INTERNATIONAL ALLIANCE FOR BIOLOGICAL STANDARDIZATION

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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:

- **Strassbourg 2014**
  - http://dx.doi.org/10.1016/j.biologicals.2015.10.003
- **Washington 2017**
  - https://doi.org/10.1016/j.biologicals.2018.02.002
- **Langen 2019 (Quality of the challenge strain)**
  - https://doi.org/10.1016/j.biologicals.2020.04.005
- **Oxford 2020**
  - https://doi.org/10.1016/j.biologicals.2020.04.004
- **Webinar 2: Challenge models for COVID 19**
  - https://doi.org/10.1016/j.biologicals.2020.08.006

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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://wellcome.figshare.com/articles/online_resource/Considerations_on_the_principles_of_development_and_manufacturing_qualities_of_challenge_agents_for_use_in_human_infection_models/19411838
- **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**

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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?**

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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…

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* National Regulatory Authority
** Ethics Committee

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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:**

Time period	Outcome	R3R+R3C		R3R		R3C		C3C	
		N	n	N	n	N	n	N	n
M0-M20	Died	205	6	-	-	-	-	158	2
M0-M20	Survived with sequelae	205	0	-	-	-	-	158	0
M0-M20	Survived without sequelae	205	199	-	-	-	-	158	156
M21-SE	Died	-	-	76	3	103	6	76	2
M21-SE	Survived with sequelae	-	-	76	1	103	0	76	0
M21-SE	Survived without sequelae	-	-	76	72	103	97	76	74

- http://dx.doi.org/10.1016/S0140-6736(15)60721-8

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Challenges for Human challenge models (4)

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**

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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…**

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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?

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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?**

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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,…**

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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-1week-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**

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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.

- **EPAR** https://www.ema.europa.eu/documents/assessment-report/vaxchora-epar-public-assessment-report_en.pdf

  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

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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**

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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.

https://www.ema.europa.eu/en/documents/scientific-guideline/influenza-vaccines-non-clinical-clinical-module_en.pdf

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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**

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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**

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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.:

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(18)30177-4/fulltext

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	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	10^3–10^7 TCID50	A/Texas/39/91 (H1N1), A/California/2009 (H1N1), A/Wisconsin/67/2005 (H3N2)	Viral shedding in nasal lavage, clinical symptoms	3540	Inpatient quarantine
Plasmodium falciparum[10,11]	Mosquito bite, intravenous	5 mosquitoes, 3200 PfSPZ challenge	NF135.C10, NF54	Parasitaemia	2650	Outpatient
ETEC[12]	Oral	$\geq 5 \times 10^8$ CFU	B7A, H10407, E24377A	Diarrhoea	1215	Outpatient
Vibrio cholerae[4,13]	Oral	10^5 CFU	El Tor Inaba N16961, O139	Diarrhoea	1210	Inpatient
S Typhi[14]	Oral	$1–5 \times 10^4$ CFU	Quailes	Fever or bacteraemia	1000	Outpatient
Respiratory syncytial virus[15]	Intranasal	$4\log_{10}$ PFU/mL	M37, A2	Viral load in nasal lavage, respiratory symptoms	1000	Inpatient quarantine
Shigella spp[16]	Oral	$10–10^{10}$ CFU	*S flexneri* 2457T, *S sonnei* 53G	Diarrhoea, antibody response	850	Inpatient
Norovirus[17,18]	Oral	48 RT-PCR U	8FIIa, GI.1, GII.4	Gastroenteritis, PCR faeces, ELISA	810	Inpatient
Lactobacillus spp[19]	Oral, vaginal	Oral 10^9 CFU once daily, vaginal $7{\cdot}5 \times 10^8$ CFU	*L rhamnosis* GR-1, *L reuteri* RC-14, *L crispatus* CTV05	Clinical UTI	800	Outpatient
Streptococcus pneumoniae[20]	Intranasal	10^5–10^8 CFU	6B, 23F	Colonisation	790	Outpatient
Haemophilus ducreyi[21]	Intra-epidermal and intradermal	10–150 CFU	35 000HP	Pustule formation	550	Outpatient
Dengue virus[4]	Subcutaneous	10^3 PFU	DEN2Δ30	Viraemia, rash, neutropenia	520	Outpatient or inpatient
Francisella tularensis[22]	Aerosol	10^4–10^8 organisms	SCHU S4	Systemic symptoms	500	Inpatient
Neisseria lactamica[23]	Intranasal	10^4 CFU	Y92-1009	Colonisation	310	Outpatient
Plasmodium vivax[24]	Mosquito bite, intravenous	2–10 mosquito bites, 13 000 genome equivalents	Wild-type	Parasitaemia	300	Outpatient
Campylobacter jejuni[25]	Oral	10^4–10^8 CFU	Initially 81-176, now CG8421	Diarrhoea	260	Inpatient
Cryptosporidium spp[26,27]	Oral	10–10^5 oocysts	*C muris*: RN66, *C meleagridis*: TU1867, *C hominis*: Iowa strain, *C parvum*: Iowa strain	Stool oocysts	260	Outpatient
Necator americanus[28]	Transdermal	10–50 L3 larvae	Papua New Guinea	Eggs in stool	250	Outpatient
Escherichia coli (UTI)[29]	Urethral catheter	10^3–10^8 CFU/mL	83792, HU2117	Clinical UTI	200	Outpatient
BCG[30]	Intradermal	$1–4 \times 10^5$ CFU	BCG	Immune response	140	Outpatient
Neisseria gonorrhoeae[31]	Urethral catheter	$1{\cdot}8 \times 10^7$ CFU (Ms11mkC), $1{\cdot}0 \times 10^5$ 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	10^9 CFU	Baylor 100	Urea breath test, histology	80	Outpatient
S Paratyphi[34]	Oral	$1–5 \times 10^5$ CFU	NVGH308 strain	Fever or bacteraemia	40	Outpatient
Parvovirus B19[35]	Nasal	Up to 5^{10} viral genomes	Wild-type	Viraemia	12	Inpatient isolation

Some examples of Human challenge models

Covid-19

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)**

  https://www.gov.uk/government/news/worlds-first-coronavirus-human-challenge-study-receives-ethics-approval-in-the-uk

  https://www.imperial.ac.uk/news/218294/first-volunteers-covid-19-human-challenge-study

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

  https://www.ox.ac.uk/news/2021-04-19-human-challenge-trial-launches-study-immune-response-covid-19

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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!**

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