Ethics of controlled human infection studies

Annette Rid, Department of Bioethics, NIH Clinical Center

Disclosures & thanks

- The views expressed are my own and do not represent the views of the NIH, PHS, or DHHS
- I declare no conflicts of interest
- Thanks to international working group on ethics of controlled human infection studies (PI: Seema Shah)

FONDATION BROCHER
The Greenwall Foundation
wellcome

Overview

1) Background on controlled human infection studies (CHIs): history and scientific basics
2) Ethical framework for controlled human infection studies: SARS-CoV-2 CHIs as case study

Controlled human infection studies (CHIs)

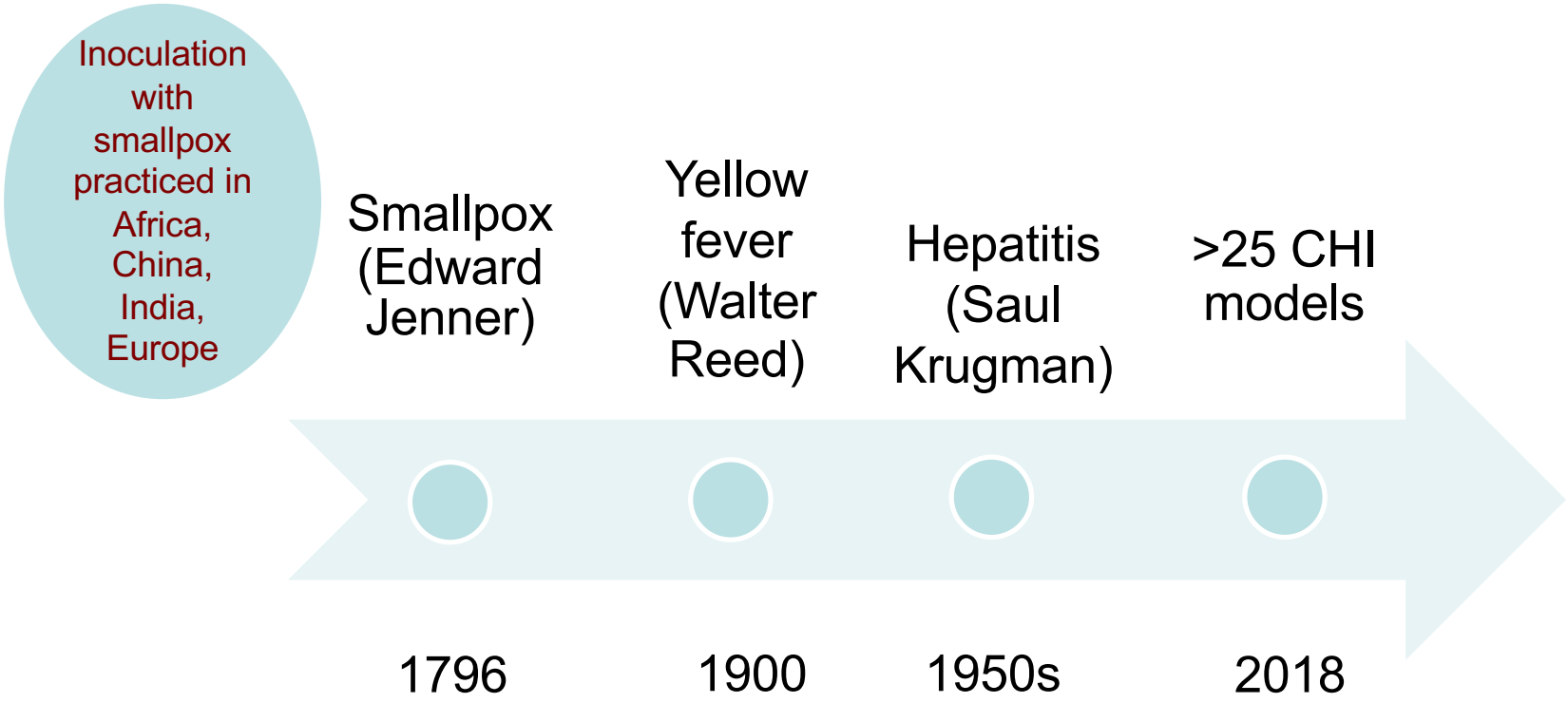
- Studies in which healthy volunteers are deliberately infected with a pathogen in order to study mechanisms of disease and accelerate the testing of vaccines and treatments
- Also called voluntary infection studies, human challenge trials, controlled human infection models etc.

Cholera

Influenza

Malaria

Rhinovirus



Long scientific history of CHIs

Established research paradigm

	Route	Dose	Strain	Endpoints	Estimated number of volunteers	Setting
Rhinovirus[9]	Intranasal	10^4 TCID50	HRV-16, HRV-39	Viral replication, clinical symptoms	5760	Outpatient
Influenza virus[2]	Intranasal	1				
Plasmodium falciparum[10,11]	Mosquito bite, intravenous	3				
ETEC[12]	Oral	≥				
Vibrio cholerae[6,13]	Oral	1				
S Typhi[14]	Oral					
Respiratory syncytial virus[15]	Intranasal	4				
Shigella spp[16]	Oral	1				
Norovirus[17,18]	Oral	4				
Lactobacillus spp[19]	Oral, vaginal	O v				
Streptococcus pneumoniae[20]	Intranasal	1				
Haemophilus ducreyi[21]	Intra-epidermal and intradermal	1				
Dengue virus[4]	Subcutaneous	1				
Francisella tularensis[22]	Aerosol	1				
Neisseria lactamica[23]	Intranasal	1				
Plasmodium vivax[24]	Mosquito bite, intravenous	2 1 e				
Campylobacter jejuni[25]	Oral	1				
Cryptosporidium spp[26,27]	Oral	1				
Necator americanus[28]	Transdermal	1				
Escherichia coli (UTI)[29]	Urethral catheter	1				
BCG[30]	Intradermal	1–4 × 10^5 CFU	BCG	Immune response	140	Outpatient
Neisseria gonorrhoeae[31]	Urethral catheter	1·8 × 10^9 CFU (Ms11mkC), 1·0 × 10^5 CFU (FA1090)	FA1090, MS11mkC	Colonisation	140	Outpatient
Giardia lamblia[32]	Oral	5–10^4 trophozoites	GS-M83/85	Cysts in stool, antibody response	120	Inpatient
Helicobacter pylori[33]	Oral	10^4 CFU	Baylor 100	Urea breath test, histology	80	Outpatient
S Paratyphi[34]	Oral	1–5 × 10^9 CFU	NVGH308 strain	Fever or bacteraemia	40	Outpatient
Parvovirus B19[35]	Nasal	Up to 5^{12} viral genomes	Wild-type	Viraemia	12	Inpatient isolation

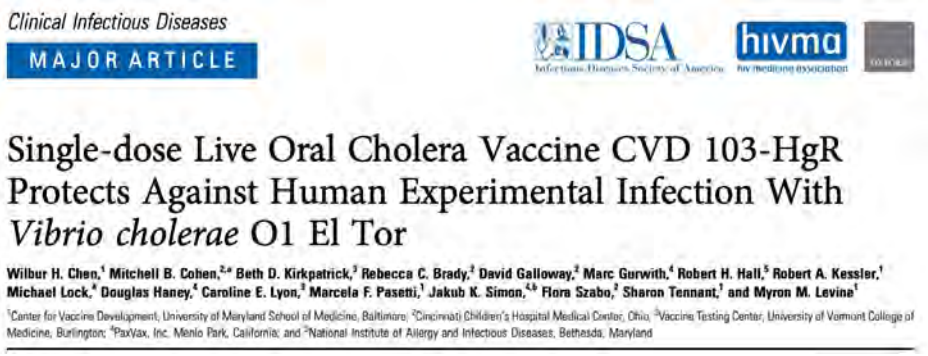
Most commonly used strains are reported and number of volunteers is estimated from publications. TCID50=50% tissue culture infective dose. HRV=human rhinovirus. ETEC=enterotoxigenic *Escherichia coli*. CFU=colony-forming unit. S Typhi=*Salmonella enterica* serotype Typhi. PFU=plaque-forming unit. RT-PCR U=reverse transcription PCR units. UTI=urinary tract infection. S Paratyphi=*Salmonella enterica* serotype Paratyphi.

Table: **Summary of characteristics per controlled human infection model based on published data**

- >25 CHI models
- Both outpatient and inpatient
- ~25'000 volunteers involved with relatively limited risks
- Rhinovirus, influenza and malaria CHIs most commonly performed

Roestenberg et al. 2018

Prominent successes



Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America hivma hiv medicine association

Single-dose Live Oral Cholera Vaccine CVD 103-HgR Protects Against Human Experimental Infection With *Vibrio cholerae* O1 El Tor

Wilbur H. Chen,[1] Mitchell B. Cohen,[2,a] Beth D. Kirkpatrick,[3] Rebecca C. Brady,[3] David Galloway,[3] Marc Gurwith,[4] Robert H. Hall,[5] Robert A. Kessler,[1] Michael Lock,[4] Douglas Haney,[6] Caroline E. Lyon,[3] Marcela F. Pasetti,[1] Jakub K. Simon,[4,b] Flora Szabo,[3] Sharon Tennant,[1] and Myron M. Levine[1]

[1]Center for Vaccine Development, University of Maryland School of Medicine, Baltimore; [2]Cincinnati Children's Hospital Medical Center, Ohio; [3]Vaccine Testing Center, University of Vermont College of Medicine, Burlington; [4]PaxVax, Inc. Menlo Park, California; and [5]National Institute of Allergy and Infectious Diseases, Bethesda, Maryland

FDA licensure of cholera vaccine

Proof of concept for malaria vaccine and first proof of efficacy for several antimalarials

AMERICAN SOCIETY FOR MICROBIOLOGY | mBio®

RESEARCH ARTICLE

CrossMark

Evaluation of Antihemagglutinin and Antineuraminidase Antibodies as Correlates of Protection in an Influenza A/H1N1 Virus Healthy Human Challenge Model

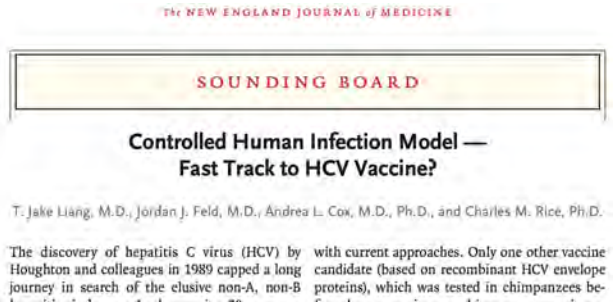
Matthew J. Memoli,[a] Pamela A. Shaw,[b] Alison Han,[a] Lindsay Czajkowski,[a] Susan Reed,[a] Rani Athota,[a] Tyler Bristol,[a] Sarah Fargis,[a] Kyle Risos,[a] John H. Powers,[c] Richard T. Davey, Jr.,[d] Jeffery K. Taubenberger[a]

Viral Pathogenesis and Evolution Section, Laboratory of Infectious Diseases, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA[a]; Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA[b]; Division of Clinical Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA[c]; Clinical Research Section, Laboratory of Immunoregulation, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA[d]

Correlates of protection for influenza

Increasing interest

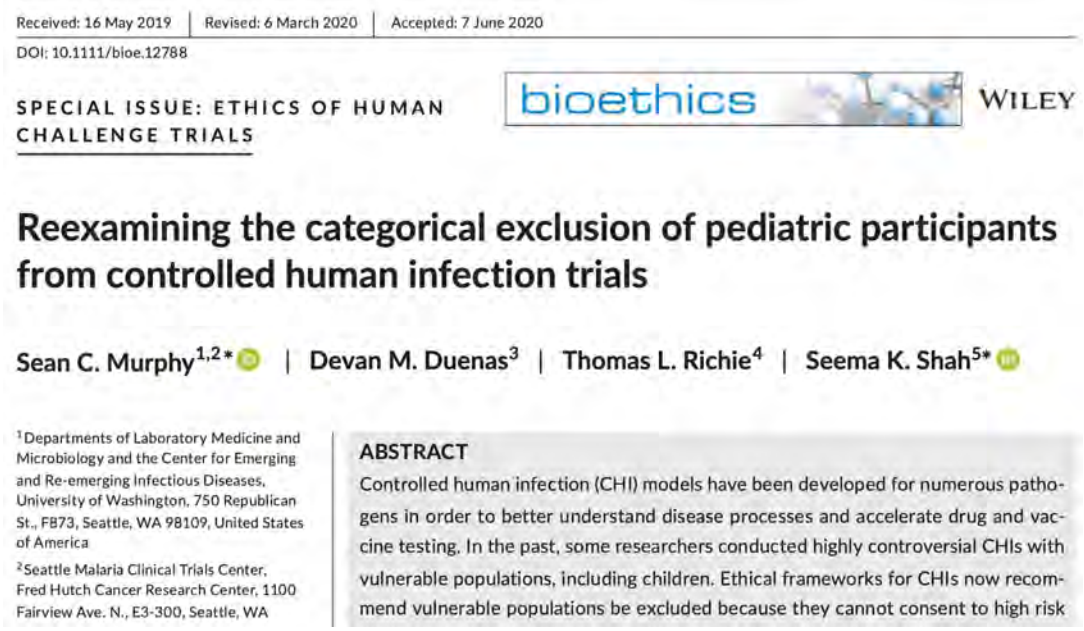
- … in expanding CHIs to new diseases



The Human Challenge Programme, part of the government's Vaccines Taskforce, is a partnership between the government, the NHS, academia and the private sector to establish human challenge studies for COVID-19 in the UK.

Increasing interest

- … in expanding CHIs to new populations



Received: 16 May 2019 | Revised: 6 March 2020 | Accepted: 7 June 2020

DOI: 10.1111/bioe.12788

SPECIAL ISSUE: ETHICS OF HUMAN CHALLENGE TRIALS

bioethics WILEY

Reexamining the categorical exclusion of pediatric participants from controlled human infection trials

Sean C. Murphy[1,2*] | Devan M. Duenas[3] | Thomas L. Richie[4] | Seema K. Shah[5*]

[1]Departments of Laboratory Medicine and Microbiology and the Center for Emerging and Re-emerging Infectious Diseases, University of Washington, 750 Republican St., F873, Seattle, WA 98109, United States of America

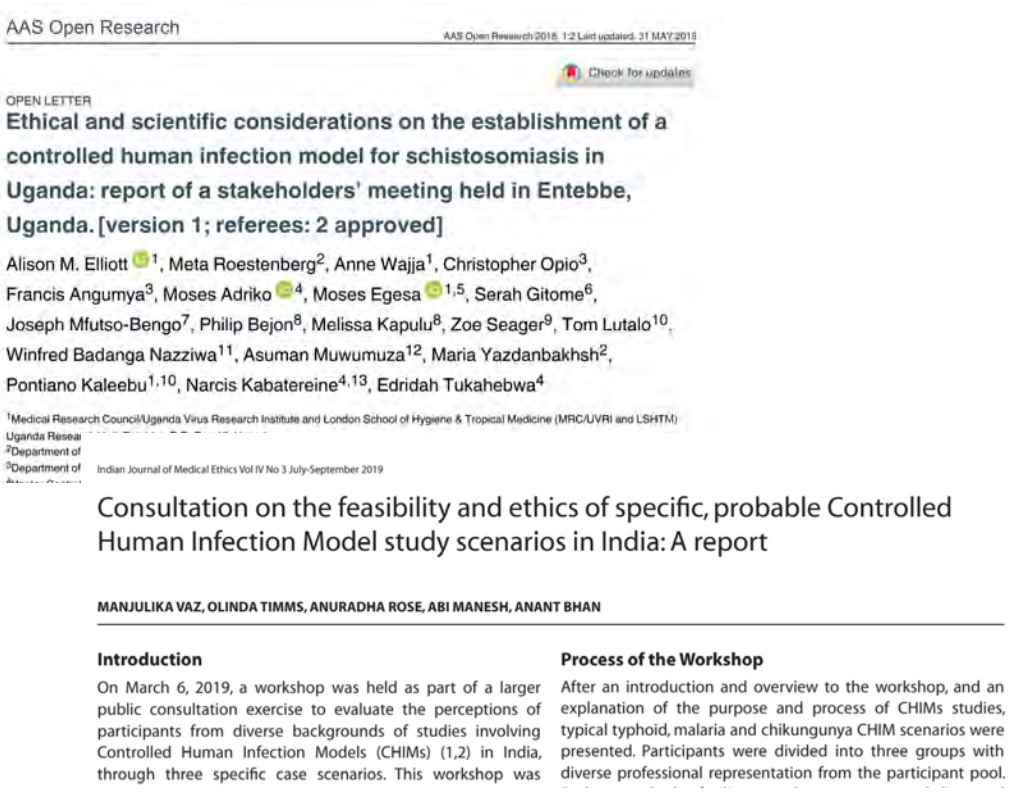
[2]Seattle Malaria Clinical Trials Center, Fred Hutch Cancer Research Center, 1100 Fairview Ave. N., E3-300, Seattle, WA

ABSTRACT

Controlled human infection (CHI) models have been developed for numerous pathogens in order to better understand disease processes and accelerate drug and vaccine testing. In the past, some researchers conducted highly controversial CHIs with vulnerable populations, including children. Ethical frameworks for CHIs now recommend vulnerable populations be excluded because they cannot consent to high risk

Increasing interest

- … in expanding CHIs to new settings



AAS Open Research

AAS Open Research 2015, 1:2 Last updated: 31 MAY 2015

Check for updates

OPEN LETTER

Ethical and scientific considerations on the establishment of a controlled human infection model for schistosomiasis in Uganda: report of a stakeholders' meeting held in Entebbe, Uganda. [version 1; referees: 2 approved]

Alison M. Elliott[1], Meta Roestenberg[2], Anne Wajja[1], Christopher Opio[3], Francis Angumya[3], Moses Adriko[4], Moses Egesa[1,5], Serah Gitome[6], Joseph Mfutso-Bengo[7], Philip Bejon[8], Melissa Kapulu[8], Zoe Seager[9], Tom Lutalo[10], Winfred Badanga Nazziwa[11], Asuman Muwumuza[12], Maria Yazdanbakhsh[2], Pontiano Kaleebu[1,10], Narcis Kabatereine[4,13], Edridah Tukahebwa[4]

[1]Medical Research Council/Uganda Virus Research Institute and London School of Hygiene & Tropical Medicine (MRC/UVRI and LSHTM)
[2]Department of
[3]Department of

Indian Journal of Medical Ethics Vol IV No 3 July-September 2019

Consultation on the feasibility and ethics of specific, probable Controlled Human Infection Model study scenarios in India: A report

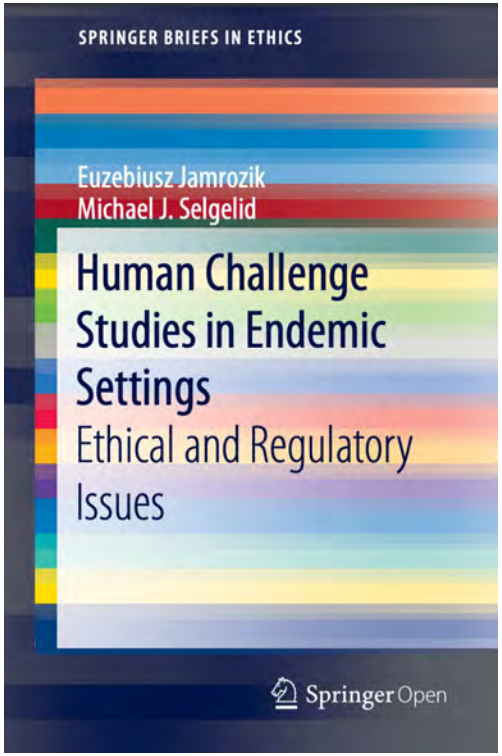
MANJULIKA VAZ, OLINDA TIMMS, ANURADHA ROSE, ABI MANESH, ANANT BHAN

Introduction

On March 6, 2019, a workshop was held as part of a larger public consultation exercise to evaluate the perceptions of participants from diverse backgrounds of studies involving Controlled Human Infection Models (CHIMs) (1,2) in India, through three specific case scenarios. This workshop was

Process of the Workshop

After an introduction and overview to the workshop, and an explanation of the purpose and process of CHIMs studies, typical typhoid, malaria and chikungunya CHIM scenarios were presented. Participants were divided into three groups with diverse professional representation from the participant pool.



Why increasing interest

1) CHIs are efficient and cost-effective
   - Require small number of participants (10-100 per study) because highly controlled
   - Can generate basic scientific insights (e.g., mode of transmission, correlates of protection) and preliminary safety and efficacy data on vaccine or treatment candidates– sometimes *in the same study*

Why increasing interest ctd.

2) CHIs can accelerate research

- When alternative research methods have important limitations, notably animal models and/or field trials
- When there is limited interest in certain research areas or investigational products

Why increasing interest ctd.

3) CHIs are ethically interesting because of these features
   - Expose few participants to risks
   - Can lead to fewer participants being exposed to lower risks in later trials
   - Can save lives by accelerating research
   - Can catalyze research investment on disadvantaged populations

Ethical concerns

- CHIs have long raised ethical concerns, even when their scientific contributions were undisputed

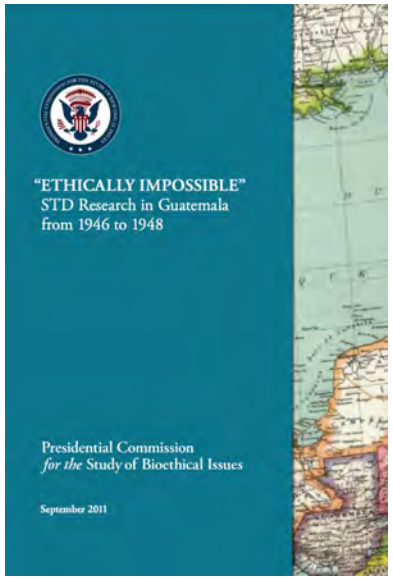
Smallpox
(Edward Jenner, 1796)

Hepatitis
(Saul Krugman, 1950s)

Ethical digressions

- History of CHIs also includes clear cases of ethical digression

Various infectious diseases (WW II)



Various sexually transmitted infections (late 1940s)

Ethical analysis

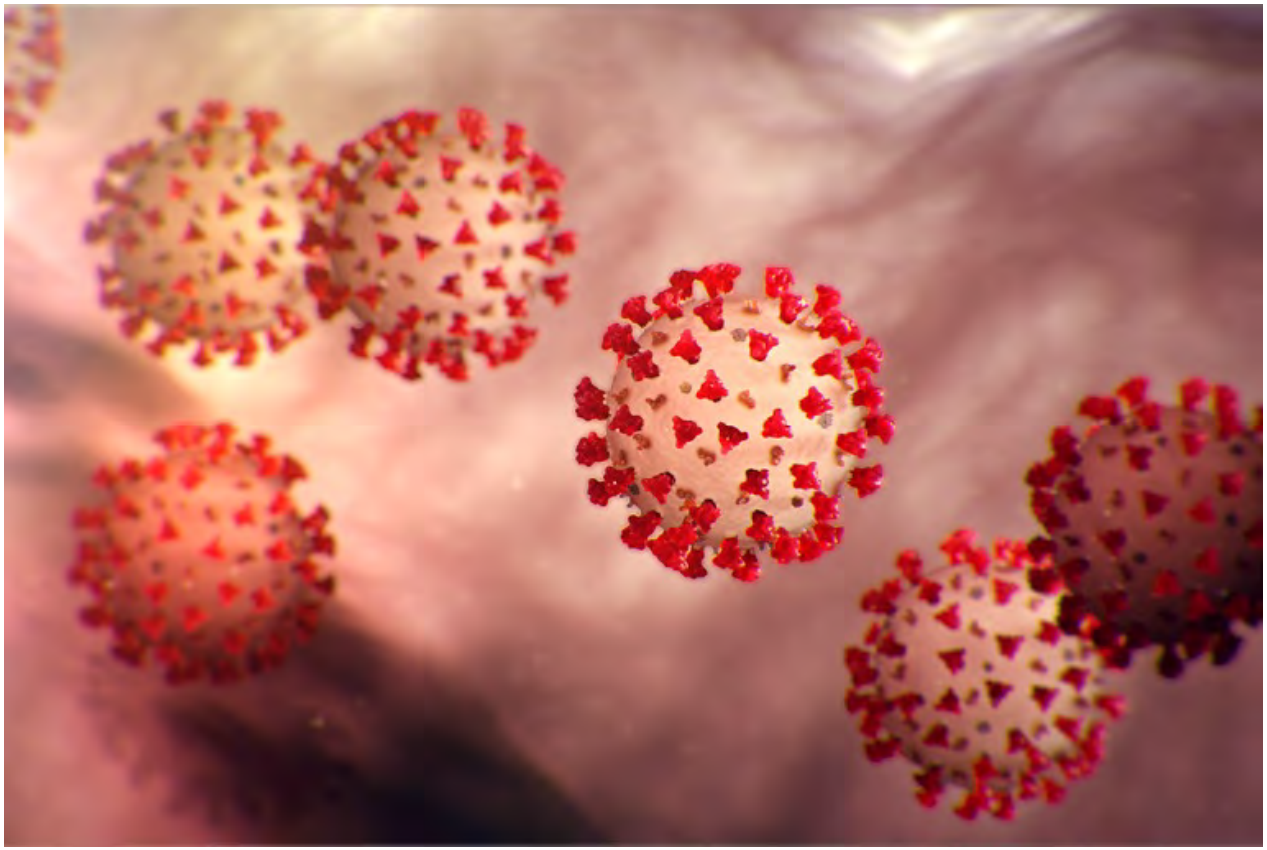
- In the modern era, CHIs have been conducted consistent with recognized ethical and regulatory requirements
- Yet until recently, there has been relatively little specific ethical analysis

The Ethical Challenge of Infection-Inducing Challenge Experiments

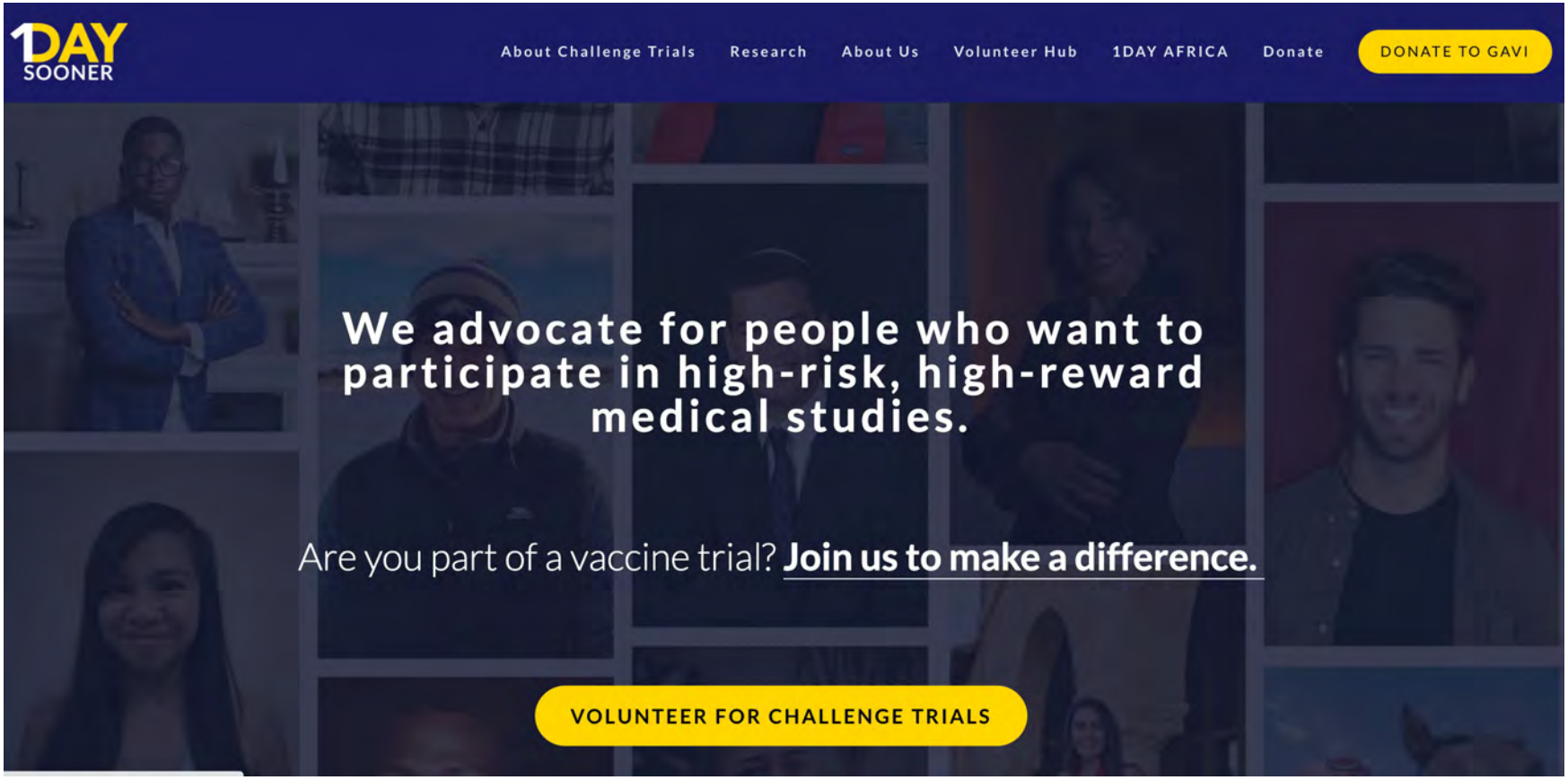
Franklin G. Miller and Christine Grady
Department of Clinical Bioethics, National Institutes of Health, Bethesda, Maryland

How should we think about the ethics of controlled human infection studies?

Case study: SARS-CoV-2 CHIs



Advocacy


1DAY SOONER
About Challenge Trials
Research
About Us
Volunteer Hub
1DAY AFRICA
Donate
DONATE TO GAVI
We advocate for people who want to participate in high-risk, high-reward medical studies.
Are you part of a vaccine trial? Join us to make a difference.
VOLUNTEER FOR CHALLENGE TRIALS

Public debate

NEWS

Why have 14,000 people volunteered to be infected with coronavirus?

SHARE THIS –

CORONAVIRUS

Why have 14,000 people volunteered to be infected with coronavirus?

They want to take part in a "human challenge trial," an ethically controversial vaccine test that infects people with a virus doesn't yet have a cure.

knowable MAGAZINE
from ANNUAL REVIEWS

HEALTH & DISEASE

First, do harm

FIRST OPINION

Human challenge trials with live coronavirus aren't the answer to a Covid-19 vaccine

By Michael Rosenblatt June 23, 2020

Reprints

Bioethics commentary

The Journal of Infectious Diseases

MAJOR ARTICLE

Human Challenge Studies to Accelerate Coronavirus Vaccine Licensure

Nir Eyal,[1,2,3] Marc Lipsitch,[4,5] and Peter G. Smith[5]

[1]Center for Population-Level Bioethics, Rutgers University, New Brunswick, New Jersey, USA, [2]Department of Philosophy, Rutgers University, New Brunswick, New Jersey, USA, [3]Department of Health Behavior, Society and Policy, Rutgers School of Public Health, Piscataway, New Jersey, USA, [4]Center for Communicable Disease Dynamics, Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, USA, [5]Department of Immunology and Infectious Diseases, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, USA, and [6]MRC Tropical Epidemiology Group, London School of Hygiene & Tropical Medicine, London, UK

Controlled human challenge trials of SARS-CoV-2 vaccine candidates could accelerate the testing and potential rollout of efficacious vaccines. By replacing conventional phase 3 testing of vaccine candidates, such trials may subtract many months from the licensure process, making efficacious vaccines available more quickly. Obviously, challenging volunteers with this live virus risks inducing severe disease and possibly even death. However, we argue that such studies, by accelerating vaccine evaluation, could reduce the global burden of coronavirus-related mortality and morbidity. Volunteers in such studies could autonomously authorize the risks to themselves, and their *net* risk could be acceptable if participants comprise healthy young adults, who are at relatively low risk of serious disease following natural infection, if they have a high baseline risk of natural infection, and if during the trial they receive frequent monitoring and, following any infection, the best available care.

Keywords. coronavirus; vaccines; human challenge studies; randomized controlled trials; risk-taking; ethics.

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/v

Extraordinary diseases require extraordinary solutions

For now, it's unethical to use human challenge studies for SARS-CoV-2 vaccine development

Jeffrey P. Kahn[a,1], Leslie Meltzer Henry[a,b], Anna C. Mastroianni[c,d], Wilbur H. Chen[e], and Ruth Macklin[f]

The prospect of a widely available severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine is an increasingly high priority for an effective response to the coronavirus disease 2019 (COVID-19) pandemic and an area of intense interest and attention for professionals, politicians, and the public alike. The understandable desire for

Typically, undertaking HCS in vaccine development requires that the disease for which a challenge would be introduced either has an available rescue therapy to treat those who become infected or the disease is known to be self-limiting. There is no rescue

Severe Acute Respiratory Syndrome Coronavirus 2 Human Challenge Trials: Too Risky, Too Soon

To the Editor—Eyal et al [1] have recently argued that researchers should consider conducting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) human challenge studies to hasten vaccine development. We have conducted (J. L.) and overseen (L. D.) human challenge studies and agree that they can be useful in developing anti-infective agents. We also agree that adults

Technical and ethical guidance

WHO R&D Blueprint

novel Coronavirus

WHO Advisory Group Tasked to Consider the Feasibility, Potential Value and Limitations of Establishing a Closely-Monitored Challenge Model of Experimental COVID-19 in Healthy Young Adult Volunteers

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

WHO Report

Key criteria for the ethical acceptability of COVID-19 human challenge studies: Report of a WHO Working Group

Euzebiusz Jamrozik [a,b,c], Katherine Littler [d], Susan Bull [a], Claudia Emerson [e], Gagandeep Kang [f], Melissa Kapulu [g,h], Elena Rey [i,o], Carla Saenz [j], Seema Shah [k], Peter G Smith [l], Ross Upshur [m], Charles Weijer [n], Michael J Selgelid [b], for the WHO Working Group for Guidance on Human Challenge Studies in COVID-19

[a] The Ethox Centre & Wellcome Centre for Ethics and the Humanities, Nuffield Department of Population Health, University of Oxford, Oxford, Oxfordshire, UK
[b] Monash Bioethics Centre, Monash University, Clayton, Victoria, Australia
[c] Royal Melbourne Hospital Department of Medicine, University of Melbourne, Parkville, Victoria, Australia
[d] Global Health Ethics Unit, World Health Organization, Geneva, Switzerland
[e] Institute on Ethics & Policy for Innovation, Department of Philosophy, McMaster University, Hamilton, Ontario, Canada
[f] The Wellcome Trust Research Laboratory, Division of Gastrointestinal Sciences, Christian Medical College, Vellore, India
[g] KEMRI-Wellcome Trust Research Programme, Centre for Geographic Medicine Research-Coast, Kilifi, Kenya
[h] Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK
[i] Centro Internacional de Entrenamiento e Investigaciones Médicas - CIDEIM, Cali, Colombia
[j] Department of Health Systems and Services, Pan American Health Organization, USA
[k] Lurie Children's Hospital & Northwestern University Feinberg School of Medicine, Chicago, USA
[l] London School of Hygiene and Tropical Medicine, London, UK
[m] Division of Clinical Public Health, Dalla Lana School of Public Health, Toronto, Canada
[n] Departments of Medicine, Epidemiology & Biostatistics, and Philosophy, Western University, London, Canada
[o] Universidad Icesi, Cali, Colombia

SARS-CoV-2 CHI landscape

- NIH developed strains for SARS-CoV-2 CHIs and never used them
- Fauci: CHIs are “Plan C or D”

- UK government sponsored dose-finding SARS-CoV-2 CHIs with naïve and previously infected participants

- SARS-CoV-2 CHIs in preparation at University of Leiden

SARS-CoV-2 CHI in UK

- Dose-finding studies completed, but publication of results is pending


Perspective

SEPTEMBER 9, 2021

SARS-CoV-2 Human Challenge Studies — Establishing the Model during an Evolving Pandemic

Garth Rapeport, M.B., B.Ch., Emma Smith, Ph.D., Anthony Gilbert, M.B., B.Ch., Andrew Catchpole, D.Phil., Helen McShane, F.Med.Sci., and Christopher Chiu, B.M., B.Ch., Ph.D.


UK Research Ethics Committee's review of the global first SARS-CoV-2 human infection challenge studies

Hugh Davies, On behalf of the HRA Specialist Research Ethics Committee

Ethical foundation

- CHIs are not fundamentally different from other research
  - Aim to generate socially valuable knowledge
  - Expose participants to risks in its pursuit
  - Similar to phase I trials with healthy volunteers
- General ethical principles for research apply to CHIs

Miller F & Grady 2001; Bambery B et al. 2016;
Shah SK et al. 2017; Selgelid & Jamrozik 2018; Jamrozik & Selgelid 2019

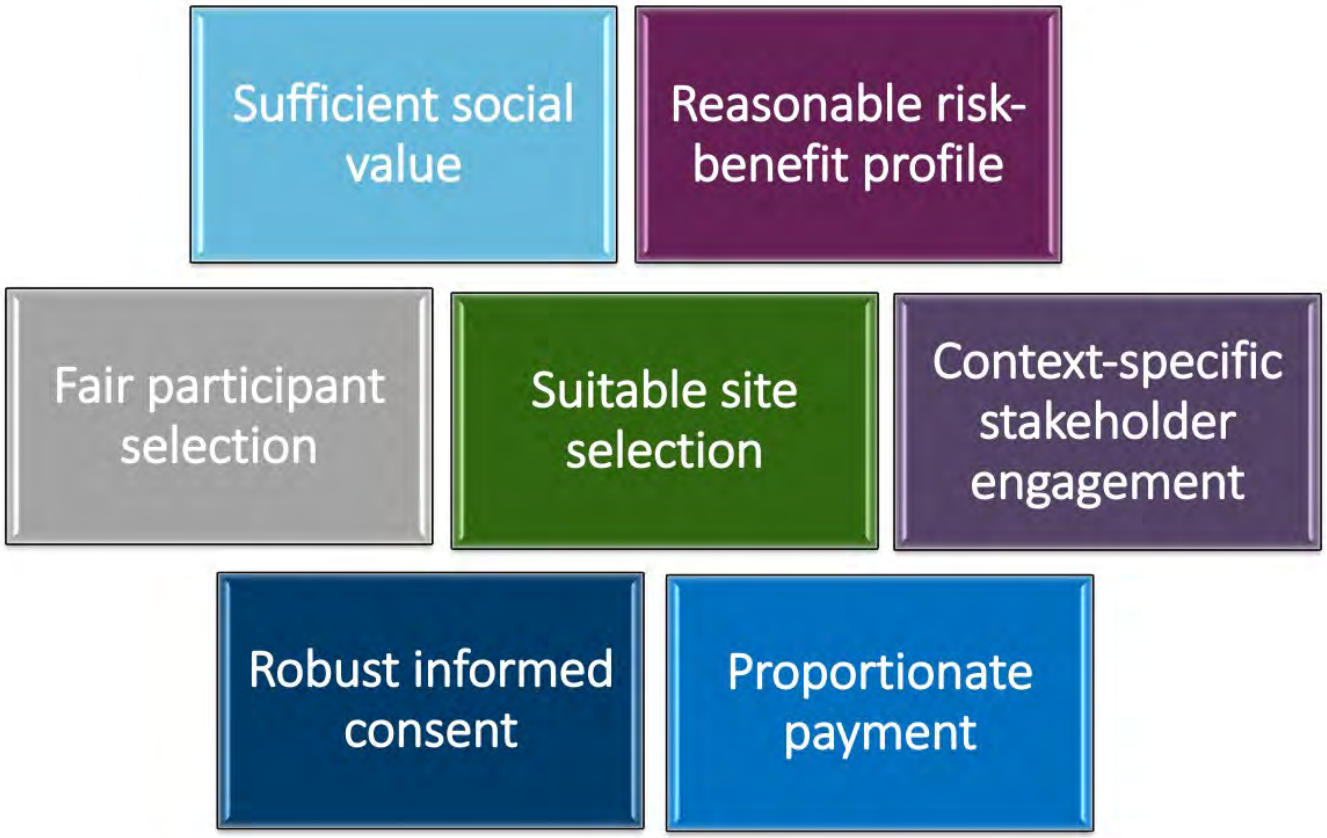
Specific ethical challenges

- CHIs raise a unique constellation of unresolved ethical challenges
  - E.g., judgments about social value, risks to third parties, upper risk limits, exclusion criteria
- Ethical analysis complicated by the fact that CHIs can be counterintuitive to the public and foster controversy or distrust

Shah & Rid (Eds.) 2020, Shah SK et al. 2020, Shah SK. et al *work in progress*

The Greenwall Foundation

Ethical considerations for CHIs



Shah & Rid (Eds.) 2020, Shah SK et al. 2020, Shah SK. et al *work in progress*

POLICY FORUM

RESEARCH ETHICS: COVID-19

Ethics of controlled human infection to address COVID-19

High social value is fundamental to justifying these studies

By Seema K. Shah, Franklin G. Miller, Thomas C. Darton, Devan Duenas, Claudia Emerson, Holly Fernandez Lynch, Euzebiusz Jamrozik, Nancy S. Jecker, Dorcas Kamuya, Melissa Kapulu, Jonathan Kimmelman, Douglas MacKay, Matthew J. Memoli, Sean C. Murphy, Ricardo Palacios, Thomas L. Richie, Meta Roestenberg, Abha Saxena, Katherine Saylor, Michael J. Selgelid, Vina Vaswani, Annette Rid

SUFFICIENT SOCIAL VALUE

CHIs have a long, complicated history. They have contributed to substantial improvements in clinical and public health practice, including the recent licensure of two vaccines (*5*), but also involved some unethical research (*3*). The first step in justifying SARS-CoV-2 CHIs, especially as they would involve major uncertainty and controversy, is to demonstrate their high

transparency and promote coordination. Research sponsors should lead by establishing and enforcing standards for rapid data collection, dissemination, and sharing that permit aggregation of results across CHIs. Medical journals should require compliance with these standards before accepting manuscripts. Regulatory agencies should collaborate with sponsors, researchers, and policy-makers to define how CHI data will inform or modify larger trials, licensure, and manufacturing. Finally, sponsors and governments should implement mechanisms to ensure widespread, equitable access to proven products whose development was accelerated by SARS-CoV-2 CHIs. Such wide-ranging stakeholder coordination is difficult but important to demonstrate high social value. Though not achieved for proposed Zika virus CHIs during the 2015–2016 epidemic, it did occur later (*6*).

SARS-CoV-2 CHIs could have high social value in other ways, and individual CHIs could address multiple scientific questions,

No major substantive differences with WHO ethical guidance

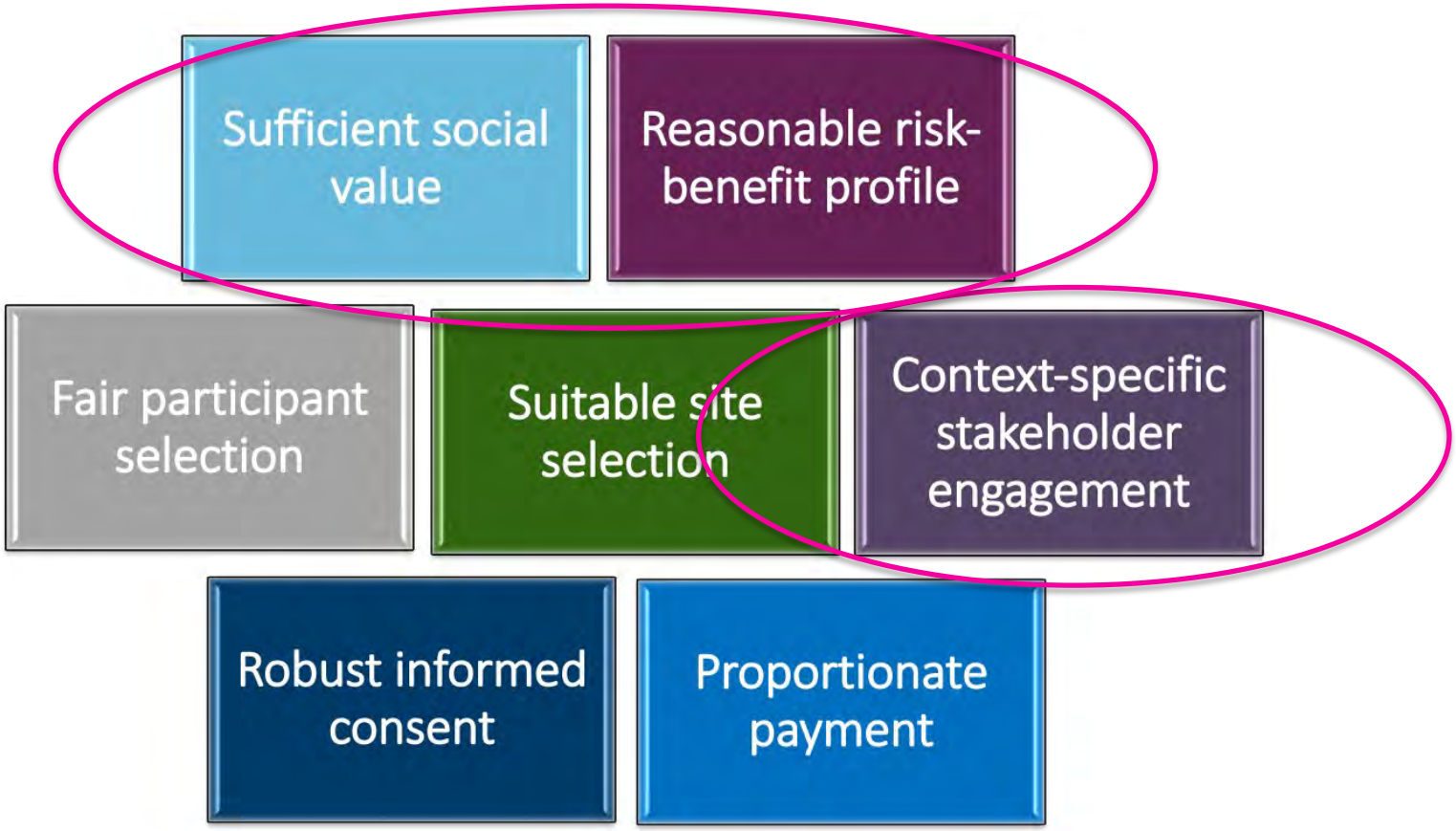
No major substantive differences

WHO Key Criteria	***Shah et al.* ethical framework**
Terminology • Human challenge studies, controlled human infection studies, human infection challenge studies	**Terminology** • Controlled Human Infection studies (CHIs)
8 ethical considerations • Focus on *scientific justification* • Does not address payment • Stakeholder coordination and community consultation • Expert review	**7 ethical considerations** • Focus on *social value* • Addresses payment • Stakeholder engagement (covers coordination & consultation) • Independent review assumed
Longer and more detailed	**Subject to 2000 word limit**

Our stance (in May 2020)

- "… we agree on the ethical conditions for conducting SARS-CoV-2 CHIs (see the table). We differ on whether the social value of such CHIs is sufficient to justify the risks at present, given uncertainty about both in a rapidly evolving situation; yet we see none of our disagreements as insurmountable."

Ethical considerations for CHIs



Shah & Rid (Eds.) 2020, Shah SK et al. 2020, Shah SK. et al *work in progress*

Sufficient social value

- High risks and potential for controversy around SARS-CoV-2 CHIs require rigorous social value judgment (i.e., magnitude, distribution and likelihood of health benefits)
  - Contribution relative to other research
  - Coordination of stakeholders to use CHI data
  - Path from CHIs to health benefits
  - Access to proven interventions

Sufficient social value

Value of SARS-CoV-2 CHIs

- Social value mainly seen in potential to accelerate *vaccine development*
- Though could be valuable in other ways
  - Accelerate development of treatments
  - Learn about mechanisms of infection and disease that help guide clinical practice and health policy
  - Etc.

Sufficient social value

Faster vaccine development?

1) Replace vaccine efficacy testing (Eyal et al 2020)
   - Claim: can save millions of people if safe and effective vaccine is identified months earlier than using alternative research methods

Timing of CHIs

- Establishing a CHI model takes *at least* 4-12 months
  - Characterize potential challenge strains
  - Identify, isolate and culture suitable strain
  - Establish CHI model in animals and humans (e.g., identify appropriate dose)
- Phase 2/3 trials are faster to establish
  - Though transmission can be difficult to predict

Darton et al 2015

Limitations of CHI data

- Data from CHIs generally play a supportive role in regulatory approval
  - Data not generalizeable (e.g., SARS-CoV-2 CHIs involve young, healthy adults)
  - Safety data not robust due to small number of participants
- Perception that approval was rushed can fuel vaccine hesitancy

Sufficient social value

Faster vaccine development?

1) Replace vaccine efficacy testing (Eyal et al 2020)
2) Identify correlates of protection
   - Current correlates are not perfectly accurate (e.g., antibody titers) or complex and costly to measure (e.g., long-term immune response)
   - More accurate, simpler and cheaper correlates could accelerate development of vaccines that meet global need

Sufficient social value

Faster vaccine development?

1) Replace vaccine efficacy testing (Eyal et al 2020)
2) Identify correlates of protection
3) Select most promising vaccine candidates
   - 127 in clinical development, 194 in preclinical development (WHO 2021)
   - SARS-CoV-2 CHIs could catalyze development of vaccines that meet global need

Sufficient social value

Value of CHIs in pandemics

- In a global pandemic of an emerging infectious disease, research moves at "warp speed"
- Because CHIs take time to establish, their social value can be difficult to predict

Reasonable risk-benefit profile

- Identify risks and potential benefits (if any)
- Recognize important uncertainties, especially in CHIs on emerging infectious diseases (e.g., mild and moderate symptoms, long-term complications from SARS-CoV-2)

Reasonable risk-benefit profile

Risks to participants

- Risks to participants should be minimized and below upper limit
  - Enroll young, healthy participants (e.g., QCovid® risk calculator used in UK)
  - Monitor closely, provide prompt treatment & compensate for research-related injury
  - No consensus on upper risk limit, but could analogize to other research or altruistic activities

Reasonable risk-benefit profile

Risks to participants

- Young, healthy people at lowest risk, though uncertainties remain and available treatments are limited
  - 18-44 yrs: 0.03% risk of death, 1.1% risk of hospitalization (Verity et al 2020)
  - <20 yrs: 0.001% risk of death, 0.2% risk of hospitalization in females (Salje et al 2020)
  - CHI: 0.0025% risk of death, 0.022% risk of hospitalization (Mannheim et al 2021)

Reasonable risk-benefit profile

Acceptable level of risk?

- Risks slightly higher than in phase I trials, other CHIs and altruistic activities

Table S1. Comparison of mortality risks in altruistic activities and daily life.

ACTIVITY	MORTALITY RISK
CLINICAL RESEARCH	
Malaria CHIs with healthy individuals (18-50 years)[1]	Not reported
Influenza CHIs with healthy individuals (18-49 years)[2]	0.0018%[§]
Phase 1 trials with healthy individuals (any age)[3]	<0.014%
SARS-CoV-2 CHIs with healthy individuals (20-29 years[4] and 20-44 years[5])	0.03-0.2%[§]
Phase I trials, typically with terminally ill cancer patients (≥18 years)[6]	0.5%
LIVING ORGAN DONATION	
Kidney (≥18 years)[7]	<0.03%
Liver (≥18 years)[8 9]	0.1-0.5%
DAILY LIFE	
Riskier car trip (any age)[10]	0.0002%
Influenza (>65 years, 2018-2019)[2]	0.05%
SARS CoV-2 infection in healthcare workers (age not specified)[11]	0.67%

[§]Likely upper mortality risk estimates because the available data report aggregate outcomes for healthy individuals and individuals with pre-existing conditions

Shah SK et al. 2020

Reasonable risk-benefit profile

Risks to third parties

- Risks to third parties not enrolled in the research should be low
  - Confine participants in research facility for as long as needed (>2 wks minimum)
  - Minimize risk of withdrawal with appropriate participant selection and robust informed consent process
  - Coordinate with public health authorities

Context-specific stakeholder engagement

Public engagement

- Public engagement is key to avoid common misunderstandings about CHIs
- Misunderstandings could foster distrust in clinical research and/or public health measures (e.g., vaccination)--though depends on context
- Limited evidence to support either concerns or public acceptability of CHIs

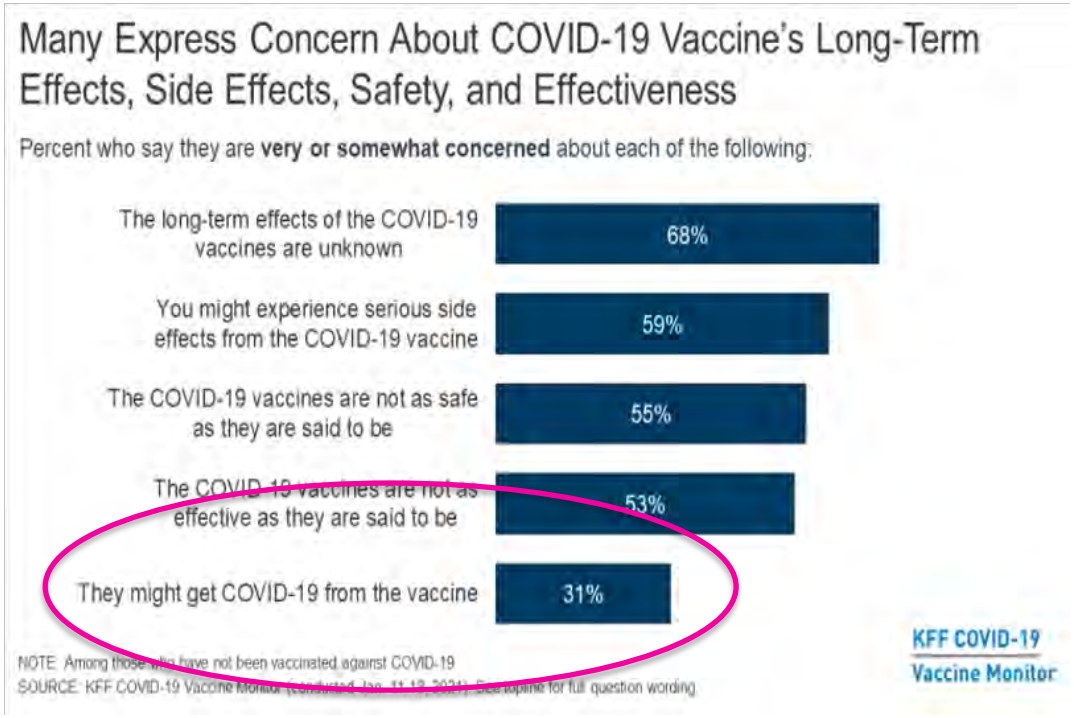
Context-specific stakeholder engagement

US context

- Public distrust of SARS-CoV-2 vaccination

More than Tuskegee: Understanding Mistrust about Research Participation

Darcell P. Scharff, PhD
Katherine J. Mathews, MD, MPH, MBA
Pamela Jackson, RN, BSN, MA
Jonathan Hoffsuemmer, MPH
Emeobong Martin, MPH
Dorothy Edwards, PhD



Take-aways

- CHIs are not ethically distinct from other types of research
- However, CHIs have a complex history and raise a unique constellation of unresolved ethical challenges
- CHIs can also be counterintuitive and might foster public controversy or distrust

Take-aways ctd.

- SARS-CoV-2 CHIs were rightly controversial, but they may have produced considerable value—stay tuned
- CHIs can be ethically acceptable and useful with careful review and planning, as well as understanding of their social value