Ethics of Vaccine Trials

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Disclaimer

The views expressed in this talk are my own. They do not represent the position or policy of the NIH, DHHS, or US government.

Vaccination

- Most immediate and definitive of preventive solutions.
  - Smallpox
    - Eradicated in 1980
  - Polio
    - 80% of global population living in certified polio-free regions
  - Measles/Mumps/Rubella
    - Preliminary data indicates 300% increase in global cases in first three months of 2019, eradication status at risk in US

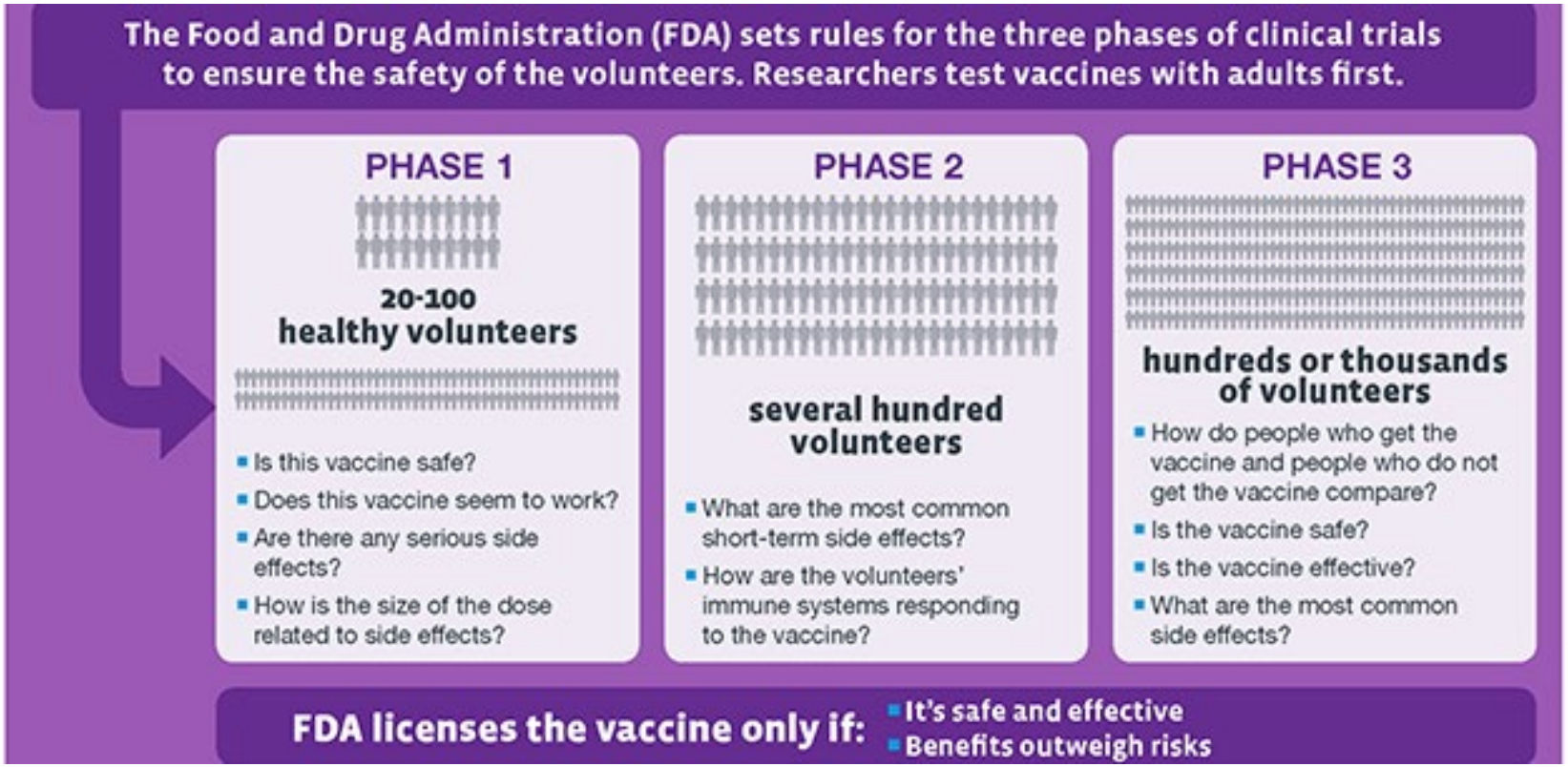
Source: Poland et al (2009); WHO (2017); WHO (2019)

Vaccination

- Population wide vaccination to achieve/maintain ‘population immunity’
  - Herd effect – 80-90% coverage
- Benefits
  - Protects individuals from infection
  - Reduces transmission in population
- Risks
  - No vaccine without risk

Source: Nuffield Council on Bioethics (2007)

Vaccine Trial



Source: CDC (2018)

HIV and Vaccine Development

1981	First cases of novel disease reported
1981	First patient admitted to NIH/Clinical Center
1982	Term Acquired Immune Deficiency Syndrome (AIDS) adopted
1984	HTLV-III identified as cause of AIDS (HIV adopted in 1986)

Source: Office of NIH History

HIV and Vaccine Development

"...we also believe that the new [diagnostic blood test] will enable us to develop a vaccine to prevent AIDS in the future. We hope to have such a **vaccine** ready for testing in approximately two years."

Margaret Heckler
Secretary, DHHS

Source: Office of NIH History

HIV and Vaccine Development

- Do we have a HIV Vaccine?
- Do we still need a HIV vaccine?

HIV and Vaccine Development

1985	CDC reported 10,000 cases of AIDS, 4,942 deaths
1987	First Phase 1 clinical trial of HIV vaccine at NIH/CC
1987	NIAID establishes AIDS Vaccine Evaluation Group
1992	First Phase 2 clinical trial of HIV vaccine, individuals at risk of infection enrolled

Source: Office of NIH History

HIV and Vaccine Development

1998	First Phase 3 trial, randomized placebo controlled trial of HIV vaccine
2000	NIAID establishes HIV Vaccine Trial Network
2009	First evidence of “modest” efficacy (RV144), Thailand (31%)
2016	Trial with new version of RV144 underway in South Africa

Source: NIAID (2018)

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Source: NIAID (2018)

HIV/AIDS in 1998

AIDS deaths – total 11.7 million

Adults and children living with HIV/AIDS – total 30.6 million

Source: WHO (1998)

HIV in 1998: US

- AZT prevents transmission of HIV from mother-to-child during pregnancy (1994)
- 94% of people with HIV in the US on combination therapy

Source: WHO (1998)

HIV in 1998: US

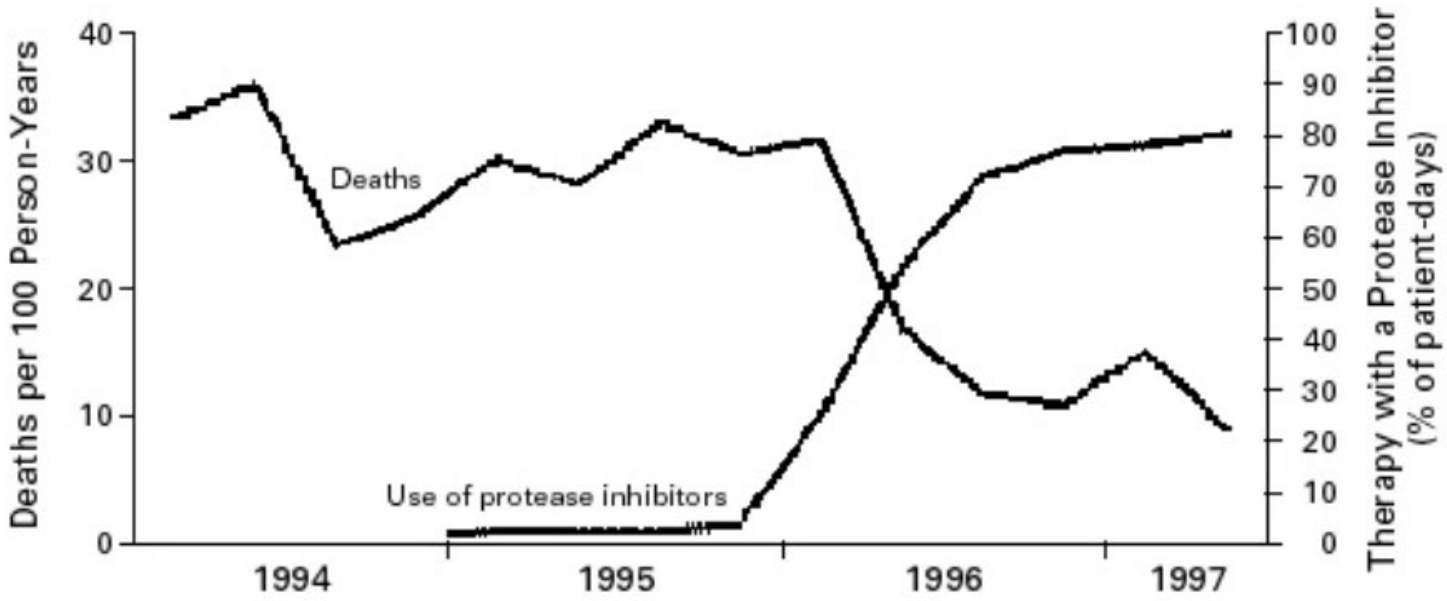

Figure 1. Mortality and Frequency of Use of Combination Antiretroviral Therapy Including a Protease Inhibitor among HIV-Infected Patients with Fewer than 100 CD4+ Cells per Cubic Millimeter, According to Calendar Quarter, from January 1994 through June 1997.

Source: Palella et al (1998)

HIV in US: 1998

- Lack of universal health care in US
  - Those with private insurance more likely to be on a protease inhibitor, less likely to get sick and die
- Hostility and discrimination towards those perceived to be HIV infected or at risk for infection

Source: AIDS Action Foundation (1994); WHO (1998)

Ethical Principles

- Collaborative partnership
- Social value
- Scientific validity
- Fair participant selection
- Favorable risk benefit ratio
- Independent review
- Informed consent
- Respect for participants

Source: Emanuel, Grady and Wendler (2008)

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HIV and Vaccine Development

- Scientific Validity
  - Sample size
  - Standard of Prevention
- Informed Consent
  - HIV positive on conventional HIV tests
- Respect for Participants
  - Treatment for those who seroconvert while on trial
- Collaborative Partnerships
  - Meaningful community involvement

SCIENTIFIC VALIDITY

Scientific Validity

- Sample Size
  - The higher the incidence, the smaller the sample you need to determine whether vaccine effective
  - The lower the incidence, the larger sample size you need to determine whether vaccine is effective

Scientific Validity

Hypothetical 2- arm trial (vaccine v. placebo)

Length of Trial	Annual HIV incidence rate			
	1%	2%	3%	4%
2.0 years	16, 725	8,399	5,624	4,234
2.5 years	11,442	5,754	3,859	2,910
3.0 years	8,775	4,419	2,968	2,242

Assumptions:
- 90% power to detect 50% reduction in new infections
- Loss to follow-up 10% per year

Source: AIDS Action Foundation (1994)

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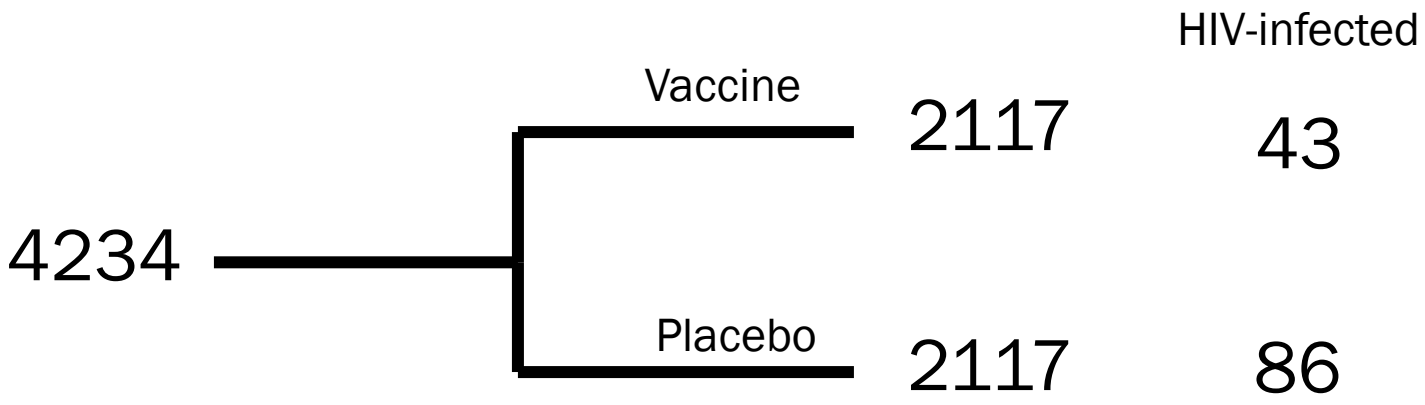
Scientific Validity

- Standard of Prevention
  - Randomized, placebo controlled trial



Scientific Validity

- Standards of Prevention
  - What do we tell subjects about prevention of HIV?

Source: AIDS Action Foundation (1994)

Scientific Validity

- Standards of Prevention
  - HIV vaccine trials must incorporate the best available behavioral risk reduction interventions to encourage participants to avoid behaviors that place them at risk for infection.
    - Abstinence, counseling, condom use, use of sterile needle equipment

Source: AIDS Action Foundation (1994)

Scientific Validity

- Standards of Prevention
  - Known to be effective in preventing HIV transmission
  - Practically achievable as a standard in the local setting
  - Reasonably accessible by those screened or enrolled in HIV prevention.

Source: Rennie and Sugarman (2010)

Scientific Validity

- **Enhanced** Prevention (not locally available)
  - Potential direct benefit
  - Not biased if same methods offered to both arms
  - Possibility of greater attractiveness to potential subjects

PRO

Source: Dawson and Zwerski (2014)

Scientific Validity

- Enhanced Prevention (not locally available)
  - Increases inequities
  - Unintended adverse biological interactions
  - Increased cost/time to trial completion
  - Concerns about adherence
  - Decreased policy relevance

CON

Source: Dawson and Zwerski (2014)

Scientific Validity

- Standards of Prevention
  - Is there a reason to make sure risk reduction message is given by someone other than the investigator?

Source: AIDS Action Foundation (1994)

Scientific Validity

- Standards of Prevention
  - Investigators must demonstrate that the conflict of interest inherent in the provision of risk reduction interventions in the course of HIV vaccine trials is mitigated.

Source: AIDS Action Foundation (1994)

HIV and Vaccine Development

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Source: NIAID (2018)

HIV and Vaccine Development

- Randomized, placebo controlled trial
- Standard of prevention:
  - Condoms
  - Counseling
  - STD diagnosis and management
- Referrals:
  - Male circumcision
  - Post-exposure prophylaxis
  - Pre-exposure prophylaxis

n=5440

Source: NIAID (2016)

Standard of Prevention

1998

- Counseling
- Condoms
- Sterile needles

2019

- Counseling
- Condoms
  - Male and Female
- Sterile needles
- Male circumcision
- Pre-exposure prophylaxis (PrEP)
- Post exposure prophylaxis (PEP)
- *Treatment as prevention*
  - *Reduction of viral load in community*

Source: AIDS Action Foundation (1994); Haire, Folayan and Brown (2014); Janes et al (2019)

INFORMED CONSENT

Screening

- Psychosocial counseling and referrals must be provided to those individuals determined to be ineligible for trial participation by virtue of a positive HIV test.
  - Referral to care

Source: AIDS Action Foundation (1994)

Informed Consent

- Certain biological and social risks inherent in HIV vaccine research are unique and deserving of special and explicit discussion.
  - Trial subjects may be rendered HIV-positive under conventional testing
  - Remote risk that vaccination could increase susceptibility
  - Participation may make them ineligible for future trials, or unresponsive to future, more effective vaccines

Source: AIDS Action Foundation (1994)

Informed Consent

- It is essential that no guarantees of protection against HIV infection be implied by participation HIV vaccine trials.

Source: AIDS Action Foundation (1994); Rennie and Sugarman (2010)

Informed Consent

- It is essential that no guarantees of protection against HIV infection be implied by participation HIV vaccine trials.
  - Behavioral disinhibition

Source: AIDS Action Foundation (1994); Rennie and Sugarman (2010)

Informed Consent

- Subjects must be apprised of the possibility that they may suffer discrimination as though there were infected with HIV merely because they participation in a HIV vaccine trial. To the extent known, participations should receive full information about possible sources of social discrimination and counselling on how to respond to it.

Source: AIDS Action Foundation (1994)

RESPECT FOR PARTICIPANTS

Respect for Participants

- Comprehensive psychosocial counseling must be available to all trial participants.
- Psychosocial counseling and referrals should be made available to partners and intimate associates of trial participants at the request of the participant.

Source: AIDS Action Foundation (1994)

Respect for Participants

- The provision of a range of comprehensive services (health care, legal and psychosocial) is ethically required and constitutes a necessary precursor for the enrollment of an appropriate cohort. Services must be in pace throughout the duration of the trial and must have both individual and community-wide components.
  - Referral to treatment to those who seroconvert

Source: AIDS Action Foundation (1994)

Respect for Participants

- Long-term follow-up is a key component of vaccine efficacy trials.
- With the consent of volunteers, all breakthrough infections must be followed extensively.

Source: AIDS Action Foundation (1994)

COLLABORATIVE PARTNERSHIPS

Collaborative Partnership

- Involvement of community in meaningful way at the earliest stages of the research.
  - Who represents community?
  - How will responsibility be shared?
  - How will fair benefits for the community be assured?

Source: Emanuel, Grady and Wendler (2008); Rennie and Sugarman (2010);

Collaborative Partnership

- Stakeholder Views (South Africa)
  - Current trial site staff involved in vaccine trials
  - Current members of Community Advisory Boards
  - Research ethics committee members

Source: Moorhouse et al (2014)

Collaborative Partnership

- Stakeholder Views (South Africa)
  - Which ethical recommendations are perceived to have more or less merit (UNAIDS, UNAIDS AVAC)?
    - Overall merit
      - Top ranked: Care related
      - Bottom ranked: Prevention related

Source: Moorhouse et al (2014)

Collaborative Partnership

- Stakeholder Views (South Africa)
  - Informed consent
    - Trial participants should be told what prevention services they will receive (#1)
    - Trial participants should be told what care and treatment services they will receive (#2)

Source: Moorhouse et al (2014)

Collaborative Partnership

- Stakeholder Views (South Africa)
  - Access to treatment
    - Who will finance, deliver and monitor care and treatment should be documented (#3)
    - Care approaches and their successes and failures should be carefully documented (#4)
    - Trial participants should get access to optimal care and treatment for HIV infection including ART (#5)

Source: Moorhouse et al (2014)

VACCINE TRIALS IN LOW AND MIDDLE INCOME COUNTRIES (LMICS)

Vaccine Trials in LMICs

- Limited economic development;
- Inadequate protection of human rights in general, and more superficially discrimination on the basis of HIV antibody status;
- Inadequate community/cultural experience with or understanding of, scientific research;

Source: Guenter, Esparza, Macklin (2000)

Vaccine Trials in LMICs

- Limited political awareness of the importance and process of vaccine research;
- Limited availability of health care and treatment options;
- Limited ability of individuals in the community to provide informed consent, often based on class, gender, etc;

Source: Guenter, Esparza, Macklin (2000)

Vaccine Trials in LMICs

- Insufficient formal experience with, or capability to conduct ethical or scientific review of proposed research; and
- Insufficient infrastructure and technical capacity to conduct the proposed research.

Source: Guenter, Esparza, Macklin (2000)

Vaccine Trials in LMICs

- Treatment Availability
  - Is there an ethical obligation for investigators to provide treatment?
  - Is the cost of providing treatment likely prohibitive for conducting trials in LMICs?
  - Is provision of treatment likely to constitute an unreasonable inducement when there is minimal treatment available in community?
  - Once treatment has started how long does it need to be provided?

Source: Guenter, Esparza, Macklin (2000)

Vaccine Trials in LMICs

- Treatment Availability
  - Care must be taken to not create or worsen inequities in access to treatment.
  - If, in the worst case scenario, it is highlight unlikely that the local health services will be able (or willing) to assume care and treatment…researchers may wish to consider alternative study sites.
    - But maybe this further exacerbates inequities?

Source: Rennie and Sugarman (2020)

Vaccine Trials in LMICs

- Obligation to provide access to vaccine once found effective.
  - How often is results on one trial adequate for determining effectiveness?
  - Who is responsible for provision?
    - For how long?

Source: Guenter, Esparza, Macklin (2000); Rennie and Sugarman (2010)

Vaccine Trials in LMICs

- Obligation to provide access to vaccine once found effective.
  - Researchers should develop plans for post study access as the research unfolds in close consultation with community and research participants (HTPN)

Source: Guenter, Esparza, Macklin (2000); Rennie and Sugarman (2010)

Vaccine Trials in LMICs

- Obligation to provide access to vaccine once found effective.
  - Ethically unacceptable to start a student without a decision about post study access of participants to beneficial interventions, communicated in consent process (Nuffield)

Source: Guenter, Esparza, Macklin (2000); Nuffield (2002); Rennie and Sugarman (2010)

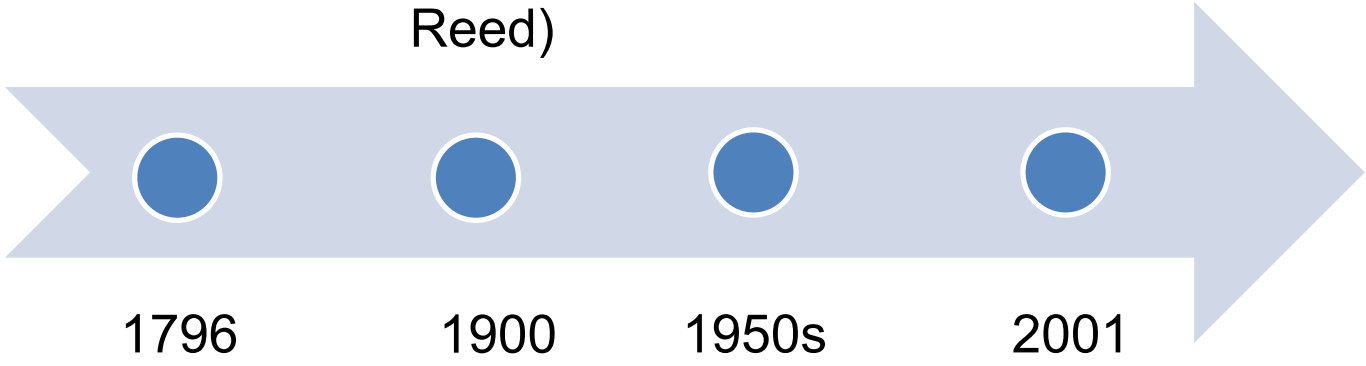
CONTROLLED HUMAN INFECTION (CHI) STUDIES

CHI Studies

- Involves exposing participants to infectious agents in order to test vaccine or treatment candidates and/or study host or pathogen biology in a controlled manner.

CHI Studies: History

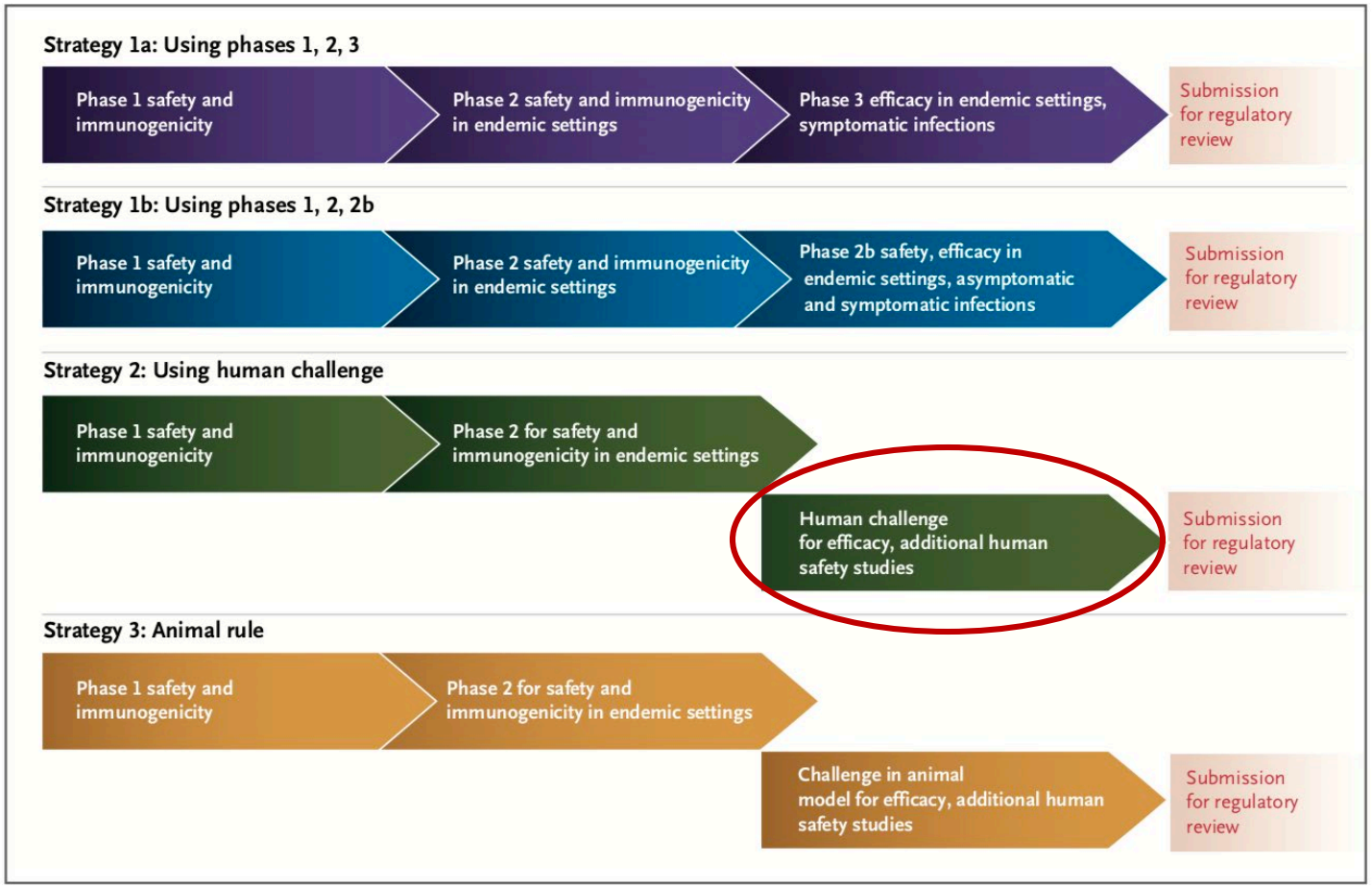
Inoculation with smallpox practiced in Africa, China, India, Europe



CHI Studies: Recent Interest

- Highly efficient research design
  - 10-100 participants per study
  - Can address basic scientific questions and obtain preliminary safety and efficacy data on vaccine candidates *in the same study*
- Recent successes (e.g. cholera vaccine)
- Broader trends (e.g. threat of emerging infectious diseases)

CHI Studies: Zika



Source: Marston et al 2016

CHI Studies: Ethical Challenges

- CHI studies *do not* present unique ethical challenges
  - Expose participants to risks for the potential benefit of others
  - Involve healthy individuals
  - Could cause public distrust in research
  - …

CHI Studies: Ethical Issues

- CHI studies *do* raise several unresolved questions in research ethics more broadly
  - Social value of research
  - Risks to third parties
  - Right to withdraw
  - Default to exclude “vulnerable” populations

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Source: Emanuel, Grady and Wendler (2008)

CHI: Cholera Study

In a 1970s University of Maryland cholera study, this man needed 26 liters of intravenous electrolytes to replace lost fluids.

Courtesy of Myron M. Levine

Social Value Judgments

- Two components:
  - **magnitude** of health benefits
  - **likelihood** of health benefits
- Prediction of how valuable the results will be in the future
- Distribution of value matters

Source: Rid & Roestenberg (under review)

Magnitude of Health Benefits

1) Magnitude of health-related harm from the disease (what happens if we do nothing)
2) Magnitude of potential health-related benefit from the research
3) Number of potential beneficiaries
4) Priority of potential beneficiaries

Source: Rid & Roestenberg (under review)

Likelihood of Health Benefits

1) Innovation/quality of research questions
2) Rigor of research design and data analysis
3) Feasibility and rigor of research conduct
4) Quality of reporting/dissemination of results
5) Influence on future research with the potential to lead to health benefits
6) Influence on clinical or public health practice

Source: Rid & Roestenberg (under review)

Summary Points

- Ethics keeps pace with scientific advancements
  - HIV vaccine trials highlight complexity of trial design
- Using a framework can help identify key concerns
  - Challenge studies highlight role of social value