DEVELOPMENT OF THE HPV VACCINE:
TRANSFORMING DISCOVERY INTO DISEASE ERADICATION

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Smallpox

- The great scourge of mankind
- Has crippled, disfigured and/or killed one quarter of all humanity
- In the 20th Century alone, nearly 200 million deaths
## The Impact of Vaccines

<table>
<thead>
<tr>
<th>Disease</th>
<th>Average Annual Reported Cases Pre-vaccine*</th>
<th>Cases in U.S. 2013**</th>
<th>Provisional Cases in U.S. 2014***</th>
<th>Provisional % Reduction In U.S. 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>48,164</td>
<td>Eradicated worldwide in 1980</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria</td>
<td>175,885</td>
<td>0</td>
<td>1</td>
<td>&gt;99.9%</td>
</tr>
<tr>
<td>Measles</td>
<td>503,282</td>
<td>187</td>
<td>628</td>
<td>&gt;99.9%</td>
</tr>
<tr>
<td>Mumps</td>
<td>152,209</td>
<td>584</td>
<td>1,151</td>
<td>99.2%</td>
</tr>
<tr>
<td>Pertussis</td>
<td>147,271</td>
<td>28,639</td>
<td>28,660</td>
<td>80.6%</td>
</tr>
<tr>
<td>Polio (paralytic)</td>
<td>16,316</td>
<td>1</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Rubella</td>
<td>47,745</td>
<td>9</td>
<td>8</td>
<td>&gt;99.9%</td>
</tr>
<tr>
<td>Congenital Rubella Syndrome</td>
<td>823</td>
<td>1</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>1,314</td>
<td>26</td>
<td>21</td>
<td>98.4%</td>
</tr>
<tr>
<td>H. Influenzae Type b Age&lt;5 years</td>
<td>20,000</td>
<td>31</td>
<td>27</td>
<td>99.9%</td>
</tr>
</tbody>
</table>

*MMWR 48(12);243-248 April 2, 1999  
** MMWR 63(32);702-715 August 15, 2014  
***MMWR 63(53);733-746 January 9, 2015
RESEARCHERS WHO DESERVE OUR CONSIDERABLE GRATITUDE

PROF. DR. HARALD ZUR HAUSEN

Nationality
Germany
Institution
German Cancer Research Centre Heidelberg
Award
2008
Discipline
Physiology or Medicine
Co-recipients
Profs. Barré-Sinoussi and Montagnier

Biography on the Official Web Site of the Nobel Prize

CURRICULUM VITAE

German virologist Harald zur Hausen was awarded half of the 2008 Nobel Prize for his discovery of the role of human papilloma viruses (HPV) in cervical cancer. Ultimately his work led to the introduction in 2006 of a vaccine to combat HPV.

Zur Hausen was born on March 11, 1936 and grew up in the city of Gelsenkirchen-Buer. He earned a place at the University of Bonn where he studied medicine and after passing his preliminary medical examination, continued his studies at Hamburg and the Medical Academy in Düsseldorf, where he completed his MD thesis in 1960. After two years as a medical assistant, during which he developed an interest in gynaecology and obstetrics, he joined the University of Düsseldorf as a laboratory assistant, exploring virus-induced chromosomal modifications. Seeking greater scientific knowledge, zur Hausen moved to the US in 1965 to work at the Philadelphia Children’s Hospital with German virologists Werner and Gertrude Henle. The Henles’ laboratory was working on the newly discovered Epstein-Barr virus (EBV) and zur Hausen helped demonstrate that a cancer virus (EBV) can transform healthy cells (lymphocytes) into cancerous cells.
RESEARCHERS WHO DESERVE OUR CONSIDERABLE GRATITUDE

University of Queensland

Georgetown University

National Cancer Institute

University of Rochester
Intellectual Property/Patent “Interference”

- 6 individual patent interference actions
- Disputed over 16 years with dozens of judges involved
- On appeal, patent ultimately awarded to Professor Ian Frazer
- License agreement created with CSL, Merck and MedImmune
“When we started this work, there was no greater optimism for an HPV vaccine than there was for an HIV vaccine. In fact, there was skepticism that it could work at all.”

—Dr. John Schiller, Ph.D.
Assembly of VLPs

Expression of L1/L2 proteins together (Queensland) 1991
L1 expression in mammalian cells (Georgetown) 1992
Self-assembling L1 VLPs (NCI) 1992
Self-assembling HPV11 L1 VLPs (Rochester) 1993
HPV16 Vaccine Clinical Trial (NEJM) 2002
qHPV Clinical Trials FUTURE I/II (NEJM) 2007
HPV4 expanded to men 2009
2 dose regimen 2016
HPV4 FDA Approved 2006
HPV2 FDA Approved 2007
HPV9 FDA Approved 2014
HPV9 FDA Approved to 45 yoa 2018
Vaccines Are Always Political
Perfect political storm in 2006

• qHPV vaccine approved by the Therapeutics Goods Administration.
• Australian vaccine with an iconic inventor.
• National Immunization Program initially rejected it.
Perfect political storm in 2006

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- Health Minister with a dubious reputation in women’s health.

“I won’t be rushing out to get my daughters vaccinated…”

Tony Abbott
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• **First Lady** with cancer of the cervix
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• National Immunization Program initially rejected the HPV Vaccine
  • Election year, with a budget surplus.
• Health Minister with a dubious reputation in women’s health.
  • First Lady with cancer of the cervix.
    • De-stigmatized the disease
    • Influenced husband
Proportion of Australian-born females with GW, by age group, 2004–2011

Proportion of Australian-born heterosexual males with GW by age group, 2004–2011

High-grade cervical abnormalities in young Victorian women, by age group, 2003–2010

Brotherton JM et al. Lancet 2011; 377: 2085
High-grade cervical abnormalities in young Victorian women, by age group, 2003–2010

Equity in cervical screening v HPV vaccination

National Cervical Screening Program by socioeconomic status, Victoria

National HPV Vaccination Program by socioeconomic status, Victoria

Current global vaccination patterns will only have a marginal reduction on cervical cancer.
TWO DOSES IS NOW STANDARD OF CARE: WHAT ABOUT ONE DOSE? IS THAT ACHIEVABLE?
Single-dose immunogenicity

* 4-fold difference between 1 and 3 dose plateau titers
** ~10-fold difference between 1 dose and natural infection plateau titers

### Single-dose vaccine efficacy

Post-hoc analysis of bivalent HPV vaccine in Costa Rica HPV Vaccine Trial

<table>
<thead>
<tr>
<th># of Doses</th>
<th>Arm</th>
<th># Women</th>
<th>HPV16/18 6+ mo Persistence N (%)</th>
<th>HPV16/18 Vaccine Efficacy (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Control</td>
<td>3010</td>
<td>229 (8%)</td>
<td>84% (77% to 89%)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>2957</td>
<td>37 (1%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Control</td>
<td>380</td>
<td>24 (6%)</td>
<td>81% (53% to 94%)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>422</td>
<td>5 (1%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Control</td>
<td>188</td>
<td>15 (8%)</td>
<td>100% (79% to 100%)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>196</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

Kreimer AR, et al. JNCI 2011
Scientific Evaluation of One or Two Doses of the Bivalent or Nonavalent Prophylactic HPV Vaccines: The ESCUDDO Study

Estimated Enrollment: 25,000
Location: Costa Rica
Estimated Study Start Date: March 6, 2019
Estimated Primary Completion Date: December 31, 2022
Estimated Study Completion Date: December 31, 2024

Aimée R. Kreimer, Ph.D.
Senior Investigator
National Cancer Institute
Why can’t we do the same for HPV and cervical cancer?