Advac 2023
Controlled Human Infectious Models
discussion - human challenge experience
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Some background information from the recent evolution on human challenge trials

IABS has organised over the last years several conferences on the topic and the reports of these meetings were published:

• Strasbourg 2014
  o [http://dx.doi.org/10.1016/j.biologicals.2015.10.003](http://dx.doi.org/10.1016/j.biologicals.2015.10.003)

• Washington 2017
  o [https://doi.org/10.1016/j.biologicals.2018.02.002](https://doi.org/10.1016/j.biologicals.2018.02.002)

• Langen 2019 (Quality of the challenge strain)
  o [https://doi.org/10.1016/j.biologicals.2020.04.005](https://doi.org/10.1016/j.biologicals.2020.04.005)

• Oxford 2020
  o [https://doi.org/10.1016/j.biologicals.2020.04.004](https://doi.org/10.1016/j.biologicals.2020.04.004)

• Webinar 2: Challenge models for COVID 19
  o [https://doi.org/10.1016/j.biologicals.2020.08.006](https://doi.org/10.1016/j.biologicals.2020.08.006)
Some background information from the recent evolution on human challenge trials (2)

IABS has organised over the last years several conferences on the topic and the reports of these meetings were published:

- **Webinar 5: White paper for quality of challenge strain**
  - [https://doi.org/10.1016/j.biologicals.2020.04.005](https://doi.org/10.1016/j.biologicals.2020.04.005)
- **Mombasa 2023: Fourth Controlled Human Infection Model (CHIM) Meeting – CHIMs in endemic countries, May 22-23, 2023**
  - Submitted for publication
- **Mombasa 2023: Fourth Controlled Human Infection Model (CHIM) Meeting, CHIM regulatory issues, May 24, 2023.**
  - Submitted for publication
- **Brussels 2023: Ethical Approval for Controlled Human Infectious Model Clinical Trial Protocols – a Workshop Report**
  - Submitted for publication
Challenges for Human challenge models

Primum non nocere - first, do no harm:

• Is it ethically acceptable to infect someone?

What if no treatment is available?

Influenza, Dengue, Zika, COVID19:...

⇒ Benefit – Risk balance

What is the right Challenge dose?

⇒ Do we know enough about the disease?

⇒ Available knowledge of influenza versus COVID-19?

Production of challenge strain, GMP or GMP light?

⇒ How to produce Schistozomiasis parasite for challenge following GMP if you need to produce them in snails?
Challenges for Human challenge models (2)

CHIM are challenging trials 😊

- **Early discussion with NRA** regulatory authorities = MUST
- **Early discussion with responsible Ethical authorities (EC)** = MUST

Educational program is needed:

- Most regulators when confronted with first CHIM will say: no thank you.
- E.g. Summer 2023, Belgian company introduces CHIM Flu trial to Belgian NRA*:
  - The EC** gave a list of comments:
    - This is illegal
    - This is unethical
    But no further motivation…

* National Regulatory Authority
** Ethics Committee
Challenges for Human challenge models (3)

And what about children?

• Most paediatricians will tell you: No way!
• Is it ethical?
  – In a “normal” efficacy trial (RTS/S) of 16,000 children, a significant number of children will die in the control group due to malaria:

<table>
<thead>
<tr>
<th>Time period</th>
<th>Outcome</th>
<th>R3R+R3C</th>
<th>R3R</th>
<th>R3C</th>
<th>C3C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>n</td>
<td>N</td>
<td>n</td>
</tr>
<tr>
<td>M0-M20</td>
<td>Died</td>
<td>205</td>
<td>6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M0-M20</td>
<td>Survived with sequelae</td>
<td>205</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M0-M20</td>
<td>Survived without sequelae</td>
<td>205</td>
<td>199</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M21-SE</td>
<td>Died</td>
<td>-</td>
<td>-</td>
<td>76</td>
<td>3</td>
</tr>
<tr>
<td>M21-SE</td>
<td>Survived with sequelae</td>
<td>-</td>
<td>-</td>
<td>76</td>
<td>1</td>
</tr>
<tr>
<td>M21-SE</td>
<td>Survived without sequelae</td>
<td>-</td>
<td>-</td>
<td>76</td>
<td>72</td>
</tr>
</tbody>
</table>

http://dx.doi.org/10.1016/S0140-6736(15)60721-8
And what about children?

• Most paediatricians will tell you: No way!

• Is it ethical?
  – In a “normal” efficacy trial (RTS/S) of 16,000 children, 80 children will die in the control group due to malaria
  – In a challenge trial of 200 children, no children will die, as they will be diagnosed and treated even before they are symptomatic

• Children cannot give “informed consent”?
  – The foetus cannot either: and studies in pregnancy are ethical (since a few years 😊)
    Mam or dad or both can give consent if needed...
  – Children (not infants) from a certain age can give consent
Is there a need for human challenge trials

2 reasons:

1) **Proof of Concept**
   - In early development it is nice to see whether the new product works
   - To convince investors it might be a good idea to have CHIM data available
     - Small trial in a 20/20 active versus placebo setting
     - These are observational trials, although controlled (placebo), statistics are not easy...
Is there a need for human challenge trials (2)

2 reasons:

2) Regulatory

- In case field trials are not possible:
  - Pandemic/epidemic
  - Rare diseases
- A large, well-performed CHIM could replace a field trial

But are the regulators ready to accept CHIM trial data instead of a field trial?
Is there a need for human challenge trials (3)

2 reasons:

2) Regulatory

Major pitfall of CHIM: extrapolation of data:

- CHIM is a highly controlled CTA: how can you extrapolate these data to real world situation?
- Is the in vitro “infection” comparable with real world infection?
  - Concerning the route
  - The dose
- Is the strain comparable with the circulating strain?
- Cross protection?
- If you have 4 different strains (e.g. Flu) can you extrapolate the CHIM data from one strain to the three others?
Is there a need for human challenge trials (4)

2 reasons:

2) Regulatory

Other pitfall of CHIM: production of the challenge strain

• First question GMP or not:
  – Discussion is ongoing, however most Q-experts are pragmatic: GMP-like (light)
  – If possible, yes GMP (COVID-19, influenza virus, …)
  – But if not possible (Schistosomiasis, hookworm, …) document everything

• Be aware of the timelines:
  – To find a production capacity that is able and willing to produce these strains
  – Setting up a production process: 6-9 months
  – In case of a pandemic,…
Is there a need for human challenge trials (4)

2 reasons:

2) Regulatory

Other pitfall of CHIM: how to execute the cHIM trial

• Deliberate release or containment:
  – Containment: healthy volunteers need to stay 24h-48h-1 week-28 days in a closed facility
    • Bio Safety Level (BSL 2 – 3) facility
      – Access to a BSL3 facility ≠ evident
    • Acceptability???
      – Deliberate Release: healthy volunteer can go home, same day

• These measures have to be discussed with the health authorities of the country where the CHIM will be executed
Is there a need for human challenge trials (5)

One precedent: Vaxchora:

- **SmPC:**
  
  Each dose of vaccine contains 4 x 10⁸ to 2 x 10⁹ viable cells of *V. cholerae* live, attenuated strain CVD 103-HgR1.

  1 Produced by recombinant DNA technology.

  Vaxchora is indicated for active immunisation against disease caused by *Vibrio cholerae* serogroup O1 in adults and children aged 2 years and older.

  This vaccine should be used in accordance with official recommendations.


  Title: A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Efficacy Trial of a Single Dose of Live Oral Cholera Vaccine Candidate, PXVX0200 CVD 103-HgR Strain, in Preventing Cholera following Challenge with *Vibrio cholerae* O1 El Tor Inaba 10 Days or 3 Months after Vaccination
Is there a need for human challenge trials (6)

But are the regulators ready to accept CHIM trial data instead of a field trial?

The IABS Mombasa meeting gave a full day discussion with regulators (the discussion was led by Marco Cavaleri (EMA) and David Kaslow (US-FDA))

• Idea was not rejected
• **Case by case**
• Easiness of the extrapolation of the data
• Additional large safety database is a must (>3000 individuals exposure)
• And last but not least, the need for large:
  – **PASS**: post Authorisation Safety Studies
  – **PAES**: post Authorisation Effectiveness Studies
Is there a need for human challenge trials (7)

But are the regulators ready to accept CHIM trial data instead of a field trial?

Another example influenza

EMA Influenza guidance:

In principle if a new vaccine for prevention of seasonal influenza is developed that does not have appropriate comparators already authorised or reviewed by EU competent regulatory authorities (e.g. whole virion vaccines, recombinant antigen vaccines), demonstration of efficacy against relevant clinical outcomes in appropriate populations would be required to support authorisation. Applicants are recommended to discuss alternative strategies with competent regulatory authorities during the early stages of clinical development, for example to discuss the possibility of demonstrating efficacy in some age and population sub-groups and extrapolating to others based on immune response data.

Is there a need for human challenge trials (8)

But are the regulators ready to accept CHIM trial data instead of a field trial?

Another example influenza

Are field trials (PCR ILI outcome) for influenza still feasible?

• Risk of dis-match of the WHO strain
• Risk of pandemic strain
• Risk of “poor influenza” season:
  – Learnings from CoVID-19: 1,5m distance; better ventilation of premises; alcohol gel, masks, …
• Acceptability of immune bridging in the absence of a Correlate of Protection/Surrogate of protection
  – Comparability of Ab titres
  – Affinity and avidity
Some examples of Human challenge models

Challenges with live attenuated vaccines:

• Polio - Rota

Established models:

Malaria:
⇒ Treatable disease
⇒ Controlled model was used and published

Cholera
⇒ Treatable disease
⇒ Controlled model was used for registration: Vaxchora/Dukoral

Influenza
⇒ Controlled model was used and published
**Some examples of Human challenge models**

**Under development (but some have already been used)**

- *Streptococcus pneumonia*
- *Dengue*
- *Shigella*
- *Covid-19*
- *Salmonella*
- *Zika*
- *Hookworm*
- *ETEC*
- *Schistosomiasis*
- *Noro*
- *Leishmaniosis*
- *Campilobacter*

... 

**Interesting publication with a nice overview (2018):**

**Meta Roestenberg et al.:**

<table>
<thead>
<tr>
<th>Route</th>
<th>Dose</th>
<th>Strain</th>
<th>Endpoints</th>
<th>Estimated number of volunteers</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinovirus</td>
<td>Intranasal</td>
<td>10&lt;sup&gt;4&lt;/sup&gt; TCID&lt;sub&gt;50&lt;/sub&gt;</td>
<td>HRV-16, HRV-39</td>
<td>5760</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>Intranasal</td>
<td>10&lt;sup&gt;4&lt;/sup&gt;-10&lt;sup&gt;6&lt;/sup&gt; TCID&lt;sub&gt;50&lt;/sub&gt;</td>
<td>A/Texas/39′91 (H1N1), A/California/2009 (H1N1), A/Wisconsin/67′7005 (H3N2)</td>
<td>3540</td>
<td>Inpatient quarantine</td>
</tr>
<tr>
<td>Plasmodium falciparum</td>
<td>Mosquito bite, intravenous</td>
<td>5 mosquitoes, 3200 PBSPZ challenge</td>
<td>NF135, C10, NF54</td>
<td>2650</td>
<td>Outpatient</td>
</tr>
<tr>
<td>ETEC&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Oral</td>
<td>5 × 10&lt;sup&gt;8&lt;/sup&gt; CFU</td>
<td>B7A, H10470, E24377A</td>
<td>1215</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Vibrio cholera&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Oral</td>
<td>10&lt;sup&gt;5&lt;/sup&gt; CFU</td>
<td>Diarrhoea, antibody response</td>
<td>1210</td>
<td>Inpatient</td>
</tr>
<tr>
<td>S Typhi&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Oral</td>
<td>1.5 × 10&lt;sup&gt;8&lt;/sup&gt; CFU</td>
<td>Diarrhoea</td>
<td>1000</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Respiratory syncytial virus&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Intranasal</td>
<td>3.5 × 10&lt;sup&gt;8&lt;/sup&gt; CFU</td>
<td>Viral shedding in nasal lavage, clinical symptoms</td>
<td>1000</td>
<td>Inpatient quarantine</td>
</tr>
<tr>
<td>Shigella spp&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Oral</td>
<td>10&lt;sup&gt;9&lt;/sup&gt;-10&lt;sup&gt;10&lt;/sup&gt; CFU</td>
<td>S. flexneri 2457E, S. sonnei 53G</td>
<td>1000</td>
<td>Inpatient</td>
</tr>
<tr>
<td>Norovirus&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Oral</td>
<td>48 RT-PCR U</td>
<td>Diarrhoea, antibody response</td>
<td>850</td>
<td>Inpatient</td>
</tr>
<tr>
<td>Lactobacillus spp&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Oral, vaginal</td>
<td>10&lt;sup&gt;9&lt;/sup&gt; CFU once daily, vaginal 7.5 × 10&lt;sup&gt;9&lt;/sup&gt; CFU</td>
<td>L. intracellularis GR-1, L. reuteri RC-14, L. crispatus CV05</td>
<td>850</td>
<td>Inpatient</td>
</tr>
<tr>
<td>Streptococcus pneumonia&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Intranasal</td>
<td>10&lt;sup&gt;9&lt;/sup&gt; CFU</td>
<td>Diarrhoea, antibody response</td>
<td>850</td>
<td>Inpatient</td>
</tr>
<tr>
<td>Helicobacter pylori&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Oral</td>
<td>5 × 10&lt;sup&gt;10&lt;/sup&gt; oocysts</td>
<td>Diarrhoea</td>
<td>250</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Giardia lamblia&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Oral</td>
<td>5-10&lt;sup&gt;4&lt;/sup&gt; trophotrocholes</td>
<td>Giardia lamblia</td>
<td>120</td>
<td>Inpatient</td>
</tr>
<tr>
<td>H. pylori&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Oral</td>
<td>10&lt;sup&gt;8&lt;/sup&gt; CFU</td>
<td>Diarrhoea</td>
<td>120</td>
<td>Inpatient</td>
</tr>
</tbody>
</table>
Two Covid-19 challenge studies have been started (in the UK)

- Covid-19 study characterization study: study is currently ongoing (run by hVIVO / sponsor Imperial College)
  
  

- Covid-19 challenge study by Oxford, studying immune response when re-infecting with Covid
  
Conclusions

CHIM is a promising model, however...

- Ethical challenges are big
- Practical challenges:
  - Production of the challenge strain
  - Extrapolation of data
  - Which strain to chose
  - How to execute:
    - Deliberate release
    - Containment
  - How to extrapolate
    - Are CHIM data representative for Real World situation?
    - Are CHIM data acceptable for Regulatory approval?
- Early discussion with the NRA’s is crucial!