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

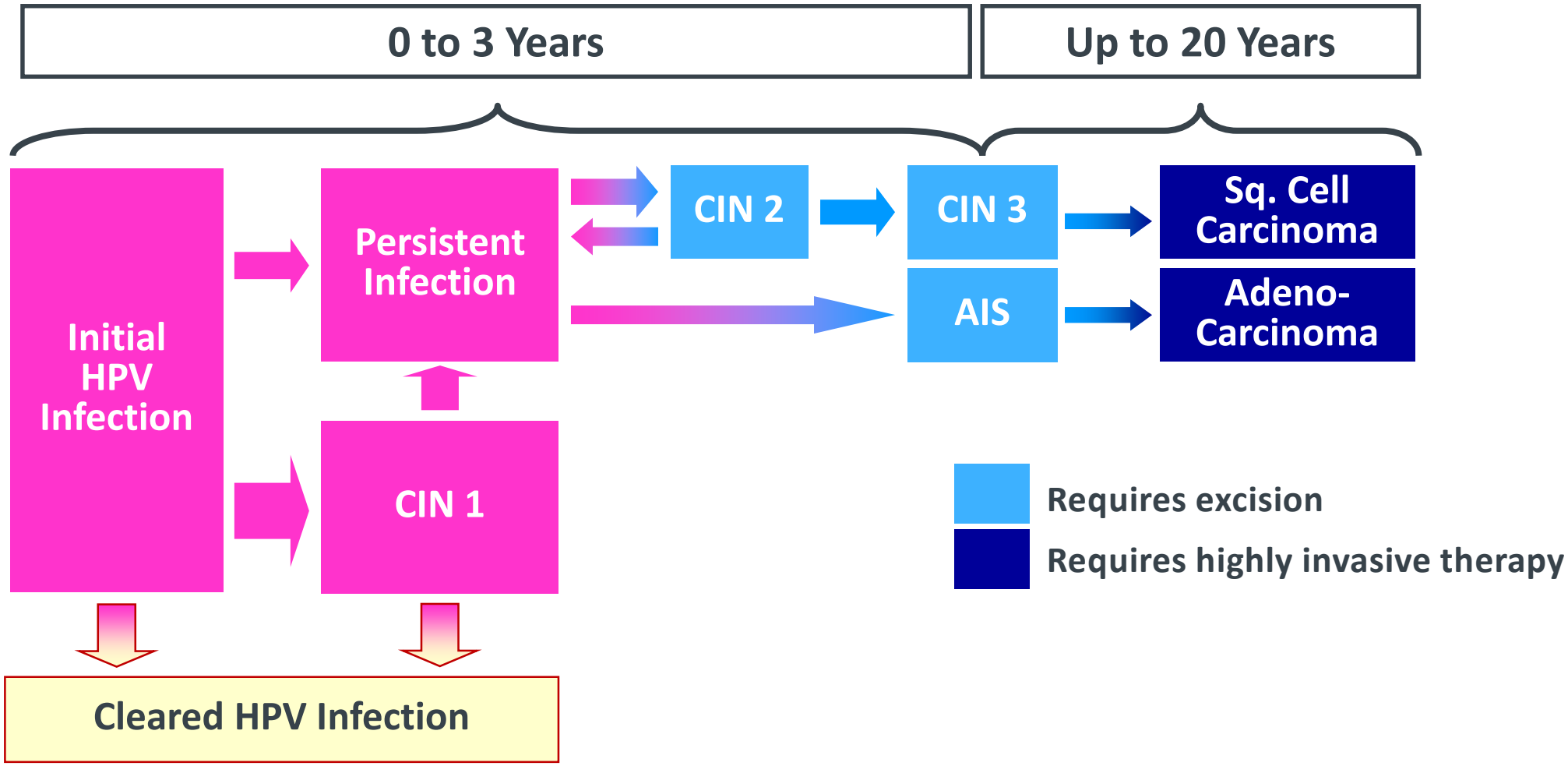
Research – Development - Implementation

EFFICACY / SAFETY / QUALITY	VALUE/AFFORDABILITY	INFORM PRACTICE	CARE DELIVERY

The First 3 Steps: Safety / Efficacy / Quality	Step 4: Value/Affordability	Step 5: Inform clinical practice	Step 6: Care delivery
Regulatory requirements	Payer/NITAG requirements	Provider/Health System requirements	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



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?**

MoH: Ministry of Health

The Choice of Coverage (First Gen Vaccine)

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)

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 → STI stigma

Focusing only on HPV 16/18

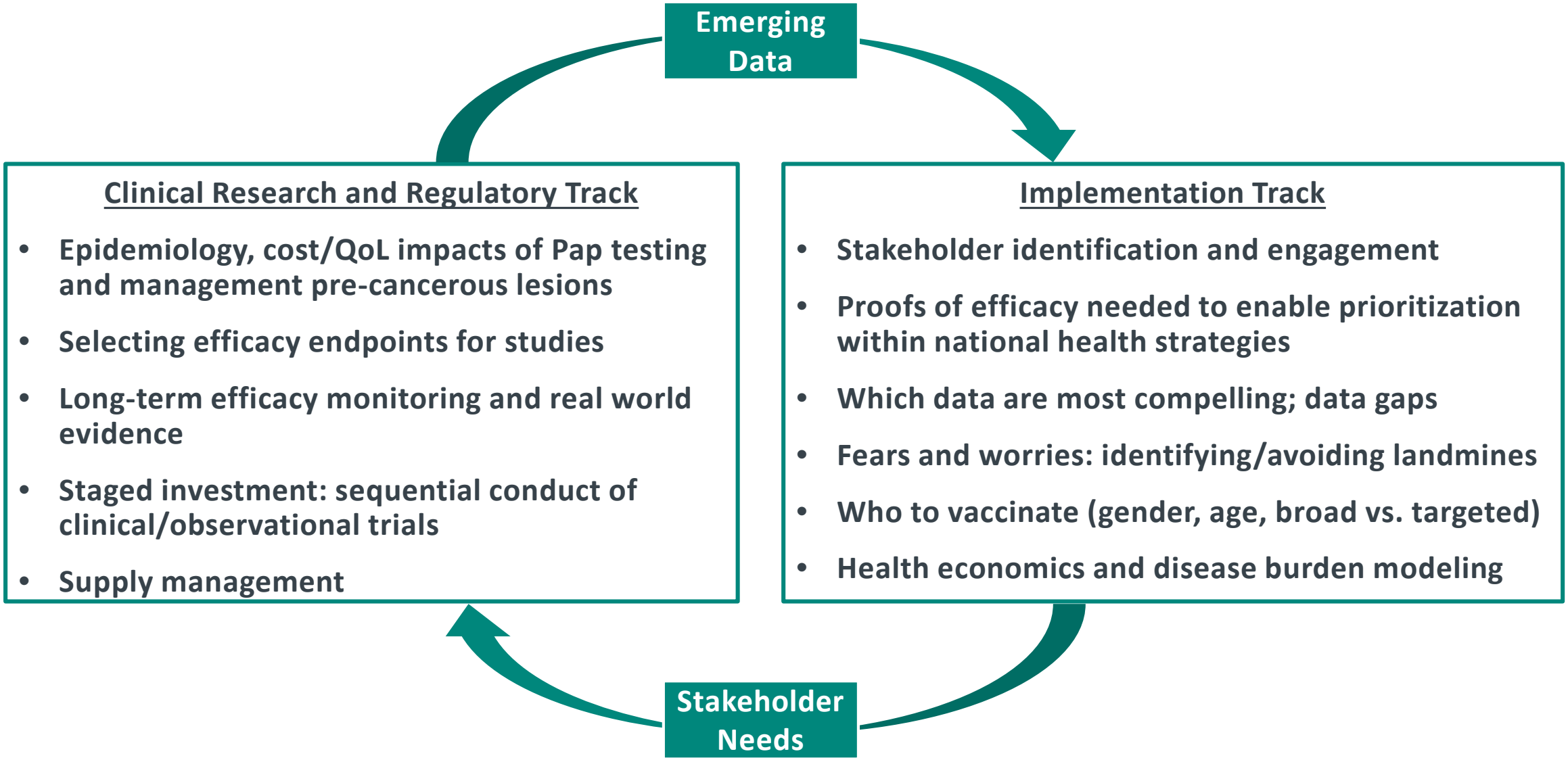
- Simpler clinical program
- Simpler manufacturing scheme
- Less up-front costs (factory)
- This is a cancer vaccine → less STI stigma

But…

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

QoL: Quality of Life

Development Program: Two Highly Collaborative Tracks



Implementation Team Insights: Impact on the Clinical Program

Outreach Output

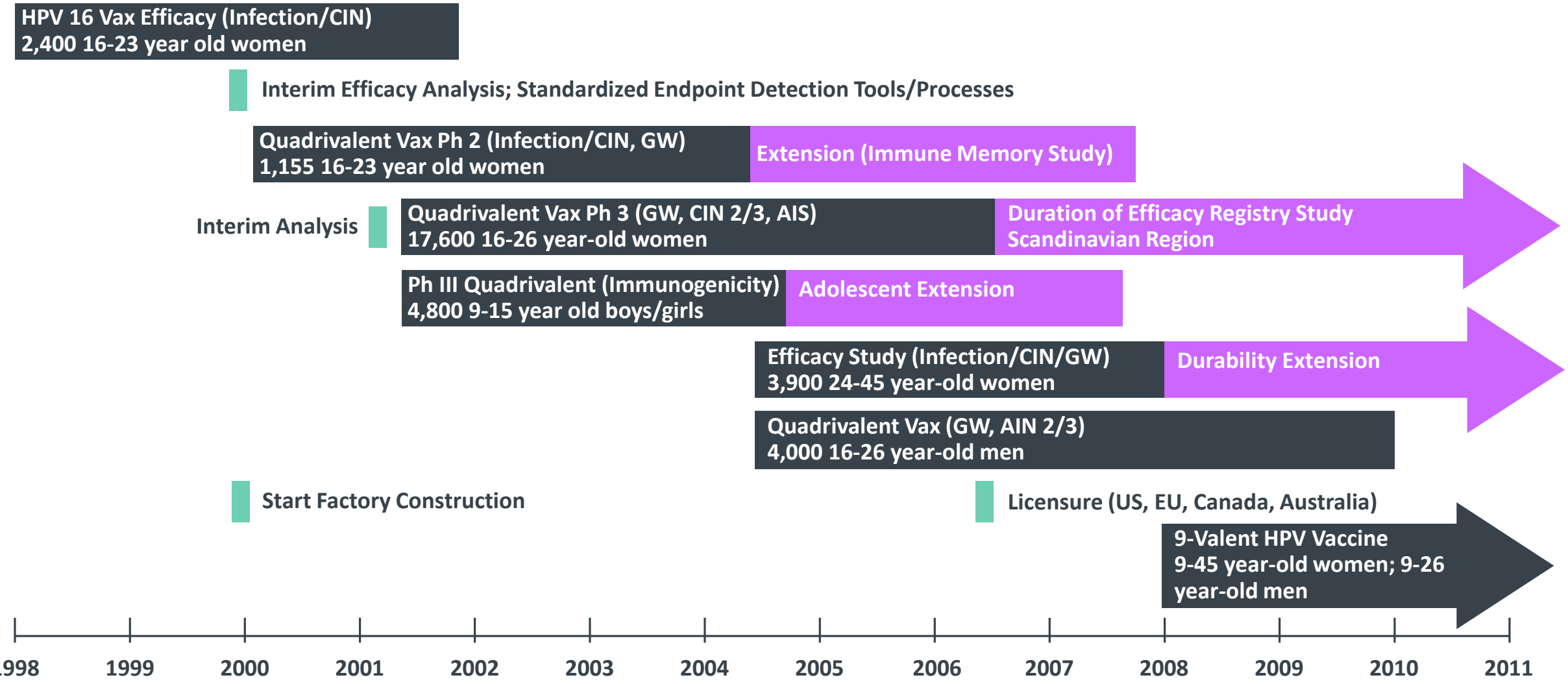
- **Governments**
  - Must show efficacy on "hard" endpoints; durability
  - Skeptical of single gender vaccination (gender equity)
  - Worry vaccine will be expensive
- **Gynecologists + Pathologists**
  - The vaccine does not replace screening
- **Civic, Religious, and Advocacy Groups**
  - Worry that 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**

CIN: Cervical Intraepithelial Neoplasia HNSCC: Head and Neck Squamous Cell Cancer C-E: Cost Effectiveness
AIS: Adenocarcinoma in Situ BoD: Burden of Disease

Merck's HPV Vaccines Clinical Program: >50,000 subjects, 20 Yrs



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