# The Agony and the Ecstasy:
## The Dynamic field of HIV Prevention Research

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**Family Health International**

**MTN Annual Conference**
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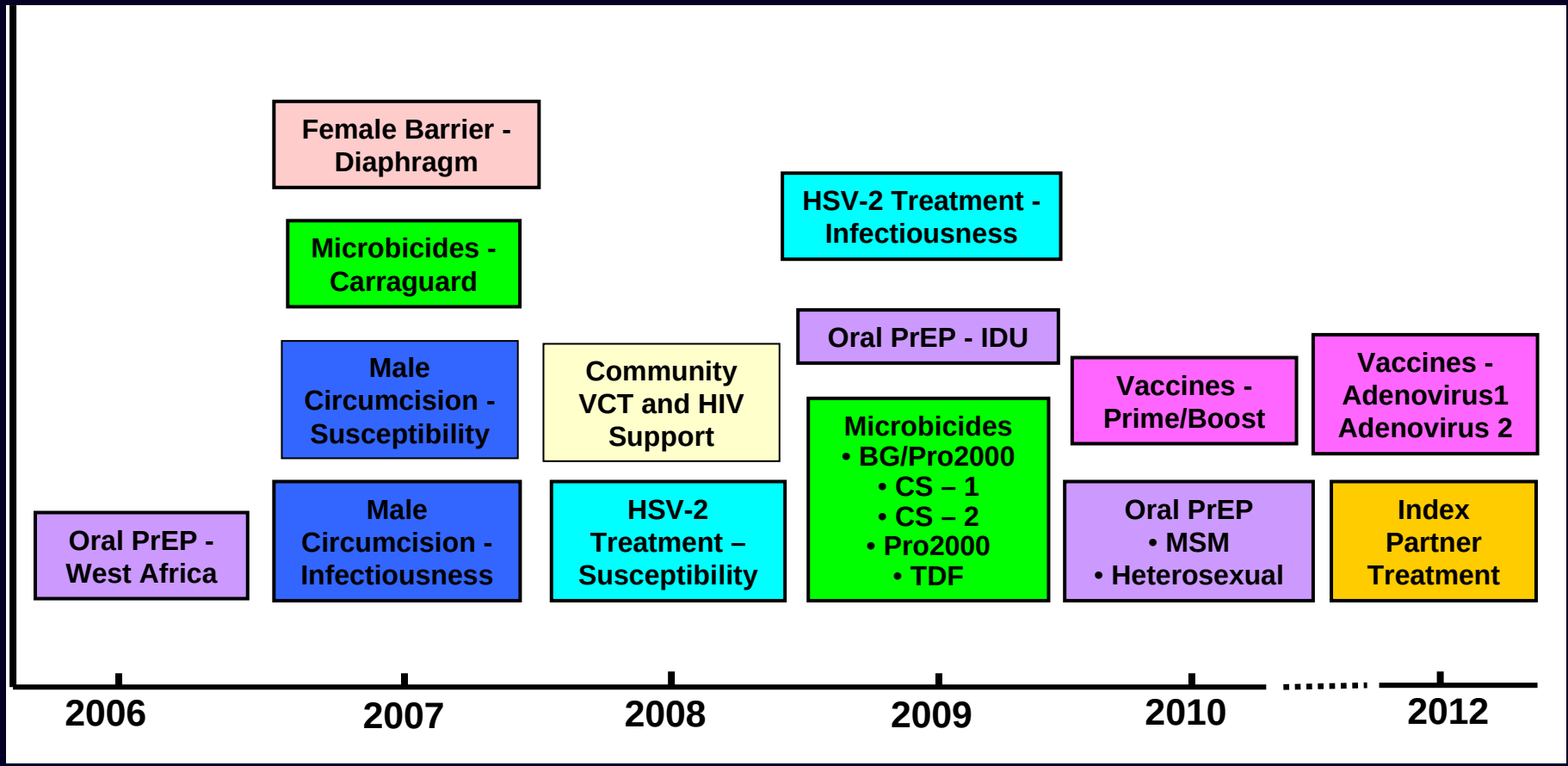
# September 2006 – Anticipated Prevention Trial Results

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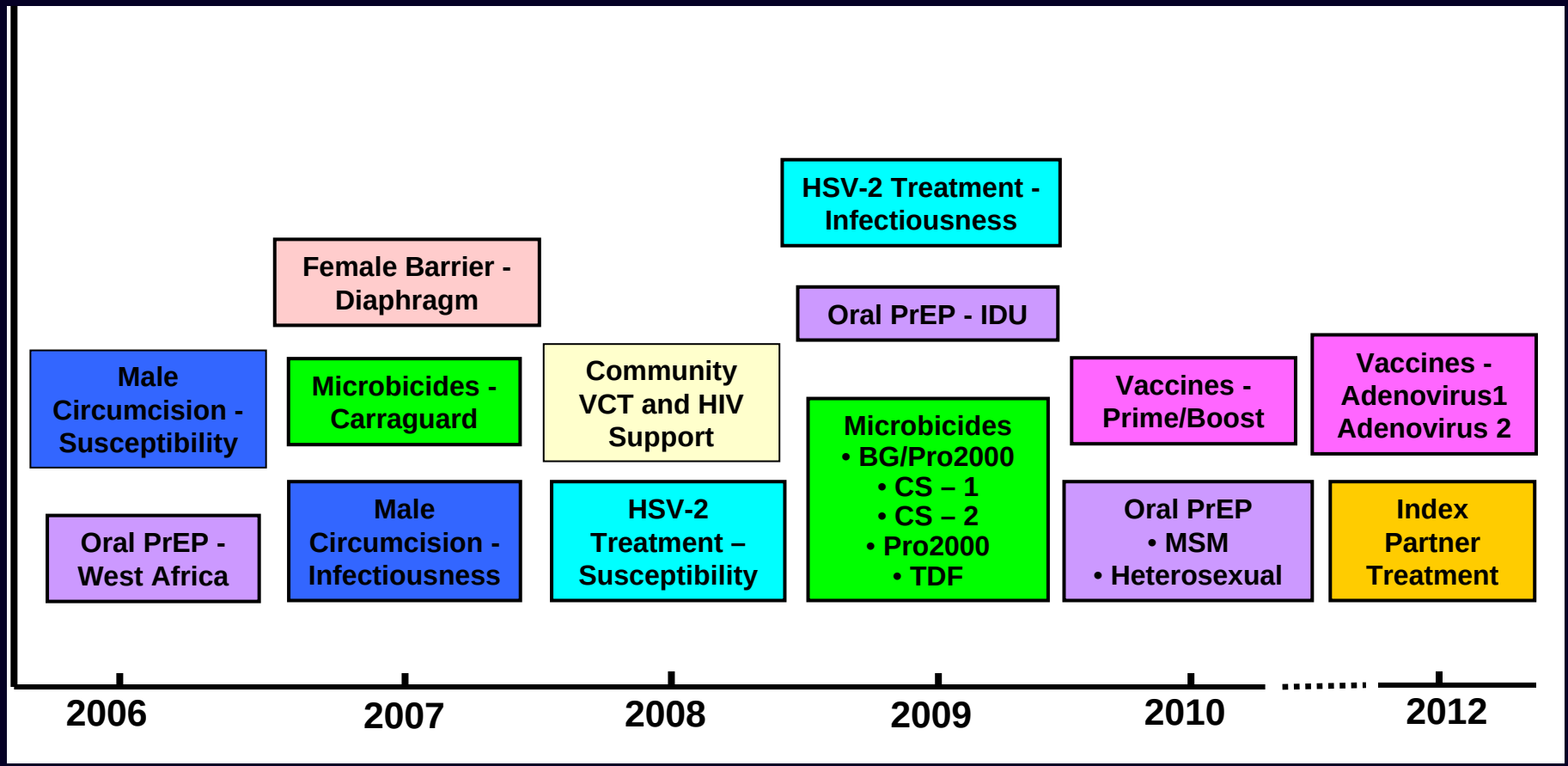
# December 2006 – Anticipated Prevention Trial Results

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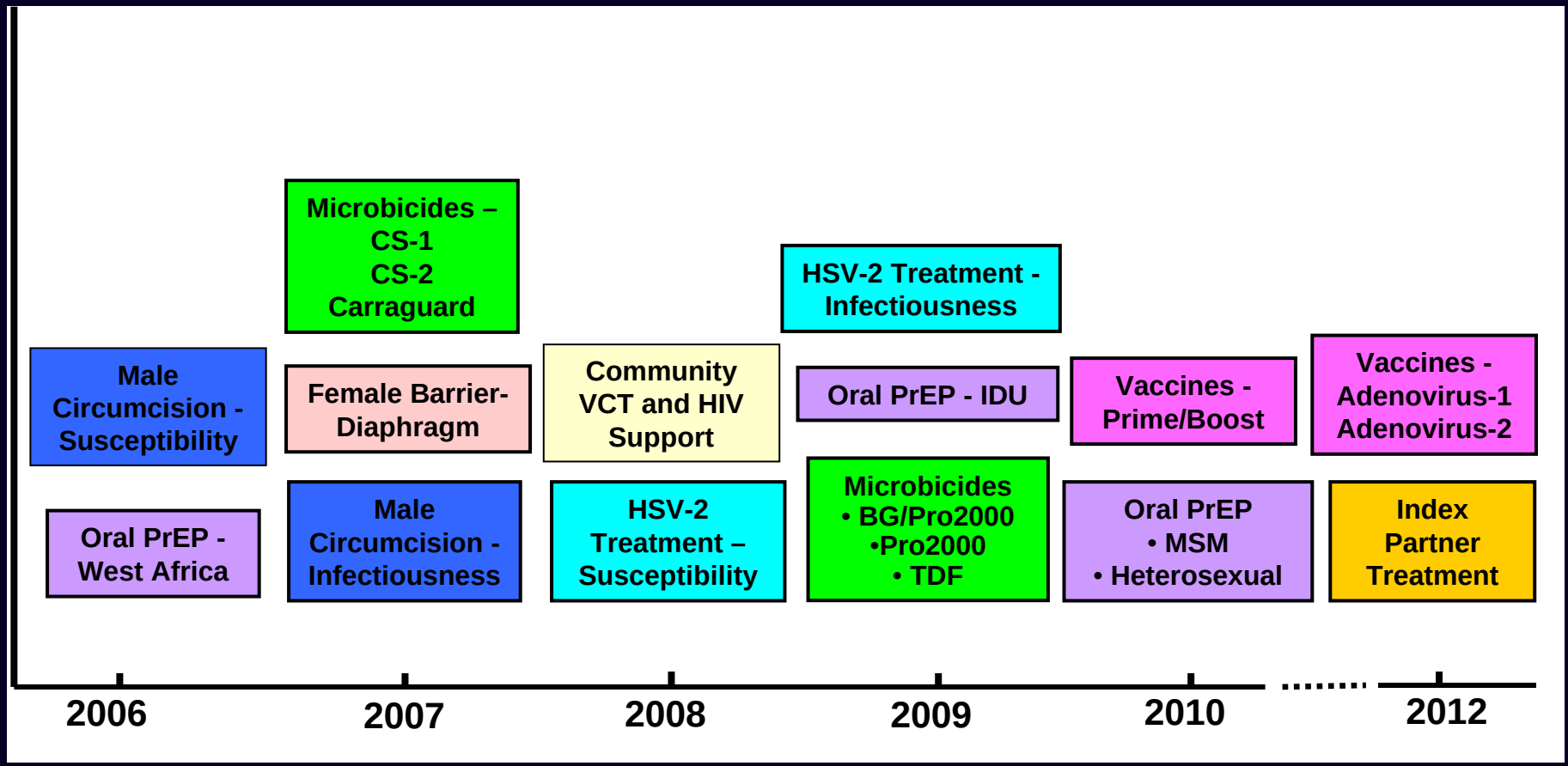
# January 2007 – Anticipated Prevention Trial Results

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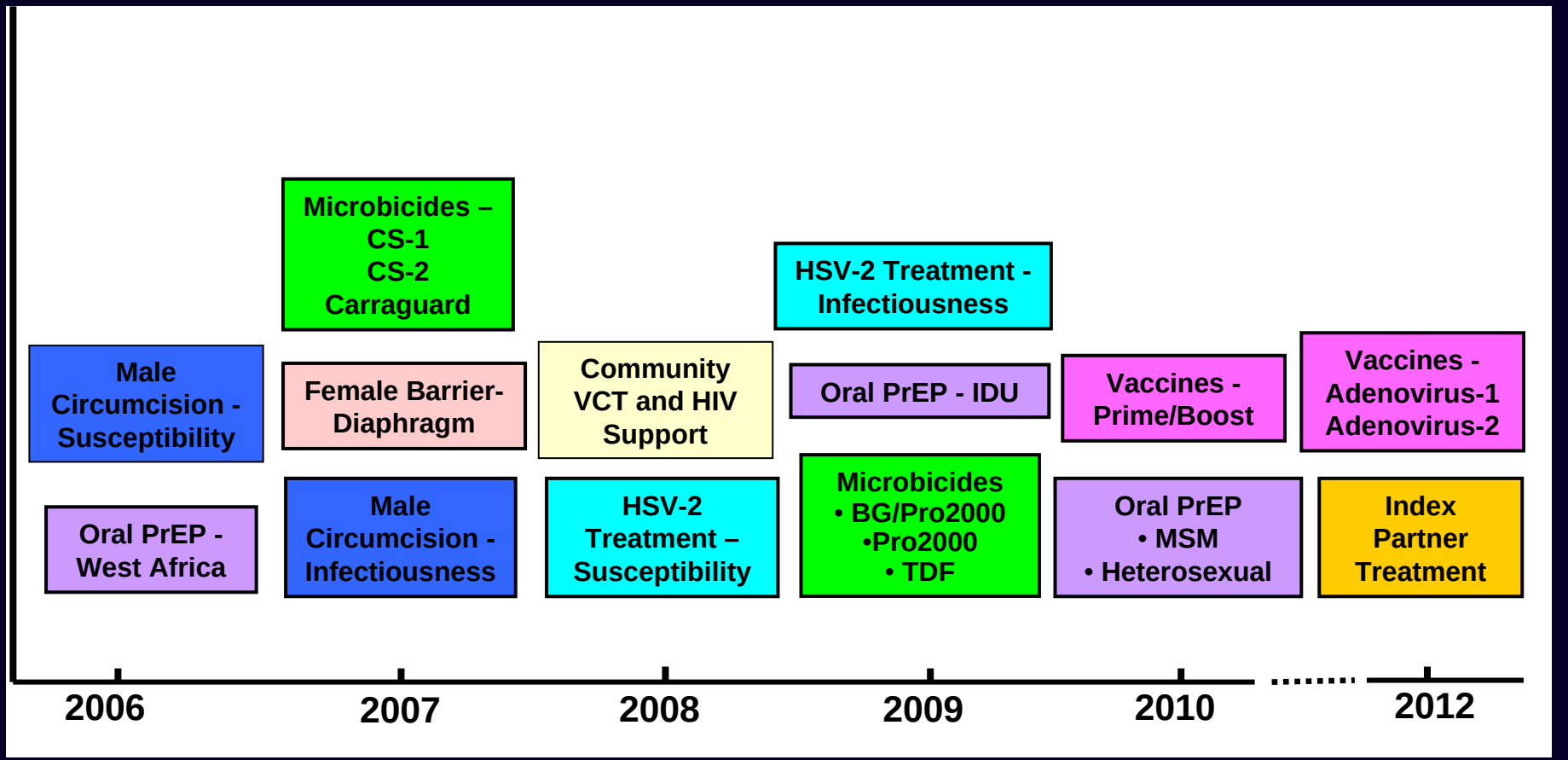
# March 2007 – Anticipated Prevention Trial Results

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# Outline

- Current HIV Prevention Tools
  - Levels of evidence
  - Effective/ineffective tools
- Ongoing trials
  - What if they work?
  - What if they don't?

# Why New Prevention Tools? Do the HIV Math

- Major success in ART access
  – 1.65 M on treatment, **BUT**
- 4.3 M new HIV infections
- We're losing our fight against HIV
- We need better prevention tools

# Evaluation of Evidence

## Quality of Evidence

I. Good evidence
   - large RCT
   - clinical outcomes

II. Fair evidence
   - smaller RCT
   - observational studies
   - surrogate outcomes

III. Weak evidence
   - anecdotes
   - expert opinion

## Strength of Recommendation

A. Stronger
   - important benefits
   - broadly applicable

B. Weaker
   - smaller benefit
   - limited generalizability

C. Insufficient evidence
   - expert opinion

# Current HIV Prevention Approaches - Level I Evidence of Effectiveness

- ARTs Pre/Post exposure to prevent MTCT
- Male circumcision to prevent acquisition
- Treatment of curable STIs - 1 study
- Contraception to prevent MTCT

# Effect of Current Contraceptive Use by HIV+ Women

- 577,000 unintended births averted annually in HIV+ women – implications for orphanage
- 30% vertical transmission if no ARTs
- 173,000 HIV+ births prevented annually
- If unmet need for contraception addressed, this number could be doubled.

*Source: Reynolds, et al., 2005*

# Current HIV Prevention Approaches - Level I Evidence of Ineffectiveness

- Nonoxynol-9 sponge/film/gel
- Treatment of curable STIs – 4 studies
- Vaccines – VaxGen
- Behavior change - individual

# Current HIV Prevention Approaches - Level II-III Evidence of Effectiveness

- Male condoms
- HSV suppression
- Partner reduction/selection
- Female barriers
- Malaria treatment

# Ongoing HIV Prevention Trials

- 15 Phase IIb/III trials
- 8 complementary fields
- Dynamic process of review for effectiveness/safety
- A tale of two topics
  - Male circumcision
  - Cellulose sulfate

# Male Circumcision – 3 RCTs

| | Orange Farm | Rakai | Kisumu |
|---|---|---|---|
| Population | Semi-urban | Rural | Urban |
| MC Rate | 20% | 16% | 10% |
| HIV Incidence | 1.6% | 1.0% | 1.6% |
| Age Range | 18-24 yrs | 15-49 yrs | 18-24 yrs |
| Sample size | 3,128 | 4,996 | 2,784 |
| DMC Stopped | Nov. 2004 | Dec. 2006 | Dec. 2006 |
| RR – ITT | 0.40 | 0.49 | 0.47 |
| RR – PP | 0.24 | 0.45 | 0.40 |

# Modeling the Impact of Circumcision on HIV Prevalence/Incidence

- In SSA, 100% uptake of MC could avert 2 million new infections and 300,000 deaths over ten years
- In Soweto, 50% uptake of MC could avert 32,000 – 53,000 new infections over 20 years
- Prevalence would decline from 23% to 14%

***Sources: Williams et al., 2006; Mesesan et al., 2006***

# Male Circumcision "Worked" – So What?

- Differential endpoints
- Regulatory approval
- Level of impact on individuals and populations – adherence, access
- Effect on current and future trials
- Ability to scale up

# Differential Endpoints

- HIV acquisition - proven
- HIV transmission – concern if sex before healing
- HIV disease progression – unlikely for circumcision, but for other technologies (vaccines, oral PrEP)

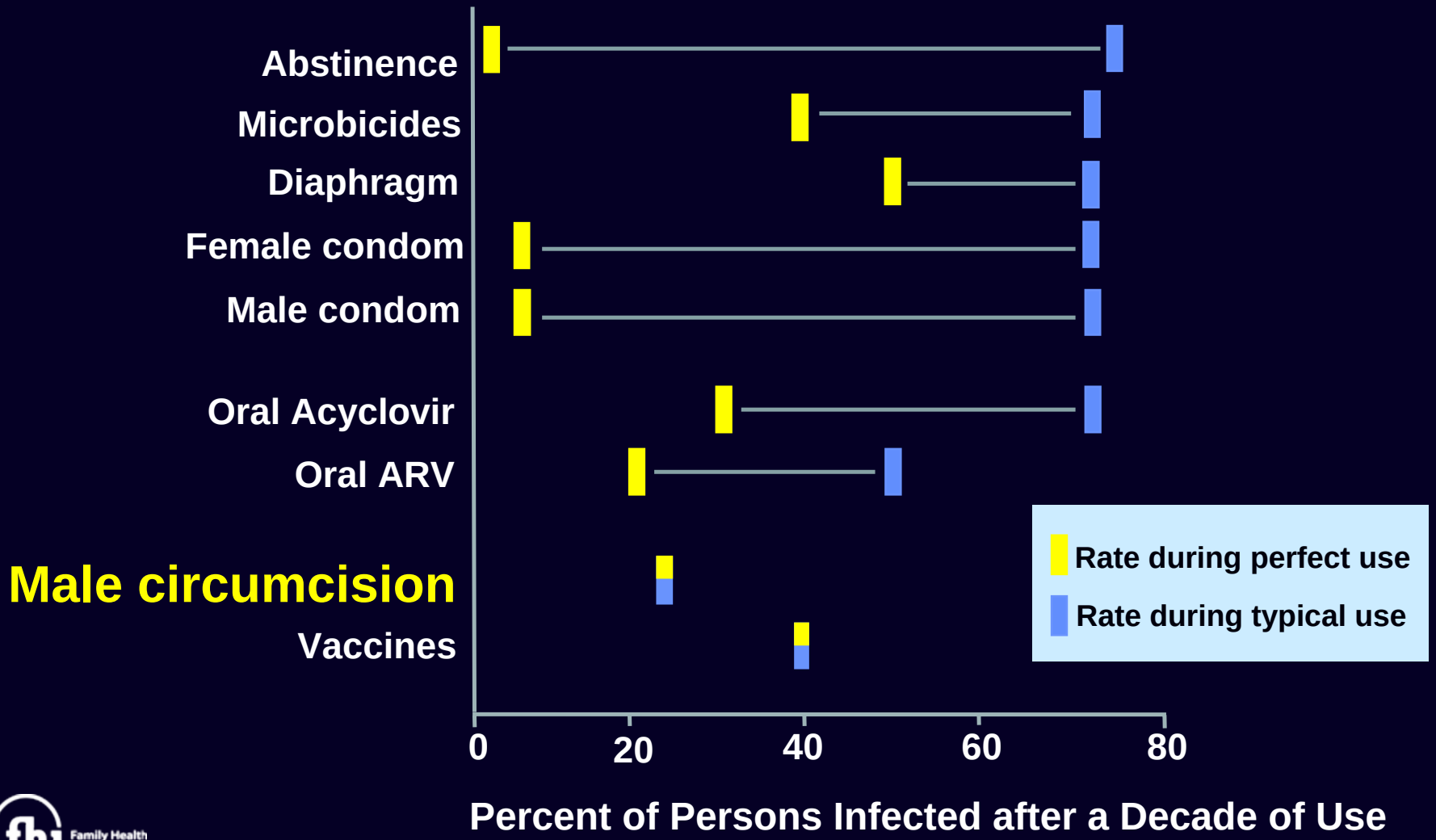
# Regulatory Approval

- Unnecessary for circumcision
- But for other technologies
  - How many trials?
  - What level of significance?
  - What if inconsistent results?
  - What if toxicity/resistance issues?

# Level of Impact on Efficacy and Effectiveness – Adherence, Access

| Level | Efficacy | Effectiveness |
|---|---|---|
| Individual | Perfect Use | Typical Use |
| Population | Clinical Trial Setting | Scale-Up |

# HIV Prevention Tools - Infection Rates

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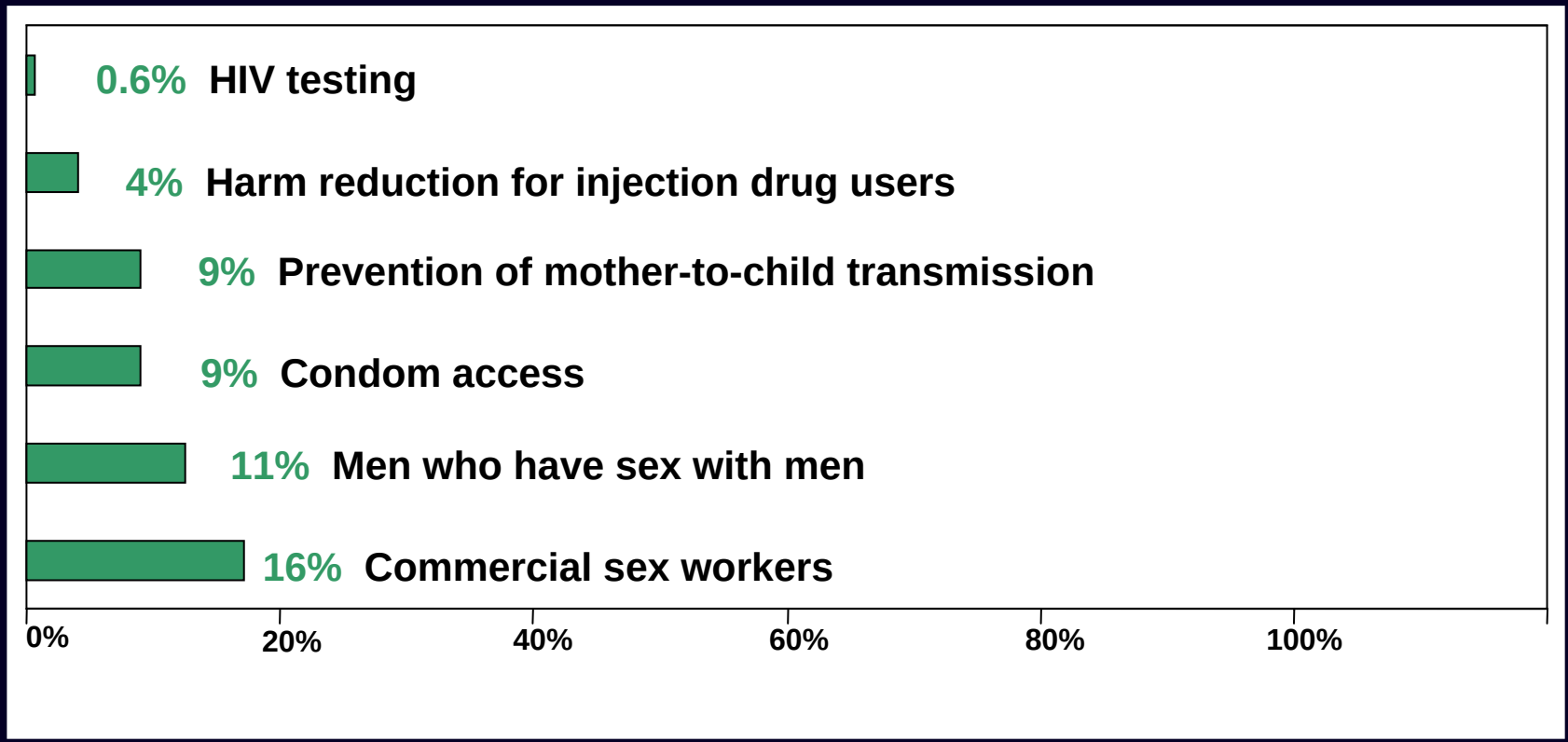
# Percentage at Risk Globally with Access to HIV Prevention Tools




*Source: UNAIDS, 2006; USAID et al., 2004*

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# Amplification of Effectiveness – Population-Level

- Multiplicative dynamics of ID epidemiology
- RCTs examine only one generation of HIV transmission
- Scale up – if successful – amplifies the causal association and the public health impact

*Source: Koopman and Longini, 1994*

# Male Circumcision: Impact on Other Prevention Trials

- How we counsel participants about the benefits and risks of MC?
- Must we offer MC to all participants (or their partners)?
- Require controls to be circumcised?
- Stratify enrollment by MC status?
- By how much will MC affect our power?

# Scale Up in Real World

- Key to PH impact
- Requires immediate investment
- Need for trained personnel/supplies
- Phase IV surveillance for safety and disinhibition?
- Continued search for better technologies

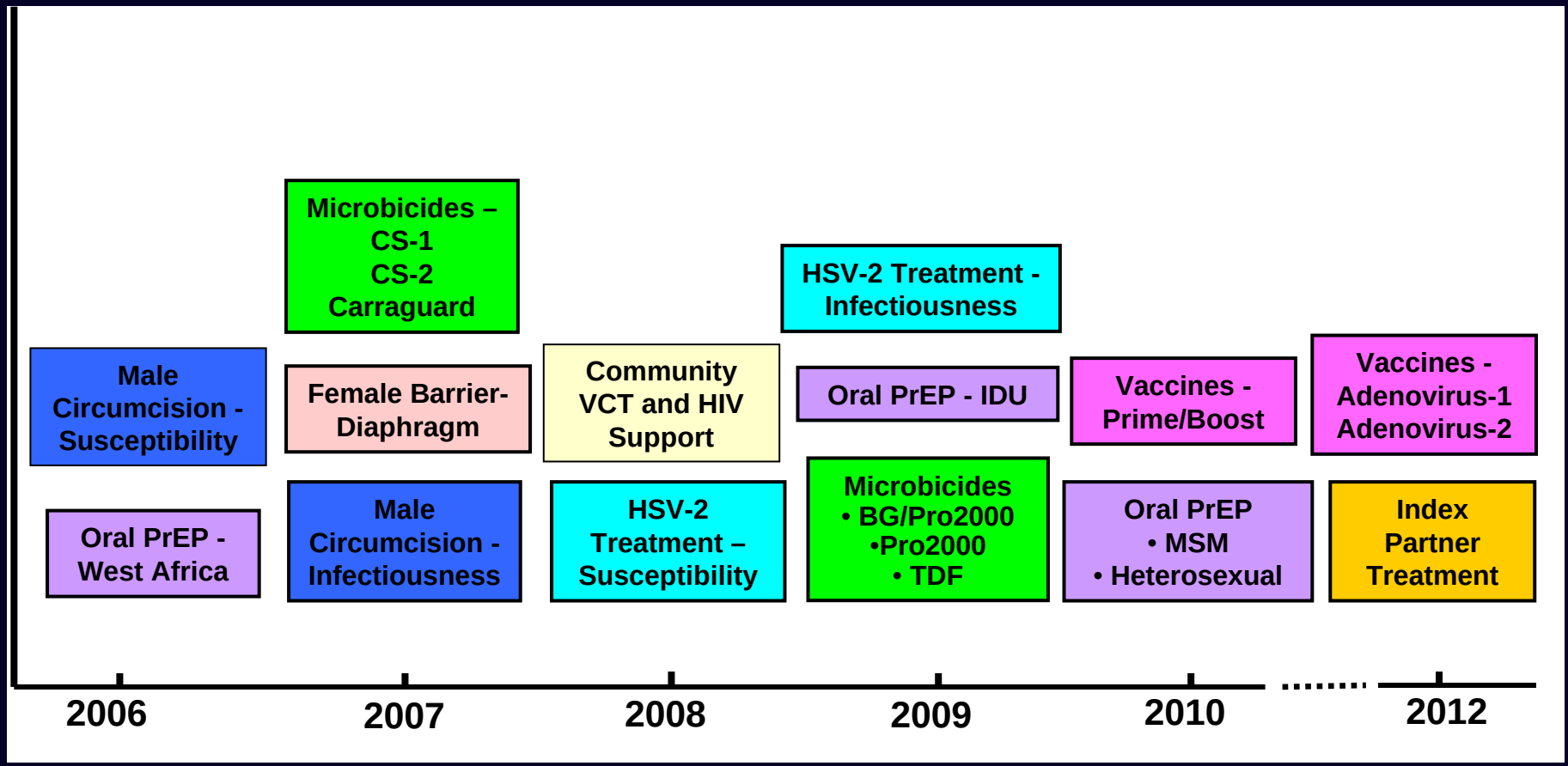
# Cellulose Sulfate – "Doesn't Work" – So What?

- CS Trials
- DSMB coordination/decision
- Communications plan
- Operational follow-up

# Conclusion

- Dynamic field
- Broad lessons learned
- Stay tuned for implications

# March 2007 – Anticipated Prevention Trial Results

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