Lessons Learned from the Development and Implementation of HPV Vaccines

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Disclosure

I am an employee of Merck & Company, Inc.

Merck is the manufacturer of GARDASIL and GARDASIL-9, which are prophylactic HPV vaccines

HPV: Human Papillomavirus
Research – Development - Implementation

The First 3 Steps: Safety / Efficacy / Quality
Regulatory requirements

Step 4: Value/Affordability
Payer/NITAG requirements

Step 5: Inform clinical practice
Provider/Health System requirements

Step 6: Care delivery
Pathways/protocols to optimize outcomes

NITAG: National Immunization Technical Advisory Group
HPV Infection is a Necessary First Step in a Long March to Cervical (and other) Cancers, but Most HPV Infections Clear

- Initial HPV Infection
- CIN 1
- Persistent Infection
- CIN 2
- CIN 3
- AIS
- Requires excision
- Requires highly invasive therapy
- Sq. Cell Carcinoma
- Adeno-Carcinoma

CIN: Cervical Intraepithelial Neoplasia
AIS: Adenocarcinoma in situ
HPV Vaccine: Key Development Questions

- Which vaccine will be most attractive to MoHs/payers, healthcare providers, and the general population?
  - What will be the impact of HPV vaccination on public health, and over which time horizon?

- What do we need to know about HPV infection to develop a vaccine?

- Development strategy: how to balancing scientific certainty, timelines, and financial risk?

- Anticipating HPV vaccine implementation risks up-front:
  - Who should be vaccinated?
  - Who are stakeholders/decisionmakers at the national, provider, and family levels? What are their data needs?
  - How to place the vaccine within current practice?
  - How to engage pediatricians given the age of infection and mode of transmission?
  - How to educate/inform the general public regarding HPV infection/disease and the HPV vaccine?
  - How to address stigma and cultural sensitivities, given the mode of transmission?

- Forecasting demand → how quickly to build capacity?
The Choice of Coverage (First Gen Vaccine)

**Including HPV 6/11**
- Broader coverage
- Immediate benefit to recipients
- Reduces false positive Pap Test results
- Economic benefit to payers
- Attractive to younger people, esp young men
- Easier to track population impact

But...
- More complex clinical program
- More manufacturing complexity
- More up-front costs (factory)
- Genital Warts $\rightarrow$ STI stigma

**Focusing only on HPV 16/18**
- Simpler clinical program
- Simpler manufacturing scheme
- Less up-front costs (factory)
- This is a cancer vaccine $\rightarrow$ less STI stigma

But...
- Less coverage
- Benefit is mostly long-term
- No immediate benefit for men/young people

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*HPV 16/18 cause >70% of HPV-related cancers; HPV 6/11 cause >90% of genital warts (high incidence, occur soon after exposure/sexual debut, heavy QoL impact, but not life-threatening)*

QoL: Quality of Life
Development Program: Two Highly Collaborative Tracks

**Clinical Research and Regulatory Track**
- Epidemiology, cost/QoL impacts of Pap testing and management pre-cancerous lesions
- Selecting efficacy endpoints for studies
- Long-term efficacy monitoring and real world evidence
- Staged investment: sequential conduct of clinical/observational trials
- Supply management

**Implementation Track**
- Stakeholder identification and engagement
- Proofs of efficacy needed to enable prioritization within national health strategies
- Which data are most compelling; data gaps
- Fears and worries: identifying/avoiding landmines
- Who to vaccinate (gender, age, broad vs. targeted)
- Health economics and disease burden modeling
Implementation Team Insights: Impact on the Clinical Program

**Outreach Output**

- **Governments**
  - Must show efficacy on “hard” endpoints; durability
  - Skeptical of single gender vaccination (gender equity)
  - Worry vaccine will be expensive

- **Gynecologists + Pathologists**
  - The vaccine does not replace screening

- **Civic, Religious, and Advocacy Groups**
  - Worry that the vaccine will encourage promiscuity
  - Worry that the vaccine will fall victim to “culture wars”
  - HPV should not be stigmatized: everyone is at risk, incidence is high, so vaccination should be universal

- **Pediatricians**
  - Hard to reach pre-teens (no routine visits)
  - Highly uncomfortable with discussing HPV

**Clinical Research Plan**

- **Clinical studies**
  - Enlarge, prolong studies to show efficacy vs. CIN3/AIS
  - Nordic cancer registry program
  - Accelerate male program; assess feasibility of HNSCC study

- **Data to inform funding**
  - Show vaccine’s impact on invasive procedures
  - Intensify/localize studies to quantify HPV BoD and costs
  - Well-validated and socialized C-E model

- **Conduct/encourage studies of teen decisions re: sexual debut**

- **Communications**
  - Vaccination and screening are complementary
  - Focus vaccine rationale on cancer prevention, not STI
  - Develop communication tools for pediatricians

- **Initiate Development of the 9-Valent Vaccine**
Merck’s HPV Vaccines Clinical Program: >50,000 subjects, 20 Yrs

HPV 16 Vax Efficacy (Infection/CIN)
2,400 16-23 year old women

Interim Efficacy Analysis; Standardized Endpoint Detection Tools/Processes

Quadrivalent Vax 2 (Infection/CIN, GW)
1,155 16-23 year old women

Quadrivalent Vax 3 (GW, CIN 2/3, AIS)
17,600 16-26 year-old women

Ph III Quadrivalent (Immunogenicity)
4,800 9-15 year old boys/girls

Adolescent Extension

Efficacy Study (Infection/CIN/GW)
3,900 24-45 year-old women

Efficacy Study (Infection/CIN/GW)
3,900 24-45 year-old women

Quadrivalent Vax (GW, AIN 2/3)
4,000 16-26 year-old men

Duration of Efficacy Registry Study
Scandinavian Region

Interim Analysis

Start Factory Construction

Licensure (US, EU, Canada, Australia)

9-Valent HPV Vaccine
9-45 year-old women; 9-26 year-old men


CIN: Cervical Intraepithelial Neoplasia
AIS: Adenocarcinoma in situ
GW: Genital Warts
AIN: Anal Intraepithelial Neoplasia
Reflection: Success Factors, Challenges

Factors Contributing to Success
• HPV natural history study data prior to Phase 3
• Commitment to meaningful “hard” endpoints
• Heavy investment in clinical trial infrastructure
• Collaboration with registries (Scandinavia)
• Pre-planned long-term effectiveness studies
• Early, frequent stakeholder engagement
• Clear, consistent, frequent communication

Challenges (Program)
• Male program started too late
• Should have evaluated oral HPV infection (HNSCC)

Challenges (Implementation)
• We got ahead of consensus in the early days
• Difficulty in vaccinating teens (US)
• Vaccine hesitancy – HPV vax as a lightning rod
• Missed the demand inflection point (ca. 2014/5)
• Increasing barriers to coordination w/government
What is Needed for a Successful STI Vaccine Program?

In addition to a plausible vaccine candidate...

• Recognition that STI vaccines will be subjected to a higher standard vs. infections acquired via ‘involuntary’ contact
  – Pathogens that cause mortality/morbidity beyond the acute infection (e.g. HIV, chlamydia) will be easier to develop

• Early consensus on relevant efficacy, safety, and QoL/HECON endpoints
  – Hard endpoints required (e.g. for chlamydia, demonstrate reduction in symptomatic PID and infertility)
  – Long-term follow-up (durability, safety outcomes)
  – Endpoints meaningful to payers (e.g. near-term cost benefit, benefit accrues to the payer funding the vaccination program)

• Identify a broad set stakeholders (likely different from traditional pediatric vax stakeholders); early, frequent engagement
  – Avoid landmines
  – Build consensus – stakeholders gain ownership of program, communication plan
  – Pre-empt concerns

• Public/private coordination is essential: each of us has a role, even as barriers must be maintained
  – Investment in characterizing burden of disease, patient impact, natural history to inform clinical trials program
  – Consistent messaging and education regarding the disease; reducing stigma; mobilizing political will
  – Mechanism to rapidly track impact of vaccination – positive feedback loop

QoL/HECON: Quality of Life/Health Economics