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Ethical Considerations for Human Challenge Studies

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Accelerating vaccine development in the UK Safely: enhancing Human Challenges Studies to combat infectious diseases

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Consider

- Human challenge studies are different from other non-therapeutic research
- It is difficult for current ethical guidelines to justify challenge studies → *primum non nocere*

Consider further

- Human challenge studies date back to the 18th century
- 22,000 volunteers have participated in well-regulated human challenges studies in the last 70 years
- Nearly 60 different challenge strains used in studies for vector borne, respiratory and enteric diseases
- Human challenge studies have played a pivotal role in the development of vaccines (e.g. cholera, typhoid), including providing the primary evidence of effectiveness for a new cholera vaccine licensed in the US (Vaxchora).

[Gordon et al, 2017]

Significant policy gaps

- Policy gaps and variation in the regulatory environment
  - *"In the UK, there are few guidelines for setting up new human challenge studies and a more structured pathway would be useful."*
  - *"human challenge studies have a more complex regulatory requirement in the US than the European Union, including the UK"*
  - *"The reasons why human challenges studies are not carried out in Low and Middle Income Countries (LMIC) include technical, clinical,* ***ethical and regulatory issues****, as well as cultural norms."*

    [Gordon et al, 2017]

- Ethics committees have little guidance to conduct evaluation of human challenge studies, e.g. assessment of risk and benefit

Gaps in ethics guidance

- From the report (2017) *Ethical Considerations for Zika Virus Human Challenge Trials*:

  - *"the literature provides limited guidance on the ethics of conducting challenge studies when the medical consequences of infection are more uncertain."*
  - *"the ethics literature provides very little specificity on the reasonable limits on the net risk to research volunteers"*
  - *"the question of how to address risks to third parties is unsettled in prior literature"*

On risk

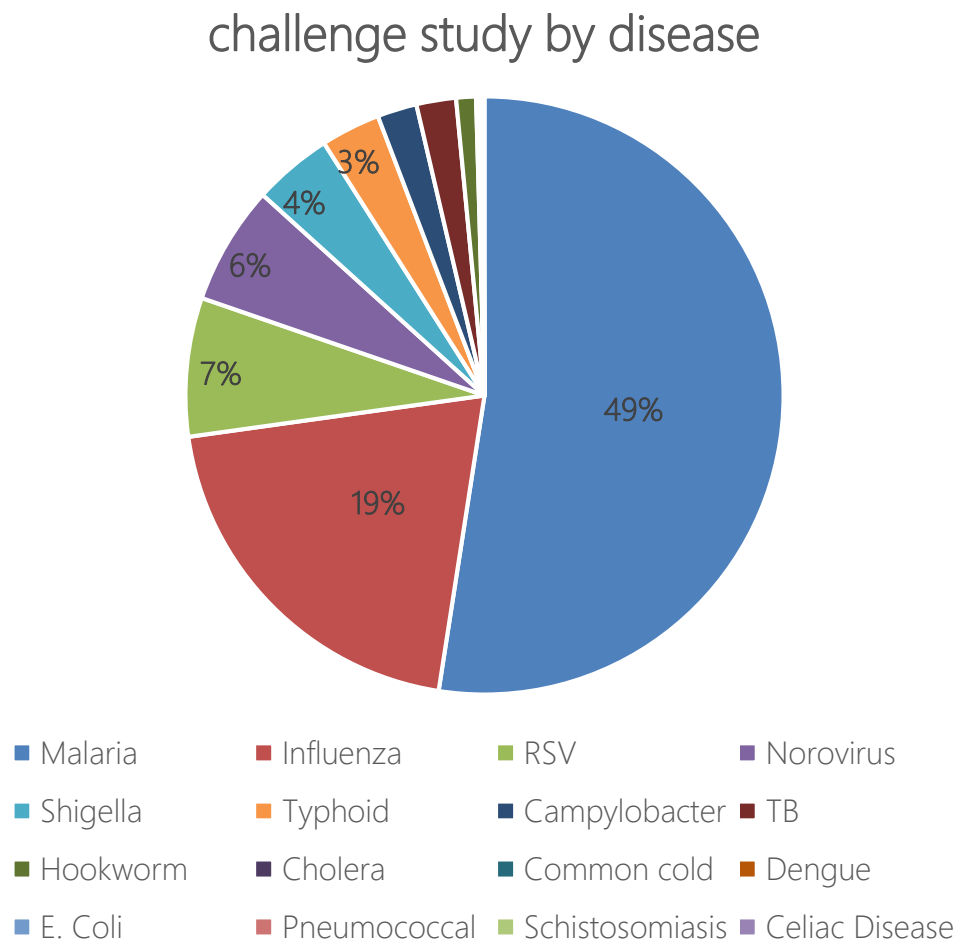
- Risk (even elevated risk) does not make a study unethical
- What is the acceptable threshold for risk?
  - Minimal risk (Hope & McMillan, 2004)
  - Risk assumed by volunteer firefighters (London, 2007)
  - Risk assumed by kidney donors (Miller and Joffe, 2009)
  - Risk greater than 1% chance of death, permanent disability or severe injury (Resnick, 2012)
  - Risk cannot be so great as to expose volunteers to irreversible, incurable or possible fatal infections (Bamberry et al, 2016)
- In the absence of challenge studies, more people would be placed at risk of exposure to ineffective vaccines and potentially harmed → *challenge studies might be ethically required, and not merely ethically permissible* (Bamberry et al, 2016)

On justification, and risk/benefit balance

- Greater ethical justification, and risk/benefit balance to conduct human challenge studies in disease endemic settings
  - Comparative risk of participation is lower than non-endemic settings
  - Research is relevant to the local community
  - Provision of optimal care in controlled environment
  - Subsequent immunity to wild-type infection (in case of challenge studies testing vaccines)
  - Build local capacity: in clinical facilities; laboratory diagnostics; experimental medicine; clinical governance and regulatory confidence
  - Accelerate or streamline vaccine/treatment relevant to the national health burden

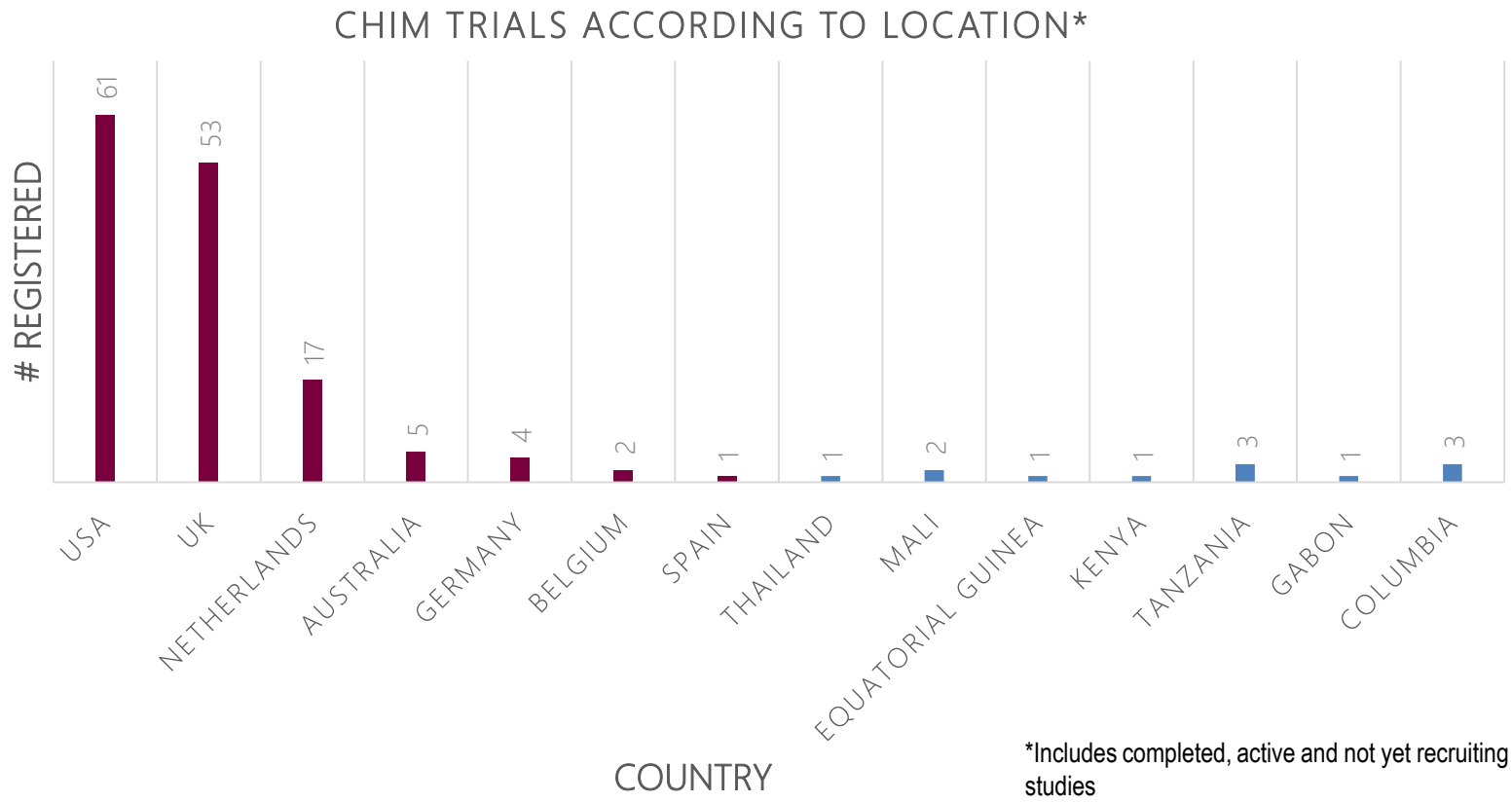
Registered human challenge studies on clinicaltrials.gov

155 Trials	
76	Malaria
30	Influenza
12	RSV
9	Norovirus
6	Shigella
5	Typhoid
4	Campylobacter
4	TB
2	Hookworm
1	Cholera, Common Cold, Dengue, E. Coli, Pneumococcal, Schistosomiasis, Celiac Disease



Where are human challenges studies conducted?

- In a sample of 155 human challenges studies registered on clinicaltrials.gov: 12 (~7%) were located in an LMIC



*Includes completed, active and not yet recruiting studies

Challenges of conducting human challenge studies in LMICs

PRACTICAL	ETHICAL
Infrastructure and clinical facilities may not be ready, specifically to monitor and support adverse events (e.g. on intensive care units)	Fair recruitment and inclusion of healthy volunteers
Poor community hygiene and sanitation infrastructure could prevent effective control measures	Inherent vulnerabilities may impact fully informed consent in the local context (e.g. language, cultural family/group consent)
Production of challenge strain locally may have QA issues but "international" strains may be less relevant	Consensus on appropriate compensation for monetary and opportunity costs is lacking

[Gordon et al, 2017]

Expanded framework for ethical evaluation of human challenge studies

Ethical Issue	Sample questions and considerations
1. Rationale for CHIM	• What is the justification for using infection-inducing challenge model? • Have alternative methods been considered?
2. Risks	• Is there possibility of serious risk or harm? • Are there potential risks of transmission to others?
3. Discomforts	• How will discomforts be minimized?
4. Vulnerable subjects	• How will vulnerability be assessed?
5. Informed consent	• Is there adequate information about purpose, procedures, (including isolation, if relevant), risks, discomforts, lack of benefit?
6. Financial compensation	• Is it commensurate with the time and effort required? • Does it constitute undue inducement?
7. Right to withdraw from research	• Is the time and method of isolation limited to that necessary to protect others? (Miller & Grady, 2001)
8. Independent review	• If new challenge model, has it been reviewed and approved by 2 independent experts in infectious diseases?
9. Publicly available rationale	• Has a clear publicly accessible rationale for the study been made available, explaining the nature of the benefits and risks, the inadequacy of alternatives, and the adequacy of the measures to protect participants and the community from harm?
10. Protection of the public	• Are there measures in place to protect the community from spread outside the research setting?
11. New model of compensation for harm	• Compensation for risk (ex ante) versus compensation for harm (ex poste) (Bamberry et al, 2016)

Data gap

- *"Estimates of severe complication rates from FDA-regulated first-in-human trials are not available"*
- *"Many of the published influenza challenge studies, however, did not indicate whether adverse events occurred."*
- *"it is also unclear whether the data about the risks to volunteers in human challenge studies are comprehensive"*
- *" A key aim is to share data and information gained, aggregating data from multiple studies to enhance the information and interpretation."*

[Shah et al, 2017; Sheets et al, 2016]

Further expansion of the expanded framework for ethical evaluation of human challenge studies*

Ethical Issue	Sample Considerations
12. Knowledge and Data Sharing	• To promote collaboration and strengthen capacity (scientific, regulatory, ethics), mitigate risks and increase benefits • Build a 'community of practice', and develop best practices
13. Community Engagement**	• A critical adjunct to the informed consent process • Essential for trust building: participant communities, public, policy and decision-makers (**Zika Virus Human Challenge Research Writing Committee, 2017)
14. Governance	• SOPs, Standardized Materials, and Principles to set standards in the field to promote high scientific and ethical practices

[*Emerson & Cullen, unpublished manuscript, 2018]

Building a 'Community of Practice'

Guiding Principles for Funders and Supporters of Human Challenge Studies *(forthcoming 2018)*

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