Enteric Pathogen Safety Considerations in Human Challenge Trials

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Controlled Human Infection Model Studies Use in Foodborne Pathogens

- Bacteria: cholera, shigellosis, salmonellosis (typhoid and non-typhoidal), *Campylobacter jejuni*, diarrheagenic *E. coli, Helicobacter pylori*
- Viruses: Norovirus, Rotavirus
- Parasites: *Giardia*, *Cryptosporidium*

Volunteer Experimental Infection Studies

Objectives

- Study pathogenesis
  - dose-response
  - virulence determinants
- Study immunology
  - IR type and kinetics
  - correlates of protection
- Vaccine efficacy

Generalized Methodology

- Apply control across the disease triangle
  - Host: selection criteria
  - Pathogen: specific strain, dose, virulence
  - Environment: delivery method
- Pre-assigned outcomes
- Randomized/blinded

Risk mitigation at multiple steps

Meeting report

Human challenge trials in vaccine development: Strasbourg, September 29 – October 1, 2014

Dr. Karen Kotloff (CVD, Univ MD) – Enteric Bacteria HCT

What makes an enteric pathogen amenable for HCT development and utility (may vary by purpose)?

- Well-characterized disease
- Known mode of transmission
- Well-defined study endpoints
- Knowledge of expected attack rate
- Effective treatment of symptoms with antimicrobials and replacement fluids/electrolytes
- Tolerable discomfort

Enteric Disease HCT: Risk Mitigation

What is expected?

- Short-term illness
- Moderate to severe illness
- Precise clinical endpoints with predetermined therapy provided once endpoint met
- Capable of prompt and straightforward clinical management leading to rapid return to pre-challenge health
- No persistent illness or morbidity
- No transmission risk beyond inoculation for other subjects, their contacts, or staff

Risk Mitigation Issues for Consideration: Microbial strain selection

- Initial selection from clinical case
  - Susceptible to commonly used antibiotics for the specific pathogen
  - Absence of known virulence characteristics associated with severe clinical consequences
- Examples – specific risks to consider
  - *H. pylori* - Gastric cancer association with CagA positivity (Cag$^-$ challenge strains)
  - *C. jejuni* – Guillain-Barré syndrome
  - *S. flexneri* - Shiga toxin negative
  - Norovirus - Challenge virus derived from donor stool filtrate—donor followed up for >10 years (syphilis, HCV, HBV, HIV, HTLV)

Darton et al. Design, recruitment, and microbiological considerations in human challenge studies. Lancet ID 2015;15: 840–51

Campylobacter jejuni: Challenge strain selection

- Guillain-Barré Syndrome & *Campylobacter*
  - Autoimmune-mediated disorder of peripheral nervous system
  - Estimated 30% of GBS cases associated with antecedent Campylobacter infection (past 2-4 weeks)
  - Outer LOS core of most *C. jejuni* strains contain sialic acid that may mimic human gangliosides
- Strategy to select current challenge strain
  - Select strain that lacks sialic acid naturally
  - Search criteria
    - Obtain clinical isolate from an individual with a clinical illness consistent with *Campylobacter* infection.
    - No copathogens identified during the microbiological evaluation.
    - Susceptible to nalidixic acid, fluoroquinolones, and erythromycin.
    - Negative PCR screen for Parker LOS class A, B, or C previously demonstrated to be indicative of ganglioside mimicry

Risk Mitigation Issues for Consideration: Subject eligibility

- Healthy adults (age range)
- Includes consideration of past medical and surgical history (not currently active problems)
- May need to consider family history (such as rheumatologic and/or autoimmune disease)
- Screening – comprehensive medical history, review of systems, known allergies, physical examination, and laboratory tests (general or specific based on documented risk associations – such as HLA-B27)
- Pregnancy testing
- Assessment of likely susceptibility to challenge organism based on prior exposures (history ± immunological tests)

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Evaluation of the Clinical and Microbiological Response to *Salmonella* Paratyphi A Infection in the First Paratyphoid Human Challenge Model

CID 2017:64 (15 April)

Hazel C. Dobinson,[1,a] Malick M. Gibani,[1,a] Claire Jones,[1,a] Helena B. Thomaides-Brears,[1] Merryn Voysey,[1,2] Thomas C. Darton,[1] Claire S. Waddington,[1] Danielle Campbell,[1] Iain Milligan,[1] Liqing Zhou,[1] Sonu Shrestha,[1] Simon A. Kerridge,[1] Anna Peters,[1] Zoe Stevens,[1] Audino Podda,[3] Laura B. Martin,[3] Flavia D'Alessio,[4] Duy Pham Thanh,[5] Buddha Basnyat,[6] Stephen Baker,[5,7,8] Brian Angus,[9] Myron M. Levine,[10] Christoph J. Blohmke,[1] and Andrew J. Pollard[1]

Selected eligibility criteria

- Required notifications
  - Their General Practitioner
  - Public Health England
  - Their employer (if employed in health or social care)
  - Close household contacts (also offering them voluntary stool culture screening)
- Continuous availability/Connectivity
  - 24-hour contact (by mobile phone) with study staff during the four weeks post challenge until antibiotic completion
  - internet access to allow completion of the eDiary and real-time safety monitoring

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Selected eligibility criteria

- Unique exclusions based on complication or transmission risk
  - Presence of implants or prosthesis
  - Full-time, part-time or voluntary occupations involving:
    - Direct contact with young children (pre-school, nursery or age< 2 years)
    - Highly susceptible persons in whom typhoid infection would have particularly serious consequences (unless willing not to work during at-risk period)
    - Commercial food handling
  - Close household contact with children (< 2 years) and/or immunocompromised individuals
  - Biliary tract disease, including biliary colic, asymptomatic gallstones or previous cholecystectomy (including RUQ ultrasound)

Risk Mitigation Issues for Consideration: Clinical monitoring

- Location: Hospital versus ambulatory
- What to monitor and how frequent?
  - Vital signs, solicited and unsolicited symptoms, targeted exam
  - Scheduled (often at least twice daily) and ad hoc
- Phases
  - Pre-inoculation
  - Post-inoculation/Pre-treatment
  - Treatment
  - Clinical resolution/ward release (if in hospital)
  - Post-symptom resolution/microbial eradication
- Independent oversight (such as independent safety monitor, DMSB)

Phase 3 Cholera Vaccine Efficacy Following Challenge With *Vibrio Cholerae:* Clinical management

- Definition of Diarrhea:
  - Passage of ≥2 loose stools (grade 3–5) over a 48-hour period ≥200 mL or a single loose stool ≥300 mL
  - Moderate or severe diarrhea was defined as the passage of at least 3.0 L or 5.0 L of loose stool, respectively
- Individuals who developed diarrhea were given glucose/electrolytes oral rehydration solution at a volume 1.5 times the diarrheal stool volume.
- Participants unable to ingest sufficient oral rehydration solution to maintain hydration were given intravenous Lactated Ringer's solution.
- Ciprofloxacin, 500 mg twice daily for 5 days, was **administered when a subject reached 5.0 L of cumulative diarrheal stool output** or **on day 4 post-challenge**, whichever occurred first.

Phase 2b *Shigella flexneri* 2a vaccine efficacy challenge study: clinical management

- **Shigellosis** is clinically defined as one of the following:
  - Severe diarrhea [≥6 loose (grade 3-5) stools within 24h or >800gr loose (grade 3-5) stools within 24h]
  - Moderate diarrhea [4 to 5 loose (grade 3-5) stools within 24h or 401-800gr loose (grade 3-5) stools within 24h] with fever or with one or more moderate constitutional or enteric symptom
  - Dysentery [≥ 2 loose (grade 3-5) stools with gross blood within any 24h (confirmed by hemoccult) and reportable constitutional symptoms]

- **Early antibiotic treatment** after challenge, may commence when **any** of the following criteria are identified and a study physician considers it to be warranted:
  - When volunteers met the primary endpoint (clinical definition of shigellosis)
  - Oral temperature ≥ 39°C
  - Any other reason warranting the early treatment in the physician's opinion

Clinical monitoring: Late events

- Surveillance for post-infectious sequelae (such as functional GI disorders, reactive arthritis/arthralgia, *Salmonella enterica* serovar Typhi chronic carriage)

Recrudescent *Campylobacter jejuni* Infection in an Immunocompetent Adult following Experimental Infection with a Well-Characterized Organism[▽†]

Shahida Baqar,[1,2] David R. Tribble,[1,2] Marya Carmolli,[3] Katrin Sadigh,[3] Frederic Poly,[1] Chad Porter,[1] Catherine J. Larsson,[3] Kristen K. Pierce,[3] Patricia Guerry,[1] Campylobacter Study Team,[1,2,3] Michael Darsley,[4] and Beth Kirkpatrick[3]*

CLINICAL AND VACCINE IMMUNOLOGY, Jan. 2010, p. 80–86

Risk Mitigation Issues for Consideration: Clinical decisions based on pre-defined endpoints

- Illness severity scales accompanied by specific therapy approaches (including early treatment)
- Threshold endpoint needed to prompt ‘early’ antimicrobial therapy (all are treated at some fixed time if not receiving early treatment) – considerations:
  - Clinically based on illness severity to prevent complications and alleviate intolerable symptoms – not controversial
  - Once primary endpoint met, is there rationale for delay in treatment? – not as clear
    - Critical consideration of defining the primary endpoint for vaccine efficacy evaluation
    - Moderate-severe illness (diarrhea) often used as a primary endpoint but significant variation in clinical severity across this binary threshold

Risk Mitigation Issues for Consideration: Research environment / Research staff

- Closed research ward ('Quarantine') versus clinic-based
- Infection control/hand hygiene - applies across all enteric infection HCTs; particular challenges in highly communicable agents (Shigella) plus ones with environmental persistence (Noro)
- Infectious waste disposal
- Staff training expertise (nursing and physicians)
- Availability of care and predetermined pathway for acute complications as well as post-infectious sequelae if relevant

Risk Mitigation Issues for Consideration: **Well-informed Volunteer**

- Cornerstone for all CHIM studies
- Informed consent is a process not a single event
  - Informed consent documents tend to be lengthy, confusing, and may ‘under-inform’ differentially across a range of prospective subjects
  - So, ICD is not enough
  - Addition of briefings, comprehension tests, repeat consents, time to ‘think about it’/talk to family/others
- Informed consent needed for close contacts if potential for transmission?

Conclusions

- Exposing a human subject to an enteric pathogen introduces several risks that must be thoroughly considered prior to proceeding with a HCT.
- Effective measures to mitigate risk must be in place for the HCT to be approved to proceed accompanied by sound scientific rationale.
- Enteric pathogen HCTs are almost always undertaken in an inpatient research facility during the inoculation (although very successful approach in UK Typhoid studies)
- Early monitoring and management phase with extended follow-up in an ambulatory setting with specific focus on pathogen-specific risks.