Measuring the Public Health Impact of Microbicides

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Statistical Center for HIV/AIDS Research & Prevention
SCHARP

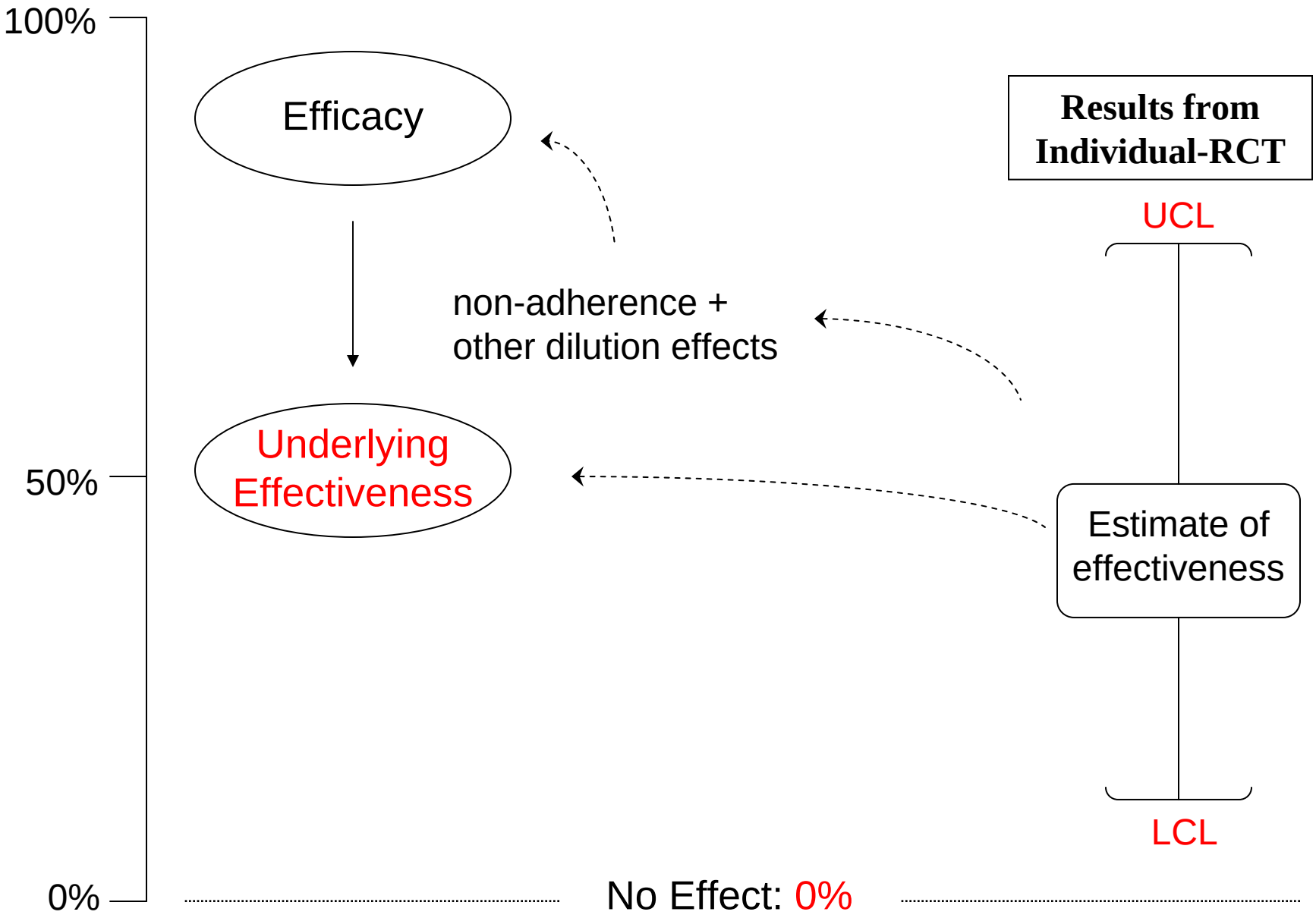
FRED HUTCHINSON CANCER RESEARCH CENTER
VACCINE AND INFECTIOUS DISEASE INSTITUTE

MTN microbicide trials network

Overview

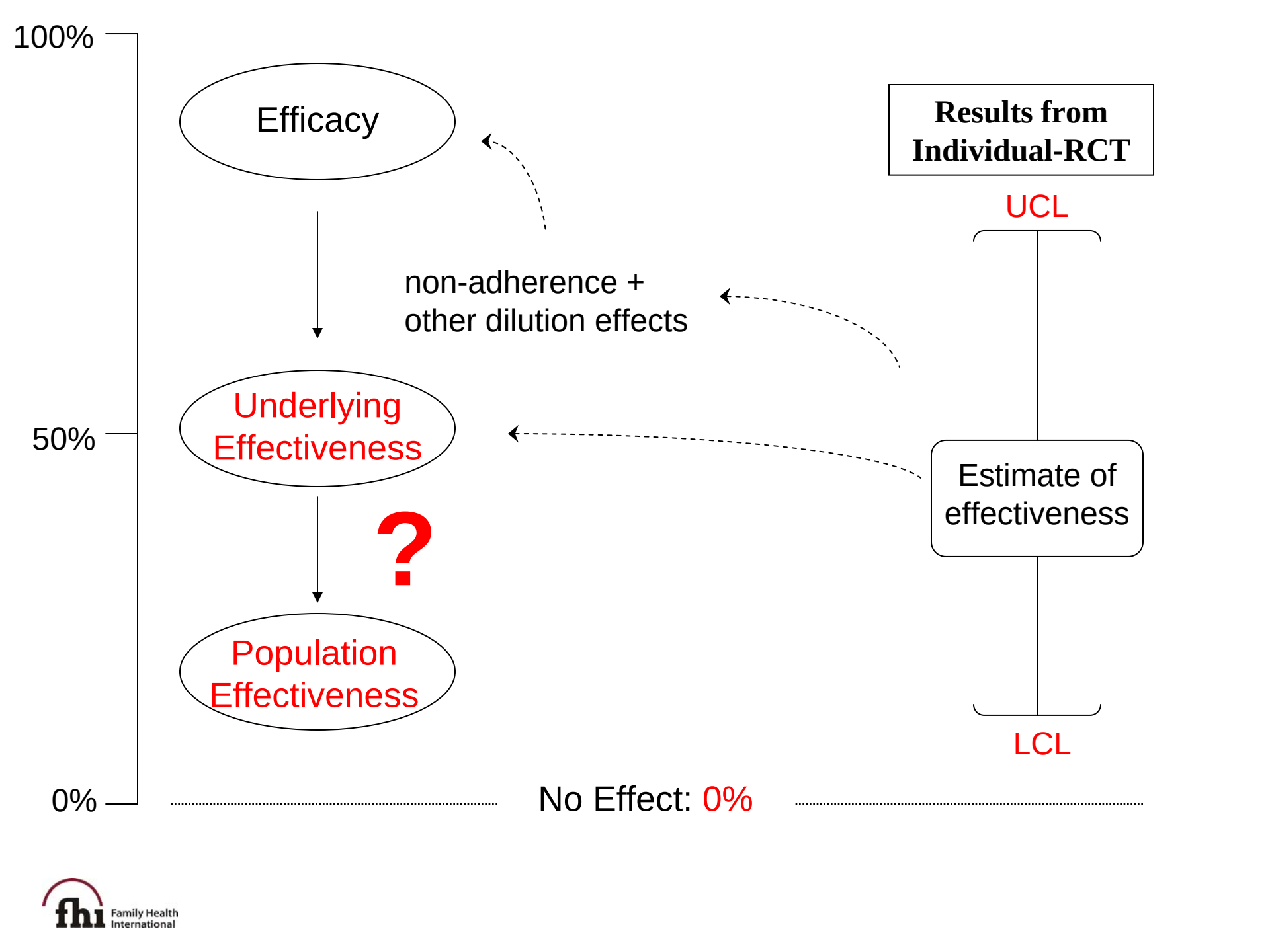
Measuring Public Health Impact of Microbicides:

- Why?
  - Effectiveness in I-RCT versus Population Effectiveness
- How?
  - Population effectiveness of an intervention, how can it be evaluated?
  - Integrated mathematical modeling approach
  - An example: CHARME
- Conclusions



Family Health International

Slide courtesy of Dr. Doug Taylor



Family Health International

Effectiveness in I-RCT > Population Effectiveness

	Individual RCT	Population Level	Effectiveness of Intervention
Adherence	Optimized and ideal	Best practice and routine	Decreased
Delivery of intervention	Ideal	Best practice and routine	Decreased
Source of infection	Mainly from vaginal intercourse	All route of transmission	Decreased
Population Heterogeneities	Trial population rather homogeneous	High level of heterogeneities	Decreased
HIV Dynamics eg herd immunity	Not relevant	Additional benefit	Increased
Behavioral changes eg dishinibition	Not relevant	Possible	Decreased

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Evaluation of Large Scale Intervention

- Need to be evaluated at the population level
  - Small scale intervention in I-RCT
- Population evaluation often not done
  - Harder than an I-RCT!
- Is it better to invest in:
  - Evaluating the impact of the intervention

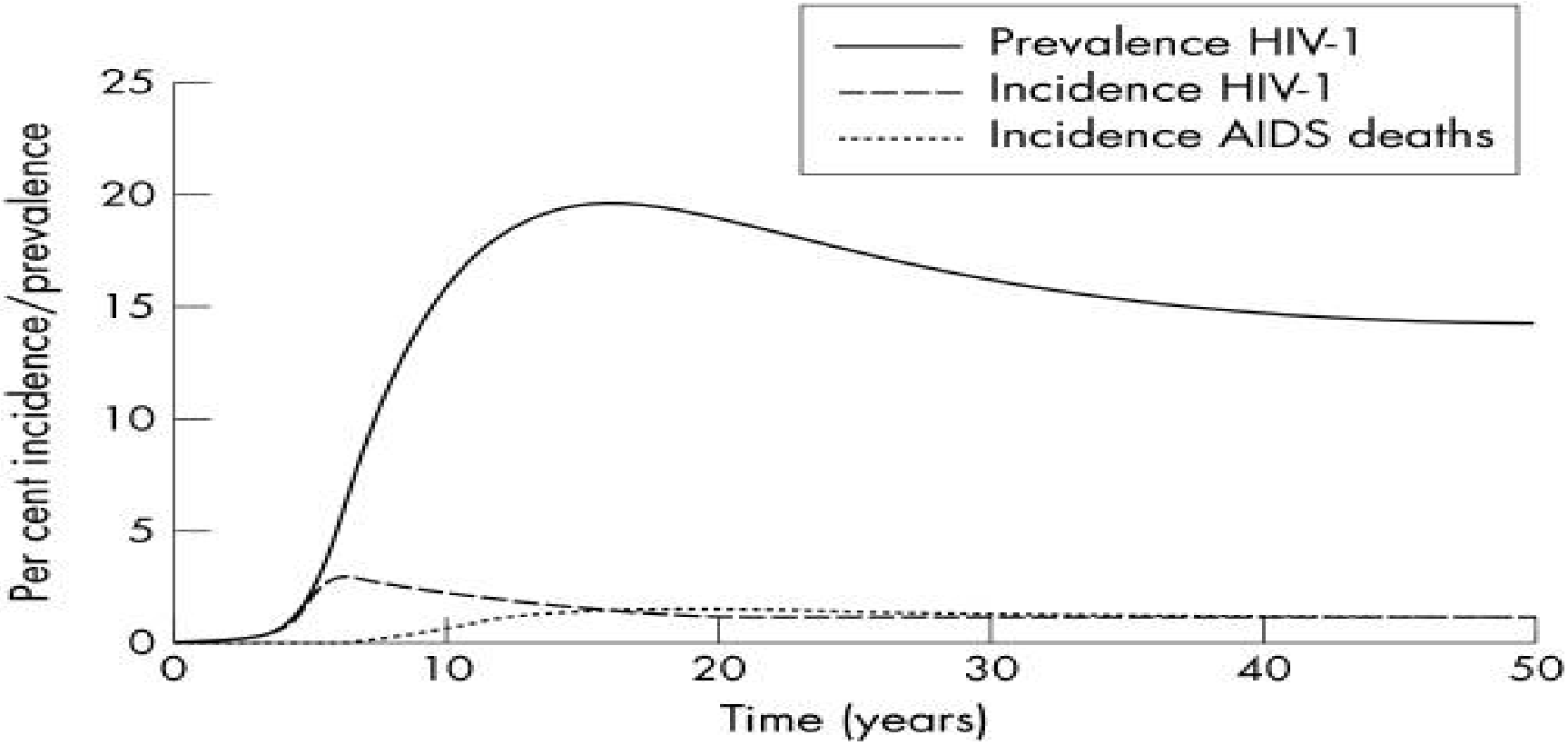
    or
  - Implementing an intervention that ‘should’ work

  => Ideally should do both but what is the right balance between evaluation & implementation?

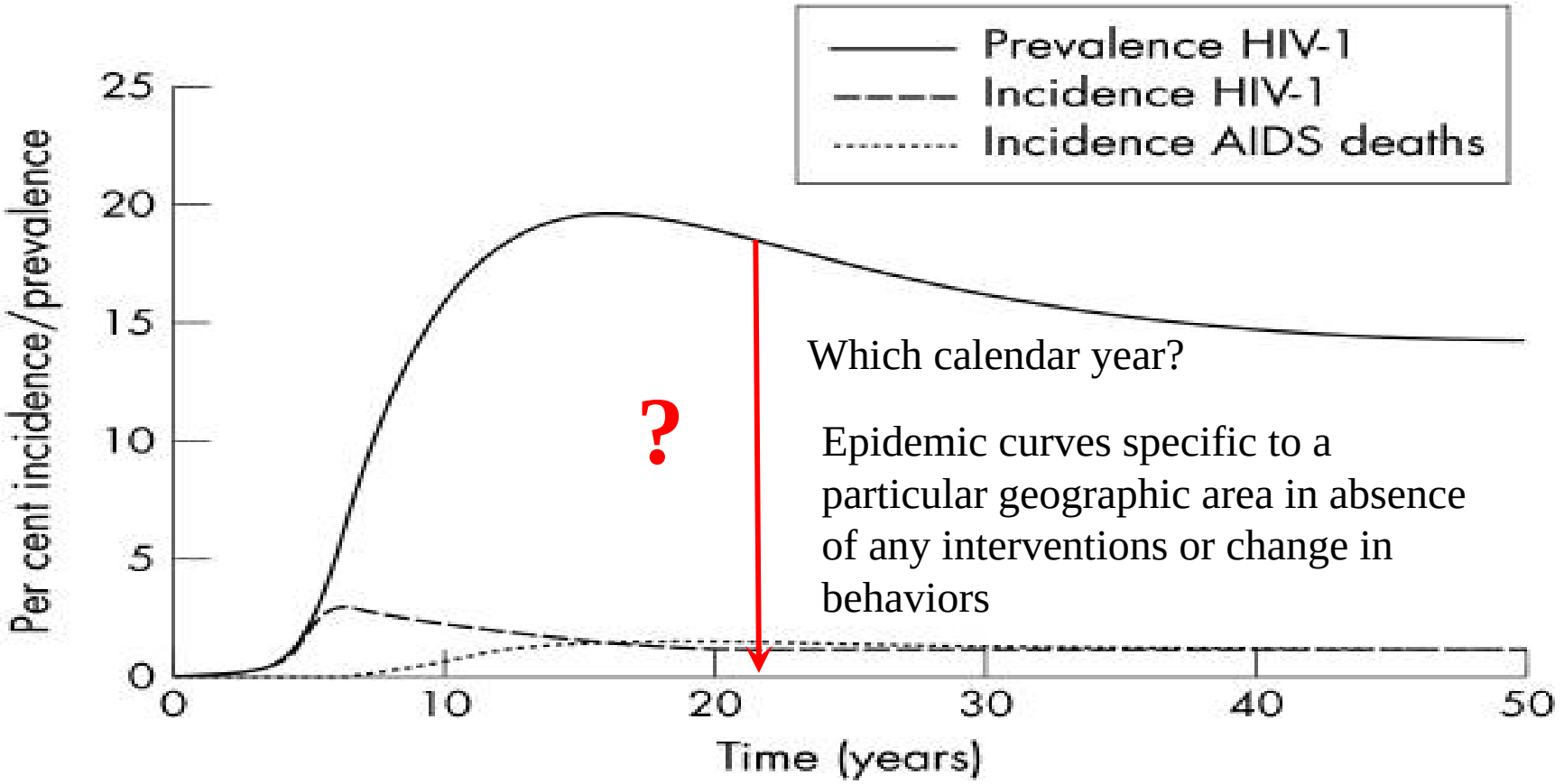
When they are evaluated …

- Ad hoc
- Most often done years after the intervention
  - or at the same time of implementation
- Often based on surveillance data over time
  - Difficult to interpret trends over time in the context of infectious diseases

Basic HIV Transmission Dynamics



Basic HIV Transmission Dynamics



Using Antenatal Clinic (ANC) HIV Prevalence

- Fraught with biases!

Example:

- 32% and 52% decline in ANC HIV prevalence in Avahan districts (Karnataka, India) between 2004-6
- Was this the result of an HIV intervention on FSW and their clients?

⇒ '*Very unlikely*' that the intervention could have yield such a decline over such a short period see Boily et al, AIDS, 2008

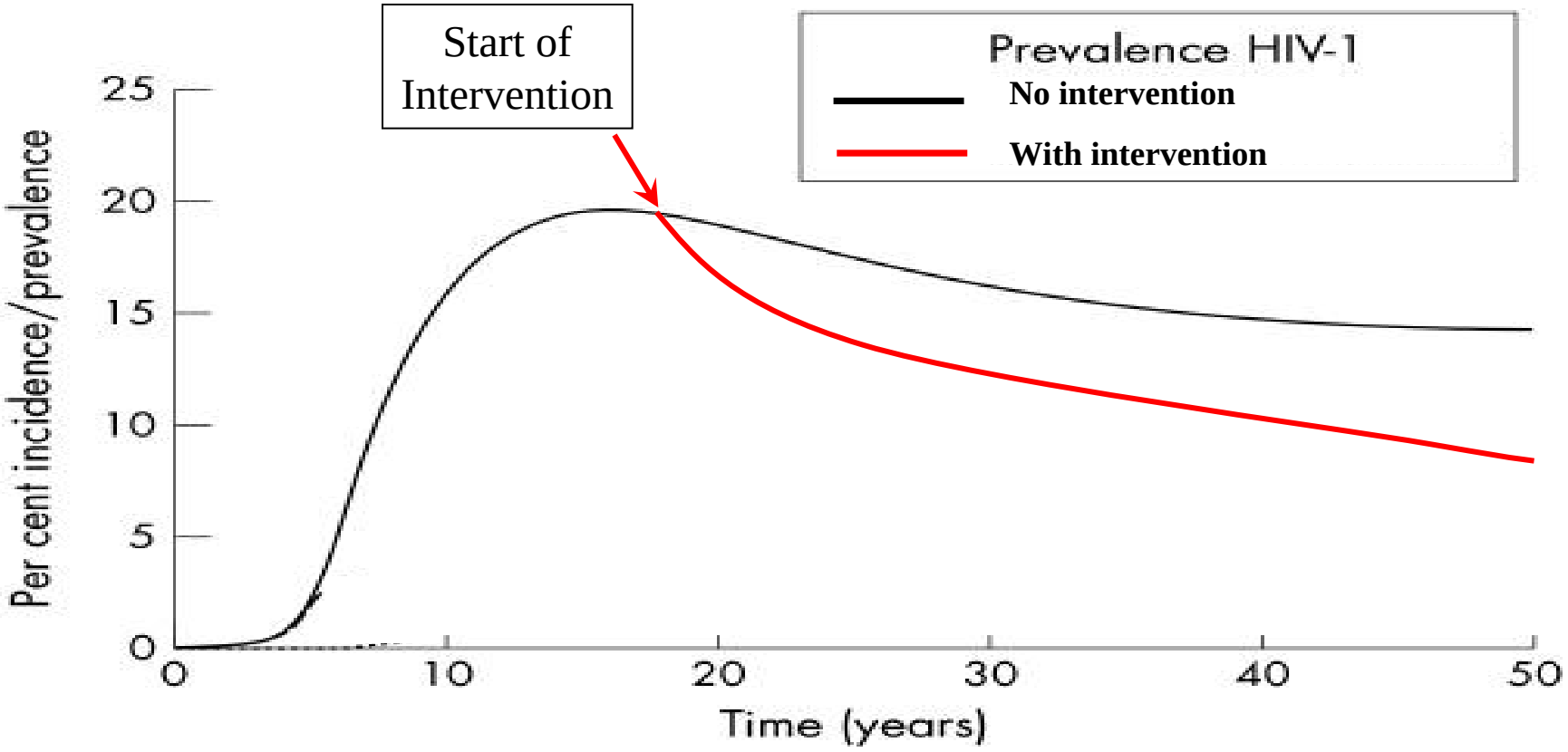
Factors to Take into Account

- Magnitude of impact of intervention depends on:
  - Coverage of intervention
  - Intensity of intervention
  - Local HIV transmission dynamics
    - Careful choice of population evaluated
      - eg Concentrated versus generalised epidemics
- Confounding factors:
  - What else is going on besides this particular intervention
  - Natural course of epidemic (eg AIDS differential mortality, other intervention)
    - Careful interpretation of trend over time
    - Importance of control group

Other important factors

- External validity
  - Heterogeneity of epidemics
    - Many sites may need to be evaluated
  - Heterogeneity of intervention package
- Intervention had already started in many sites
- Feasibility/Costs
- Length of evaluation

Ideally, we would like to observe this ….



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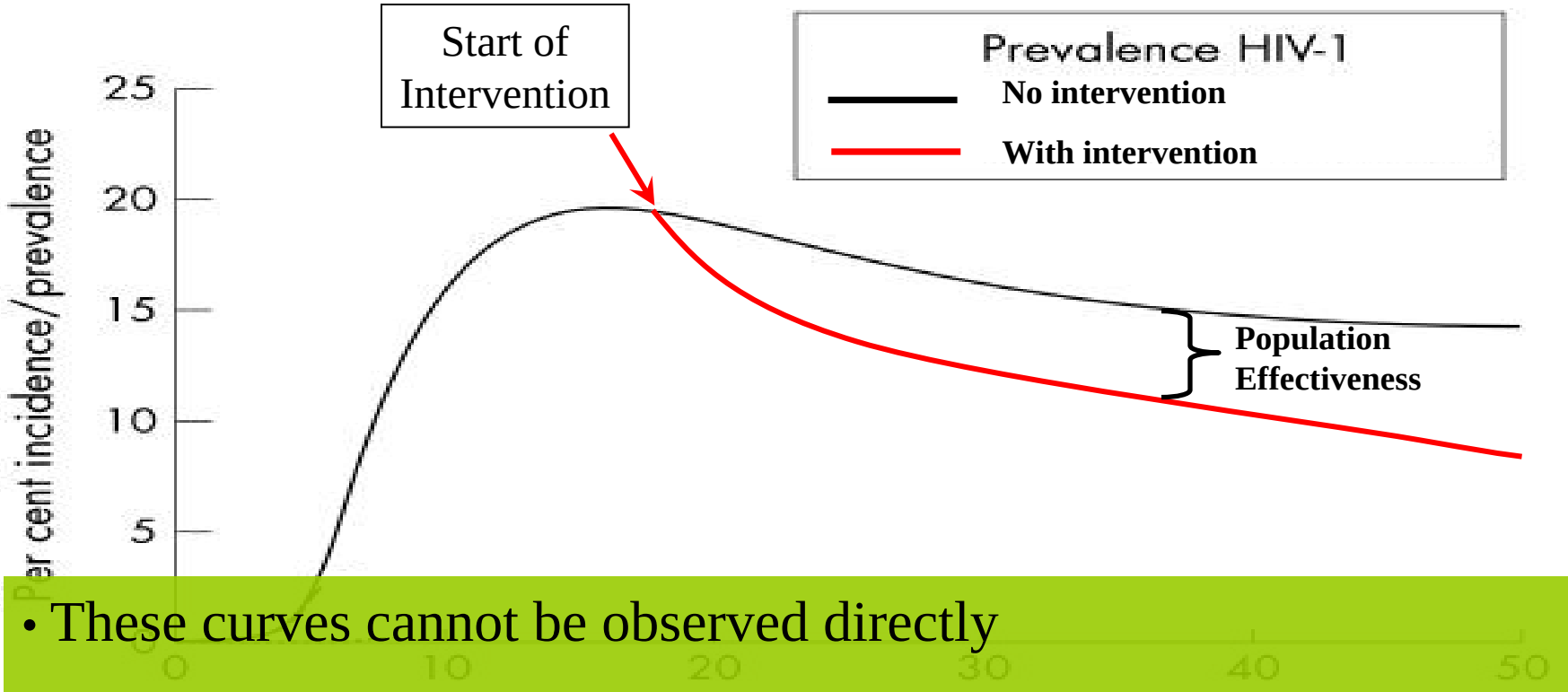


- These curves cannot be observed directly
- Can be done via an integrated mathematical framework that combines empirical biological/behavioral data from subpopulations in the intervention areas

CHARME-INDIA

HIV/AIDS Research Monitoring and Evaluation in India

Centre hospitalier affilié universitaire de Québec

- **Centre hospitalier affilié universitaire de Québec (Laval University): lead institution:** direction and coordination
  - Michel Alary (principal investigator)
- **Imperial College of Science, Technology and Medicine**
  - Marie-Claude Boily
  - Michael Pickles
  - Roy Anderson
  - Anna Philipps
- **London School of Hygiene and Tropical Medicine**
  - Charlotte Watts
  - Peter Vickerman
  - Lilani Kumanarayake
  - Michael Pickles
  - Azra Ghani (Collaborator)
- **University of Manitoba / Karnataka Health Promotion Trust**
  - Stephen Moses; James Blanchard; B.M. Ramesh; Reynold Washington; Sushena Reza Paul
  - Field data collection; project infrastructure in India
- **INDIAN PARTNERS AND COLLABORATING INSTITUTIONS**
  - St John's Medical College (IPHCR), Bangalore
  - Tata Institute of Social Sciences, Mumbai
  - Academic Staff College of India, Hyderabad
  - Centre for Media Studies, Hyderabad
- **Dept. HIV&STIs, HPA, London, UK**
  - Catherine Lowndes
- **University of Montreal**
  - Annie-Claude Labbé

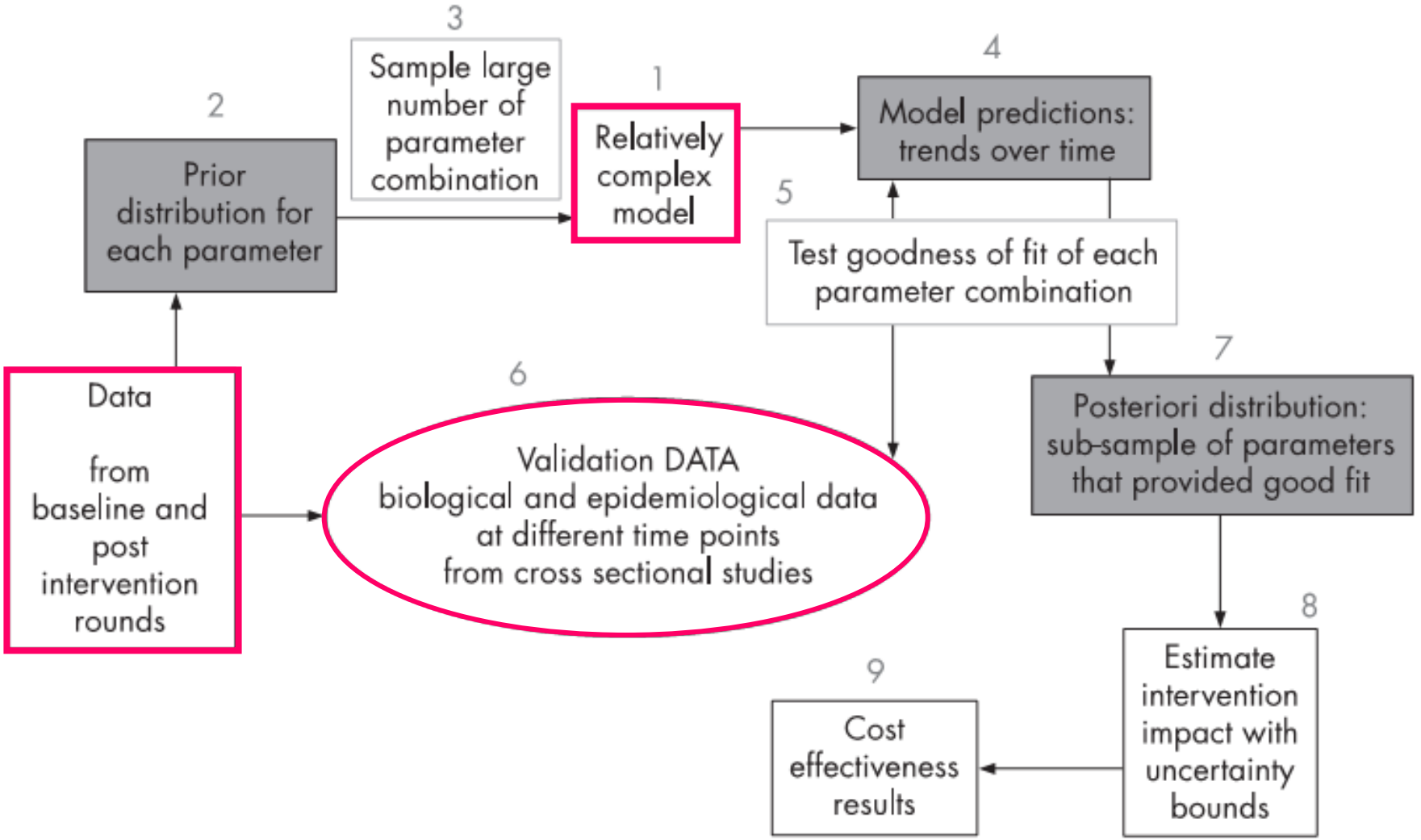
AVAHAN: Large Scale Core Group Intervention

- >$200 million dollars over 7 years
- Highest prevalence district
  - 4 southern and 2 north eastern states: 140 million pop
- Targeted to High-risk groups:
  - Throughout India - highways - truckers
  - CSW (male and female); clients; IDUs;
- Intervention components
  - Distribution and social marketing of condoms and STI services
  - STI management (with presumptive treatment SWs)
  - Behaviour change communication: safer sex
  - Harm reduction interventions for IDUs

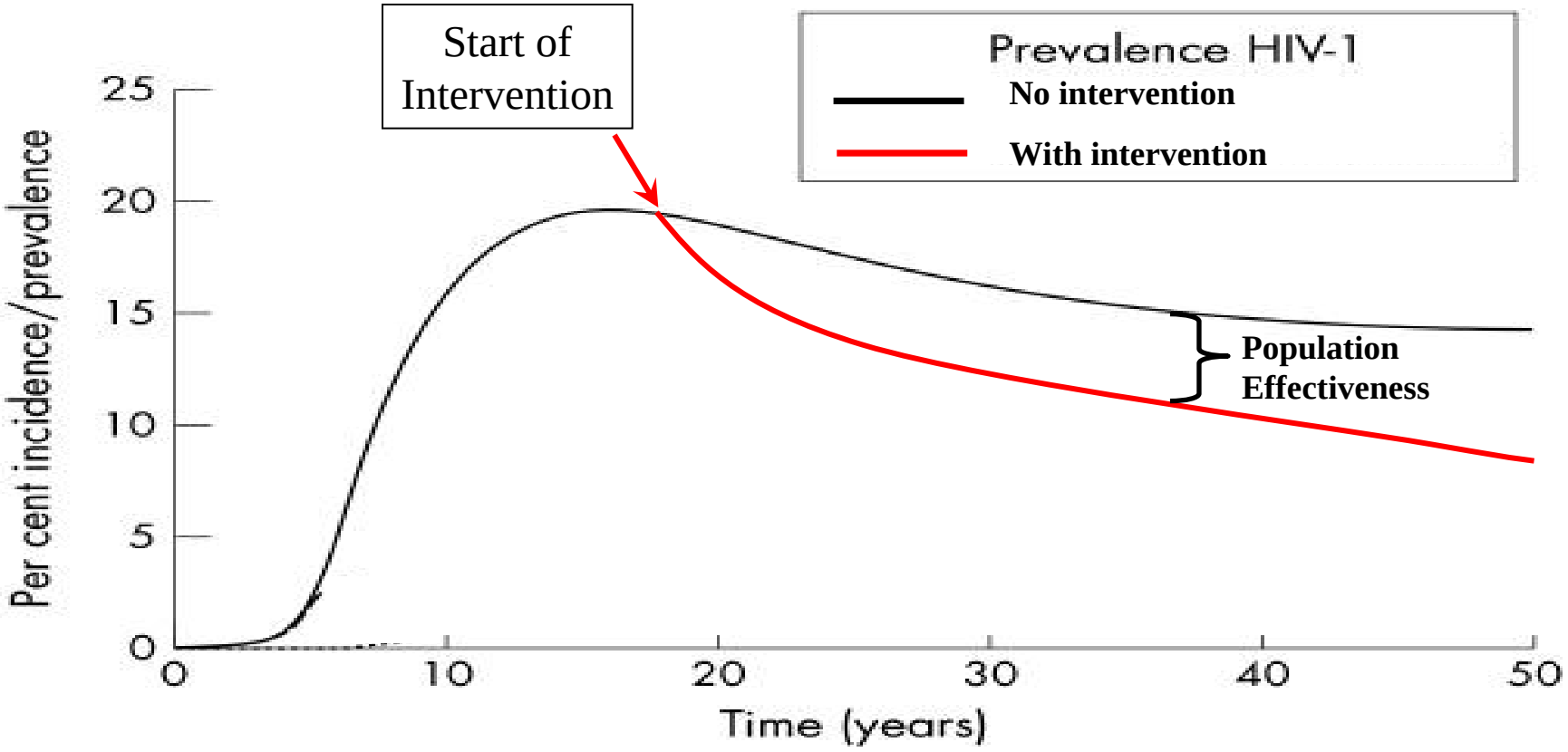
CHARME : Evaluation Framework

- Mathematical modeling and empirical behavioral and biological data:
  1. High-quality serial cross-sectional biological and behavioural data in target and general populations
     - Process indicators embedded in interventions
     - Intensity
     - Coverage
  2. Mathematical modelling using recent methodological advances
  3. Costing studies and cost-effectiveness analysis:
     - Natural complement
     - Estimates obtained by combining costing data and outputs from mathematical models (number of HIV cases and DALYs averted)

Mathematical Evaluation Framework



Ultimately, this framework allows …



Conclusions

- Population effectiveness likely to be smaller than effectiveness observed in microbicide I-RCT
- Evaluation of population effectiveness
  - More challenging than I-RCT
  - Surveillance data over time – difficult interpretation
- Large scale microbicide intervention:
  - Likely to be part of an intervention package
    - What is the independent 'contribution' of the microbicide?
  - A formal evaluation of the population effectiveness will be required
  - **$$$$$$$ …** how much goes toward → **Evaluation**
    → **Implementation**

Conclusions

- Use of an integrated mathematical modeling approach
- Interesting question:
  - Should we evaluate the public health impact before licensing a microbicide?
    - *At the very least, a suitable microbicide would provide some individual benefit to users and not be detrimental to the population at large.*

Personal View

Measuring the public-health impact of candidate HIV vaccines as part of the licensing process

Marie-Claude Boily, Laith Abu-Raddad, Kamal Desai, Benoit Masse, Steve Self, Roy Anderson

Lancet Infect Dis 2008; 8: 200–07

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Department of Infectious Diseases, Faculty of Medicine, Imperial College, London, UK (M-C Boily PhD, K Desai PhD, Prof R Anderson FRS); Department of Social and Preventive Medicine, Laval University, Quebec, Canada (M-C Boily); and Statistical Center for HIV/AIDS Research

The full impact of vaccines against infectious diseases is manifest at both the individual and the community levels. We argue that evaluating the community-level impact of HIV vaccine candidates should be an integral part of the licensing process. We describe a framework for the public-health evaluation of an HIV vaccine, which is based on the interactive use of mathematical models and community randomised clinical trials (C-RCTs) following completion of individual-based clinical trials (I-RCTs). Mathematical models of HIV vaccine can be used to take public-health considerations into account during the licensing process and can also help to select promising vaccine candidates for testing in C-RCTs. We also describe community and individual-based measures useful for defining public-health criteria necessary to guide the licensing process. To move forward, it is crucial to reach a consensus on what should constitute adequate public-health criteria. At the very least, a suitable vaccine would provide some individual benefit to vaccinees and not be detrimental to the population at large. In future I-RCTs and C-RCTs, quantifying each protective vaccine characteristic (eg, reductions in susceptibility or viral load) is important if regulators are to evaluate adequately the potential community-level impact of the vaccine across different settings, populations, and conditions of use.

Framework for public-health evaluation of HIV vaccine: mathematical models and community randomised trials

Figure 1 and figure 2 summarise how evidence from an I-RCT and transmission dynamics models can be combined to decide if a C-RCT should be initiated. They also illustrate the strength of evidence from I-RCTs, mathematical models, and C-RCTs necessary to support the licensing of a vaccine against HIV.

Transmission models of HIV infection should be used following the completion of an I-RCT to serve two main goals. First, they can be used to assess rapidly and cost-effectively whether a vaccine has any potential public-health value, given the specific type and magnitude of protection conferred to vaccinated individuals in the I-RCT. These results can help shape decisions during the licensing process or can help decide if the characteristics of the tested vaccine candidate warrant the initiation of a C-RCT. Second, mathematical models are also useful in the design stage of C-RCTs.[5,9,10] They can help determine trial parameters, such as the minimum vaccine efficacy worth measuring in the trial (ie, the vaccine efficacy that is of public-health relevance), sample sizes, follow-up duration, coverage, and target groups.[5,9,10] These analyses can be performed and validated for different populations under a wide variety of demographic and sexual behaviour and/or vaccine efficacy scenarios (eg, reduction in susceptibility to infection and fraction of individuals adequately protected).

C-RCTs and modelling approaches complement each other. The main advantage of a C-RCT is that it can measure the direct, indirect, and the full community-level

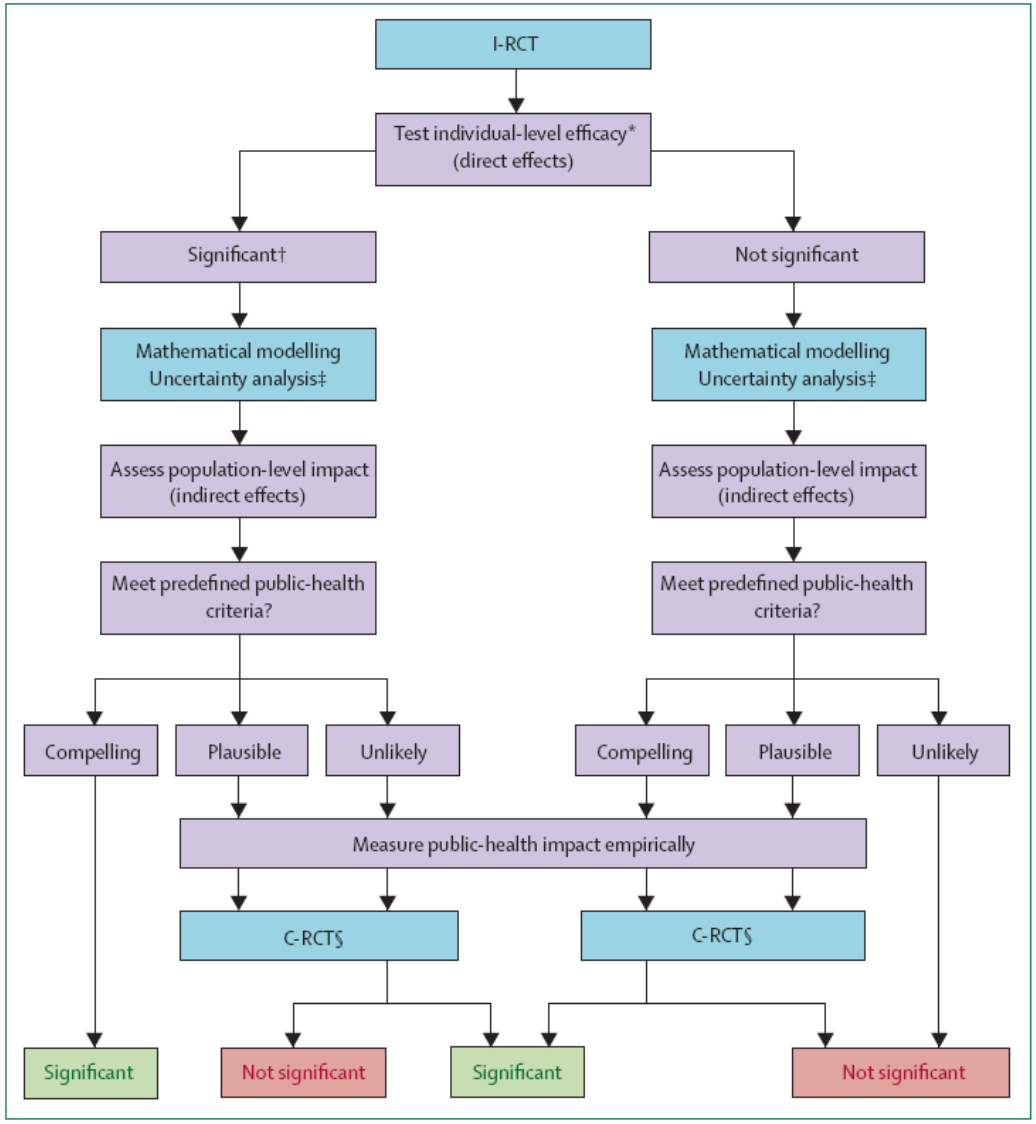

Figure 1: Factoring in public-health requirements: new proposed route

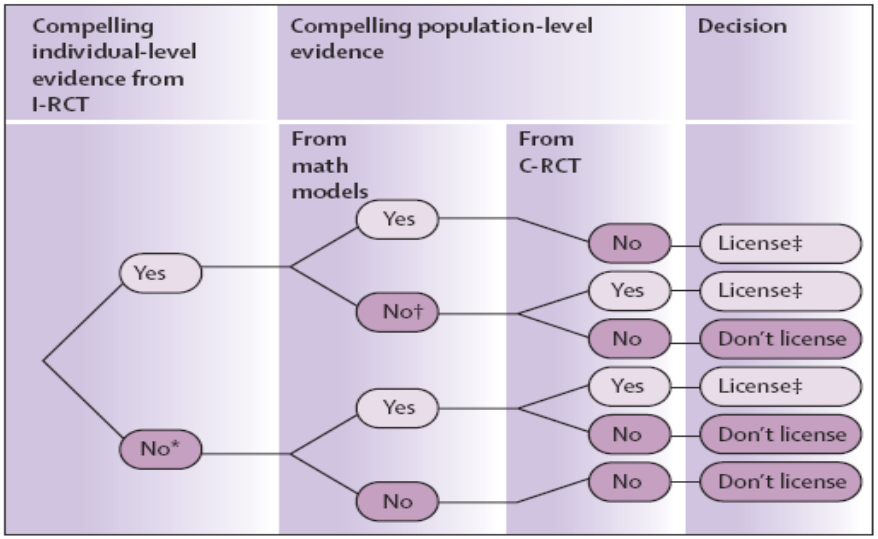

***Figure 2*: Guide to licensing**

*No significant benefit in primary endpoint (eg, reduction in HIV infection), but positive benefits in some secondary endpoints (eg, viral load) that would confer some level of individual benefits. †It would seem unethical to license a vaccine in a situation where it provides individual-level benefit but where its population-level impact may be questionable. Thus, the need for a C-RCT. ‡Once a vaccine is licensed, post-marketing surveillance is recommended to monitor the long-term benefits and potential side-effects (>5–10 years), especially for an infection such as HIV with an intrinsic propensity for genetic changes/variability.

Specifically, mathematical models highlight what needs to be measured in trials. Models can provide information in a much shorter timeframe than is possible with a full C-RCT.

Defining public-health criteria

Akin to deciding which magnitude of effect is of clinical importance when designing an I-RCT, one important question is what population-level effectiveness is of

Panel 1: Important considerations when defining the public-health criteria to guide licensing

- What is the minimum public-health criteria needed for licensing?*
- What is the minimum public-health criteria needed to undertake a C-RCT?
- What should be the minimum benefit of the vaccine at the individual level?
- What should be the minimum benefit of the vaccine at the population level?
- Can we define criteria that are independent of the population characteristics?
- Should the public-health criteria take into account potential behavioural recidivism?
- What are the additional data needed, and analysis or actions to take if the public-health impact of the vaccine differs across community or risk groups?
- Should a vaccine be licensed with public-health recommendations on how, when, and where it should be used (with recommendations on partner notification, etc)?
- Who should take part in the consultation to define unified public-health guidelines for licensing?
- Who should undertake the modelling studies and revise the combined evidence from modelling studies and trial data?
- Who should design or approve the design of the modelling studies† to ensure that current uncertainty in model structure (ie, use of stochastic versus deterministic models, and choice of simplifying assumptions) and parameter estimates (caused by uncertainty in data or lack of data) is well reflected in discussion of the results and conclusions?

Strength of Evidence Needed

- Strength of evidence needed (Habicht, Victora et al (1999))
  - Adequacy: 'Did the expected changes occur?'
    - Determine if changes in the outcome of interest is in the desired direction
  - Plausibility: 'Did the intervention seems to have an effect above and beyond other external influences?'
    - Demonstrate with a certain level of certainty if the intervention may have had an impact above and beyond other external influences
  - Probability: 'Did the intervention have an effect?'
    - Determine with a high degree of certainty if the intervention was a causal determinant of the change in outcome