with 300,000 deaths, 80% in developing world
- Therefore a large economic as well as emotional burden, particularly in developing nations
Genital warts

- Caused by “low risk” HPV (6 and 11 present in ~90%)
- Around 0.1% of people will suffer from this condition
- Primarily affects those in their late teens and twenties
- Difficult to treat and can be recurring; drain on health services
- Not life threatening but has associated morbidity
- The most common STI that results in clinic attendance
Head and neck cancer

- A number of different sites for cancer
- ~650,000 new cases and ~350,000 deaths per annum
- HPV associated with oropharyngeal cancers; HPV16 is the most common
- Some recent reports suggest up to 80% HPV prevalence
- Associated with better prognosis than HPV negative, reason not clear
- Increasing incidence of HPV HNSCCs in younger people leading to more years of life being lost
HPV related HNSCC can be considered an epidemic

This is around 4 to 1 male to female depending upon the study
Why is this happening?

• Is there an increase in sexual activity? Probably

Fig. 1. Number of diagnoses of genial warts (first, recurrent and re-registered episodes) by sex, STD clinics: England and Wales 1971–2004. Source: Health Protection Agency, 2006.
Why are males preferentially affected?

• Increase in sexual practices and/or partners in the current generation?
• Is the virus more easily transmitted female to male during oral sex than male to female?
• Do women have some immune response capability due to cervical exposure?
• We don’t really know but probably all of these things are involved.
THE SOLUTION: VACCINATION
How does the HPV vaccine work – virus like particles (VLP)?
The HPV vaccine is prophylactic

- This means it prevents infection.
- The current vaccine is not therapeutic for those with infections or HPV disease.
- There is ongoing work trying to develop therapeutic vaccines, but none available as yet.
- THIS IS WHY ADOLESCENTS ARE TARGETED! NEED TO RECEIVE VACCINE BEFORE EXPOSURE TO HPV PARTICLES.
Gardasil

- Quadrivalent targets 16, 18, 6, 11
- Nonovalent targets 16, 18, 6, 11, 31, 33, 45, 52, 58
- Consists of virus like particles (VLPs)
- Prepared in yeast cells, L1 protein (structural)
- Designed to neutralize virus and prevent infection
- Proposed delivery to 11-13 year olds
Cancers that HPV9 vaccine CAN prevent

- Cancer probably caused by HPV type
  - HPV types 16/18
  - HPV types 31/33/45/52/58
  - Other HPV types
  - HPV-negative

- Can be prevented by bivalent and quadrivalent vaccines
- Can be prevented by 9-valent vaccine

**Sex / Cancer Site**

- Cervix
- Vagina
- Vulva
- Anus
- Rectum
- Oropharynx
- Penis
- Anus
- Rectum
- Oropharynx

**Average number of cases per year**

- VCU Philips Institute for Oral Health Research
- Virginia Commonwealth University
# Potential Protection by HPV9

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Number Probably caused by HPV 16/18/31/33/45/52/58</th>
<th>Percentage Probably caused by HPV 16/18/31/33/45/52/58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>9,400</td>
<td>80%</td>
</tr>
<tr>
<td>Vagina</td>
<td>600</td>
<td>73.3%</td>
</tr>
<tr>
<td>Vulva</td>
<td>2,300</td>
<td>62.7%</td>
</tr>
<tr>
<td>Penis</td>
<td>700</td>
<td>59.3%</td>
</tr>
<tr>
<td>Anus</td>
<td>4,600</td>
<td>88%</td>
</tr>
<tr>
<td>Rectum</td>
<td>700</td>
<td>91%</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>10,800</td>
<td>65%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>29,100 cases</td>
<td>73%</td>
</tr>
</tbody>
</table>
Data from original clinical trial for Gardasil – it works and works well

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vaccine (n = 5305)</th>
<th>Placebo (n = 5260)</th>
<th>Vaccine efficacy (%; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Rate</td>
<td>No. of cases</td>
</tr>
<tr>
<td>CIN grade 2 or 3 or adenocarcinoma \textit{in situ}</td>
<td>1</td>
<td>&lt;0.1</td>
<td>42</td>
</tr>
<tr>
<td>CIN grade 2</td>
<td>0</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>CIN grade 3</td>
<td>1</td>
<td>&lt;0.1</td>
<td>28</td>
</tr>
<tr>
<td>Adenocarcinoma \textit{in situ}</td>
<td>0</td>
<td>0</td>
<td>29</td>
</tr>
</tbody>
</table>

CI = confidence interval; CIN = cervical intraepithelial neoplasia; FUTURE = Females United To Unilaterally Reduce Endo/Ectocervical Disease; HPV = human papillomavirus.

FUTURE II Study Group

Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions

ACIP (advisory committee on immunization practices – CDC) Recommendations: Timing of the Series

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Dose Schedule</th>
<th>Interval Between Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>11-14</td>
<td>2 doses</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>15-26</td>
<td>3 doses</td>
<td>1-2 month, 6 months</td>
</tr>
<tr>
<td>Male</td>
<td>11-14</td>
<td>2 doses</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>15-21+*</td>
<td>3 doses</td>
<td>1-2 month, 6 months</td>
</tr>
</tbody>
</table>

*Men through the age of 26 who have sex with men (MSM) or are immunocompromised (including persons HIV-infected)
Delivery of vaccine

- 0.5ml intramuscular injection
- 20/40/40/20μg 6/11/16/18 L1 protein made in yeast
- Originally 0,2,6 months for adolescents. Now 2 shot, 0,6.
- In clinical trials efficacious out to 10 years and counting – no booster yet required
HPV vaccine covered under vaccines for children program (9-18). Federal government pays via CDC distribution
Other points to note

• Women who receive vaccine should also receive pap smears – vaccine doesn’t cover all HR-HPV
• Vaccination of young adults can be beneficial even if they have been sexually active (may not have been exposed to all 9 viruses)
• This vaccine is NOT therapeutic so if someone has an HPV lesions it is of no use, the virus is purely prophylactic
• HPV vaccine can be given at the same time as other vaccines
• In VA, nearly 90% of adolescents get Tdap
Poor uptake of vaccine in the US - 2015

NATIONAL CANCER INSTITUTE
Improving HPV Vaccination Rates Will Help Save Lives

NATIONWIDE
6 OUT OF 10
GIRLS HAVE STARTED THE HPV VACCINE SERIES

Percentage of Adolescent Girls Who Have Received One or More Doses of HPV Vaccine

National coverage is 63%. Coverage by state:
- 59% or less
- 40-64%
- 65-69%
- 70% or greater

NATIONWIDE
5 OUT OF 10
BOYS HAVE STARTED THE HPV VACCINE SERIES

National coverage is 50%. Coverage by state:
- 39% or less
- 40-49%
- 50-59%
- 60% or greater

Percentage of Adolescent Boys Who Have Received One or More Doses of HPV Vaccine*

HPV VACCINATION IS THE BEST WAY TO PREVENT SEVERAL TYPES OF CANCER, YET MANY ADOLESCENTS HAVEN'T STARTED THE HPV VACCINE SERIES.

Source: MMWR August 26, 2016

*Estimated coverage with ≥ 1 dose of human papillomavirus (HPV) vaccine among adolescents age 13-17 years (New: National Immunization Survey—Teen, United States, 2015)

Adapted from cdc.gov/hpv

VIRGINIA COMMONWEALTH UNIVERSITY
How the US is not joined together - 2015

HPV Vaccination Policies- Mandates, Education, and Funding

State laws requiring HPV vaccinations for school entry, providing funding to cover the cost of the vaccine, or requiring public education (including for school children and parents)

NOTES: *States may have other laws relating to the HPV vaccine, such as insurance coverage mandates and research initiatives.
President’s Cancer Panel report 2012-13

Accelerating HPV Vaccine Uptake:
Urgency for Action to Prevent Cancer

A Report to the President of the United States
from
The President’s Cancer Panel
How can practitioners improve uptake?

• Take advantage of missed opportunities: 84% of girls unvaccinated for HPV had a healthcare visit to receive another vaccine such as Tdap

• If HPV had been given at same visit 94% instead of 54% would have received at least one dose of the HPV vaccine. Evidence suggests one dose offers some protection although not ideal

• Increase the consistency and strength of how they recommend the HPV vaccine
Reasons parents won’t initiate HPV vaccination for children

- Not sexually active
- Not recommended
- Safety concern/Side effects
- Not needed or necessary
- Lack of knowledge

Percent

0  5  10  15  20
An Effective Recommendation

• A recommendation from the physician is the main reason parents decide to vaccinate

• Many moms in focus groups stated that they trust their child’s doctor and would get the vaccine for their child as long as they received a recommendation from the doctor

• Same day: RECOMMEND HPV VACCINE TODAY
  Recommend HPV vaccination the same day you recommend Tdap & meningococcal vaccines.
Adolescents & Vaccines and Dentists

• 88% of adolescents value maintaining good oral hygiene
• 65% of teens believe getting recommended vaccines are important to maintaining their health
Merck cannot market Gardasil as a prevention for head and neck cancer

- Original clinical trials done on cervical cancer
- The FDA restricts Merck from discussing other possible benefits, such as prevention of HPV positive head and neck cancer (HPV+HNC)
- However, it seems logical to assume that this vaccine will prevent HPV+HNC
- As Merck is prohibited from discussing this, it makes it even more important for health practitioners to advocate for this vaccine
- The Association of State and Territorial Dental Directors (ASTDD) “endorses promotion of HPV vaccine to reduce the risk of HPV-related oropharyngeal cancer.”
HPV Vaccines Are Safe For Your Child

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 – 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 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 ages 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>Vaccine</th>
<th>How many people were tested</th>
<th>When was it approved?</th>
<th>Who is it recommended for?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gardasil</td>
<td>More than 29,000 volunteers</td>
<td>2006</td>
<td>Girls and boys at age 11 or 12</td>
</tr>
<tr>
<td>Cervarix</td>
<td>More than 30,000 volunteers</td>
<td>2009</td>
<td>Girls aged 11 or 12</td>
</tr>
<tr>
<td>Gardasil 9</td>
<td>More than 15,600 volunteers</td>
<td>2014</td>
<td>Girls and boys at age 11 or 12 years</td>
</tr>
</tbody>
</table>
Medical intervention works!!!

Pap smears reduce cervical cancer incidence
Scare stories!

• The HPV vaccine can kill you. NO IT CAN’T. 40 million doses with 34 confirmed deaths. No common pattern to these so conclusion is this is random. Even young people can literally drop dead

• It causes Guillain-Barre syndrome. NO IT DOESN’T. Zero evidence Gardasil promotes this to higher than random occurrence
The HPV vaccine battle

Some of the people misleading a lot of the people
The madness that makes money for the perpetrators and kills people

- [https://www.youtube.com/watch?v=sOK3bQLh3tU](https://www.youtube.com/watch?v=sOK3bQLh3tU)
- [https://www.youtube.com/watch?v=XK97CHQZhq0](https://www.youtube.com/watch?v=XK97CHQZhq0)
Natural News (formerly News Target, which is now a separate sister site) is a website for the sale of various dietary supplements, promotion of alternative medicine, controversial nutrition and health claims, scientific fake news, and various conspiracy theories, such as "chemtrails", chemophobic claims (including the purported dangers of fluoride in drinking water, anti-perspirants, laundry detergent, monosodium glutamate, aspartame), and purported health problems caused by allegedly "toxic" ingredients in vaccines, including the now-discredited link to autism. It has also spread conspiracy theories about the Zika virus allegedly being spread by genetically modified mosquitoes and purported adverse effects of genetically modified crops, as well as the farming practices associated with and foods derived from them.

The site's founder, Michael Allen "Mike" Adams, was the subject of controversy after posting a blog entry implying a call for violence against proponents of GMO foods, and then allegedly creating another website with a list of names of alleged supporters. He has been accused of using "pseudoscience to sell his lies." Adams has described vaccines as "medical child abuse." Characterized as a "conspiracy-minded alternative medicine website", Natural News has approximately 7 million unique visitors per month.

Founder

Michael Allen "Mike" Adams (born 1967 in Lawrence, Kansas) is the founder and owner of Natural News. According to his own website his interest in alternative nutrition was sparked by developing type II diabetes at the age of 30 and "completely curing" himself using natural remedies. He is a raw foods enthusiast and holistic nutritionist. He claims to eat no processed foods, dairy, sugar, meat from mammals or food products containing additives such as monosodium glutamate (MSG). He also says he avoids use of prescription drugs and visits to Western medical doctors.

Adams has endorsed conspiracy theories surrounding the Deepwater Horizon oil spill and those involving Malaysia Airlines Flight 370. He has endorsed Burzynski: Cancer Is Serious Business, a movie about Stanislaw Burzynski. Steven Novella characterizes Adams as "a dangerous conspiracy-mongering crank." Adams has also written a favorable review of the pseudoscientific film House of Numbers on Natural News, which is reprinted on the film's website. Adams has also endorsed the books of conspiracy theorist Jim Marrs.
Why do people universally accept tobacco is bad, but not that the HPV vaccine is good?

- The tobacco wars started before social media
- With tobacco, everyone knows from experience the damage it does
- With tobacco it is the government against big business
- With the HPV vaccine it is government and big business together
- People like to generate money through their websites, the more controversial you are the more money you can make; the HPV vaccine is ripe for exploiting people
- We live in an era where a lot of people don’t trust the government to act on behalf of the people
As a scientist it is a triumph that we...

• Identified the cause of a disease (HPV in cervical cancer initially, now also oropharyngeal)

• Spent decades working hard on developing a vaccine against HPV so that nurses and physicians can deliver the vaccine

• See that the vaccine works, it will save lives and alleviate untold misery in the future
As a scientist it is sad to see...

• That not everyone in the US who can is getting the advantage of this vaccine due to poor vaccine rates
• The lies and scare stories that are circulated about the vaccine
Some points

• HPV causes hundreds of thousands of cancer cases and deaths worldwide every year

• There is a vaccine, Gardasil, that is safe and effective and available that will likely prevent around 85% of cervical cancer and 90% of HPV related head and neck cancer

• Boys should be vaccinated as well as girls before they become sexually active

• The US is failing at delivery, local initiatives to improve this situation will save lives
Some commonwealth resources

- Tira Hanrahan, MPH. Adolescent Immunization Coordinator, VA Department of Health. Tira.Hanrahan@vdh.virginia.gov
Head and neck cancer treatment

Can we apply any of the exciting new therapeutics?
HPV positive head and neck cancer has a much better survival rate.
There is currently no strong precision medicine approach for head and neck cancer: why?

- In melanoma, BRAF is mutated in around 60% of cases
- Therefore targeting this mutant enzyme is an effective and valid approach
- For HNC there is no single dominant genetic lesion responsible for a large majority (or even minority) of cancers
- The future will involve a more in depth understanding of the genetic lesions and taking combination approaches to novel therapies. The Philips Institute is carrying out such studies
There is great hope that cancer immunotherapy will be beneficial for HNC

- There are several ongoing clinical trials for checkpoint inhibitors such as Keytruda and their effectiveness in HNC
- Ultimately, I believe this will show great potential to become part of the standard treatment for some HNC patients
- Such treatments will be done in combination with existing therapy approaches
Proton therapy for head and neck cancer – a different kind of precision medicine

- [https://www.youtube.com/watch?v=2XsJp0Y Ugig](https://www.youtube.com/watch?v=2XsJp0Y Ugig)
- [https://www.youtube.com/watch?v=MS590Xt q9M4](https://www.youtube.com/watch?v=MS590Xt q9M4)
Thank you for your attendance!

Please complete your course evaluation and drop it in the marked boxes placed around the meeting space.
The US has approved the first treatment to redesign a patient's own immune system so it attacks cancer.

The regulator - the US Food and Drug Administration - said its decision was a "historic" moment and medicine was now "entering a new frontier".

The company Novartis is charging $475,000 (£367,000) for the therapy, which leaves 83% of people free of a type of blood cancer.

Doctors in the UK said the announcement was an exciting step forward.

The "living drug" is tailor-made to each patient, unlike conventional therapies such as surgery or chemotherapy.

It is called CAR-T and is made by extracting white blood cells from the patient's blood.

The cells are then genetically reprogrammed to seek out and kill cancer.

The cancer-killers are then put back inside the patient and once they find their target they multiply.

"Enormously exciting"

Dr Scott Gottlieb, from the FDA, said: "We're entering a new frontier in medical innovation with the ability to reprogram a patient's own cells to attack a deadly cancer.

"New technologies such as gene and cell therapies hold out the potential to transform medicine and create an inflection point in our ability to treat and even cure many intractable illnesses."

The therapy, which will be marketed as Kymriah, works against acute lymphoblastic leukaemia.

Most patients respond to normal therapy and Kymriah has been approved for when those treatments fail.

Dr Stephan Grupp, who treated the first child with CAR-T at the Children's Hospital of Philadelphia, said the new approach was "enormously exciting".

"We've never seen anything like this before," he added.

That first patient had been near to death, but has now been cancer-free for more than five years.

Out of 63 patients treated with CAR-T therapy, 83% were in complete remission within three months and long-term data is still being collected.

However, the therapy is not without risks.

It can cause potentially life-threatening cytokine release syndrome from the rapid proliferation of the CAR-T cells in the body. This can be controlled with drugs.