The concept of clinical equipoise and its relevance to infectious disease clinical trials

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Conflict of Interest Statement

• No conflicts of interest to report
Traditional Scientific Approach: Models, Hypotheses and Theories

• Background: Human mind often cannot penetrate reality
• A scientific model is a conceptual representation for the purpose of logically explaining processes and phenomena
• Models are simplified reflections of reality and have inherent falsity, but are scientifically indispensable
• **Example:** How physiology and pathophysiology explain phenomena of human disease and treatment
• Interpretation is critically dependent on **Scientific Rigor**
• **Example:** Orbital Model
Building and Rejection of Scientific Models

--> Scientific/Empirical Observations Supporting a Model?

Model A

Majority of observations support model
Minor inconsistencies; may be explained

--> To keep model

Model B

Majority of observations do not support model
Minor support only

--> To reject model
Evidence-Based Medicine (EBM)

- Branch of medicine that makes conscientious, explicit and judicious use of current best evidence in making decisions
- **Measure**: real clinical outcomes after different treatment
- **Stages of evaluation:**
  1. Clinical trials: randomized clinical trial (RCT) is best
  2. Systematic reviews
  3. Meta-analyses (mathematical calculation)
  4. Evidence-based clinical practice guidelines
- De-emphasizes knowledge of disease causation and pathophysiology
- Implied: circumvents models (focuses on real outcomes)
Laboratory Sciences are at the bottom of the 'Evidence Hierarchy'!

Source: http://library.downstate.edu/EBM2/2100.htm

Note: Slightly different published versions exist
Patient Safety and Airline Safety

- Patient safety often compared to airline safety
- US: Patients dying from medical errors: ~200,000 p.a., equivalent to ~2-3 commercial planes crashing per day (!)
- Airlines: much better safety record !!!

One interesting (hardly noticed) difference:

- Airlines do NOT establish evidence by randomised trials & syst. reviews
- So, how do they do it?
  - Empirical observations and accident analyses
  - Making inferences from scientific principles (incl. physics)
  - Applying common sense
- **Question 1:** How can an industry that acts upon such "bad" evidence have such good outcomes?
- **Question 2:** Is this really such "bad" evidence?
Biological Plausibility in Epidemiological Research


(6) Plausibility: It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day.

To quote again from my Alfred Watson Memorial Lecture (Hill 1962), there was

‘... no biological knowledge to support (or to refute) Pott’s observation in the 18th century of the excess of cancer in chimney sweeps. It was lack of biological knowledge in the 19th that led a prize essayist writing on the value and the fallacy of statistics to conclude, amongst other “absurd” associations, that “it could be no more ridiculous for the stranger who passed the night in the steerage of an emigrant ship to ascribe the typhus, which he there contracted, to the vermin with which bodies of the sick might be infected”. And coming to nearer times, in the 20th century there was no biological knowledge to support the evidence against rubella.’

Famous Bradford-Hill Criteria:
Set of criteria to prove causality in epidemiological research

In other words: The cause-and-effect relationship should be biologically plausible. It must not violate the known laws of science and biology. (From: Gorman S, commentary on ScienceBlogs).
Evidence for treatments generally does NOT arise solely from clinical trials out of a prior vacuum of information!

US FDA Drug Development Pathway

- Basic Research
- Prototype Design or Discovery
- Preclinical Development
- Clinical Development
- FDA Filing/Approval & Launch Preparation

E.g. compound discovery
E.g. lab testing, animal testing, etc.
Various phases of clin. trials

--> Multiple useful information sources before/outside clinical trials
My Area of Interest: Hand and Skin Antisepsis

Mangram AJ et al. ICHE 1999; 20: 250-78 (‘CDC surgical guideline’)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Gram-Positive Bacteria</th>
<th>Gram-Negative Bacteria</th>
<th>Mtb</th>
<th>Fungi</th>
<th>Virus</th>
<th>Rapidity of Action</th>
<th>Residual Activity</th>
<th>Toxicity</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Denature proteins</td>
<td>E</td>
<td>E</td>
<td>G</td>
<td>G</td>
<td>G</td>
<td>Most rapid</td>
<td>None</td>
<td>Drying, volatile</td>
<td>SP, SS</td>
</tr>
<tr>
<td>Chlorhexidine</td>
<td>Disrupt cell membrane</td>
<td>E</td>
<td>G</td>
<td>P</td>
<td>F</td>
<td>G</td>
<td>Intermediate</td>
<td>E</td>
<td>Ototoxicity, keratitis</td>
<td>SP, SS</td>
</tr>
<tr>
<td>Iodine/Iodophors</td>
<td>Oxidation/substitution by free iodine</td>
<td>E</td>
<td>G</td>
<td>G</td>
<td>G</td>
<td>G</td>
<td>Intermediate</td>
<td>Minimal</td>
<td>Absorption from skin with possible toxicity, skin irritation</td>
<td>SP, SS</td>
</tr>
</tbody>
</table>

E, excellent; G, good; F, fair; P, poor; SP, skin prep.; SS, surgical scrubs

- Alcohols are most rapid-acting & effective hand/skin antiseptics
- Alcohols ~factor 10 better than CHX or PVI
- CHX and PVI are less potent, but have persistency on skin (CHX greater than PVI)
- Antiseptics may be combined, e.g. CHX-ALC, PVI-ALC
~2010, several RCTs and Syst. Reviews of Preop. Skin Antisepsis published

- CHX-ALC versus PVI alone (aqueous) tested
- Outcome: CHX-ALC ~9% <----> PVI ~16% SSIs
- Results highly significant!
- Trial was sponsored by the CHX-ALC manufacturer
- In Europe, IRBs would not have approved trial (more later)
- In Europe, OTs would be shut down with a 16% SSI rate!
Similar time (2010), Syst. Reviews published

Systematic Review and Cost Analysis Comparing Use of Chlorhexidine with Use of Iodine for Preoperative Skin Antisepsis to Prevent Surgical Site Infection

*Infect Control Hosp Epidemiol* 2010; 31(12):1219-1229
Ingi Lee, MD, MSCE; Rajender K. Agarwal, MD, MPH; Bruce Y. Lee, MD, MBA; Neil O. Fishman, MD; Craig A. Umscheid, MD, MSCE

Systematic review and meta-analysis of preoperative antisepsis with chlorhexidine *versus* povidone–iodine in clean-contaminated surgery

*British Journal of Surgery* 2010; 97: 1614–1620
A. Noorani¹, N. Rabey³, S. R. Walsh¹ and R. J. Davies²

- Many included trials followed this scheme:

- Often unfair 2 against 1 comparison!
But – was there really no knowledge about antiseptics before these trials???

Brief History of Antiseptic Testing

- 1890s: Different authors (e.g. Reinicke 1894, Ahlfeld 1896, Epstein 1897) tested antiseptics for hands and skin
- 1930s to 50s: Price (USA) published seminal papers; precursors to US FDA/ASTM test methods
- 1950s to 70s: Lowbury & Lilly (UK) published seminal work
- 1970s: US FDA tentative final monographs (TFMs) published
- 1970s to 90s: Various national sets of test requirements and formal testing standards in Europe and USA generated

--> History of microbiologic antiseptic testing >100 years!

Note: Listing is not comprehensive
Question: Could we have known or guessed the outcome of the above trial???

--> Most microbiologists, esp. those involved in standardised antiseptic testing – unanimous YES!
- ALC much stronger than CHX or PVI alone (~factor 10)
- Unfair 2 against 1 comparison
- Clinical reliance on microbiol. antiseptic testing >50 years
- Not a single major observation in world literature disproving validity of testing
- Note, SSIs can be life-threatening outcome

--> Would the sponsoring company have known?
- Standardised testing is a regulatory requirement for registration

--> Is there guidance from within EBM on this?
"Clinical equipoise, also known as the principle of equipoise, provides the ethical basis for medical research that involves assigning patients to different treatment arms of a clinical trial. The term was first used by Benjamin Freedman in 1987. In short, clinical equipoise means that there is genuine uncertainty in the expert medical community over whether a treatment will be beneficial." (Wikipedia)
Principle of Equipoise was already known from 1970s
"... ethics requires that each trial begin with honest null hypothesis"
Earlier equipoise: theoretical or trial clinician’s equipoise
  • Quite difficult concepts – difficult to meet
Clinical equipoise: when the community of clinicians are either uncertain or disagree
Equipoise and the RCT

M. Braakhekke¹,*, F. Mol¹, S. Mastenbroek¹, B. Willem J. Mol²,³, and F. van der Veen¹

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Scenario 1: Biological plausibility behind the effect of an intervention is known
If certain pathophysiological processes or mechanisms have—beyond doubt—identified the cause of a disease, it has traditionally been assumed that correction of these processes will cure the patient. This may well be the case, but obviously any positive effect of a treatment overcoming the pathophysiological hurdle should be observed before this treatment can be routinely implemented.

Scenario 2: Biological plausibility behind the effect of an intervention is absent
If biological plausibility behind the effect of an intervention is absent, the a priori chances that this treatment is effective are low. Bayesian logic dictates that in these situations, it is unlikely to detect any meaningful difference in an RCT. Such trials should not be performed.

Scenario 3: Biological plausibility behind the effect of an intervention is uncertain
If biological plausibility behind the effect of an intervention is uncertain and one is thus in doubt whether the proposed intervention might have a positive effect, observational data might be helpful to decide if an RCT is necessary. Treatment effects may be observed in cohorts, cases or pilot studies.

If multiple clinical observations show a negative effect of a treatment, like death or, in our field, irreversible infertility, RCTs should not be performed. If multiple observations show a positive or no effect of a treatment, we are in equipoise. The same condition is met if some cohorts show a positive effect, while others show a negative effect.

Discussion
Since our basic reasoning rests heavily on the biological plausibility behind the effect of an intervention, we feel the need to add a few remarks on the role of biologic plausibility.

First, we have framed our description of what typifies biologic plausibility in the setting of scientific medicine, in which biological hypotheses are generated and after thorough fundamental research rejected or not. The Oxford Dictionaries Online defines the scientific method as 'a method or procedure that has characterized natural science since the 17th century, consisting in systematic observation, measurement, and experiment, and the formulation, testing, and modification of hypotheses' (Oxford University Press, 2010). It fol-
A Trial of Antifungals (2013)

• Cryptococcus meningitis in HIV pats. in Vietnam (resource-lim.)
• Three trial arms:
  (1) Amphotericin B (AmB) alone
  (2) AmB plus 5-fluorocytosine (5FC)
  (3) AmB plus fluconazole (FCZ)
• Measured outcomes: (1) Death rate; (2) CSF yeast clearance
A Trial of Antifungals (continued)

• Outcomes:
  • AmB + 5FC >> AmB alone:
    • Death Rate & CSF Clearance both highly significant!
    • Deaths by day 70: 30/100 vs. 44/99
  • AmB + FCZ > AmB alone:
    • Death Rate (NS); & CSF Clearance (S)
  • Authors' justification for the trial (Intro):
    "However, this treatment [AmB + 5FC] has not been shown to reduce mortality, as compared with AmB monotherapy"
• Question:
  But – what information was available prior to the trial???
Prior Information

1971: Synergistic action of AmB + 5FC against *C. neoformans*

1973: At least additive action of AmB + 5FC in mouse model

1979: RCT
- Fewer failures/relapses
- More rapid CSF clear.
- Less nephrotoxicity
- Same no. deaths
- Study stopped early
Treatment Guidelines

NIAID Mycoses Study Group
Grade AI
Recommendation
AmB + 5FC

"There is high quality evidence that [AmB + 5FC], compared to AmB alone assoc. w. increased CSF sterilis., reduced risk of relapse, non-significant reduction in mortality"
Did this study have (clinical) equipoise at the outset?

--> In my opinion, clearly NOT!

- Microbiological studies, animal experiments, human cohort studies and RCTs all showed advantage of AmB + 5FC
- Recommended by major guidelines *before* NEJM trial (i.e. broad consensus in medical community)
- Trial done in resource-limited setting
- Authors' trial justification *"has not been shown to reduce mortality"* appears cynical (to me)
What about emerging infectious diseases – Ebola?

12 WHO-appointed ethics experts

The panel members ... concluded unanimously that it would be acceptable [in the context of the current Ebola outbreak] to offer unregistered interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans, provided that certain conditions are met.

Different View:
... RCTs are the most reliable way to identify benefits and risks ... and every effort should be made to implement them...
... because results from animal models cannot be reliably extrapolated to humans...
Ebola Ça Suffit Trial – Phase III Cluster-RCT of Ring-Vaccination

Known contacts ("ring" around) of Ebola patients enrolled

Trial arms: (1) vaccinated immediately
            (2) vaccinated after 21 days (delayed)
**Ebola Ça Suffit Trial**

(1) No Ebola cases $\geq$10 days after vaccination onwards among 2014 people in 48 clusters in immediate group

(2) 16 cases among 1496 people in 42 clusters in delayed group
• **No cases** in both groups from 6 days after actual vaccination

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**What was known before the trial?**

• There were lab tests, animal experiments, phase I & II trials
• 100% protection of non-human primates against Ebola challenge; even immunocompromised animals (SIV infected)
• Humans minor side effects, but no serious ones
• ELISA-reactive Abs detected in 100% vaccinated humans
• Virus neutralisation tests pos. in $>50\%$ vaccinated humans
Assessment of Ebola Ça Suffit

**View 1:** Biological plausibility is high from animal experiments and from human Phase I-II trial, and in a disease with >50% mortality, pre- & post-vaccination historical difference is easy to detect.

**View 2:** Real-life correlates of vaccine protection are difficult to assess before phase III trials, recent dengue 'fiasco' an example.

- Authors were fully aware of & discussed ethical challenges.
- Consciously chose non-individual RCT strategy to reduce impact of exposure to 'inferior' treatment.
- My opinion: This trial chose 'interim' path in a real difficult situation – elements of theoretical equipoise lacking, but clinical equipoise probably present.
Controversies surrounding Equipoise

Is the concept of clinical equipoise still relevant to research?

Spencer Hey, Alex John London, and Charles Weijer argue that there is no better framework for justifying patient participation in research. But Annette Rid and Franklin Miller say that it is a mistake to require clinical research ethics to align with the norms of clinical practice.

Yes—Spencer Phillips Hey, Alex John London, Charles Weijer

- State of disagreement/uncertainty in the broader med. community
- Should not be left solely to individual trial clinicians (e.g. some 'crazy' views)
- Conducting clin. trials different from clin. care
- May do procedures not in participants' interests if necessary for generating valuable knowledge

No—Annette Rid and Franklin Miller
The uncertainty principle and industry-sponsored research

Benjamin Djulbegovic, Mensura Lacevic, Alan Cantor, Karen K Fields, Charles L Bennett, Jared R Adams, Nicole M Kuderer, Gary H Lyman

Background Reporting of pharmaceutical-industry-sponsored randomised clinical trials often result in biased findings, either due to selective reporting of studies with non-equivalent arms or publication of low-quality papers, wherein unfavourable results are incompletely described. A randomised trial should be conducted only if there is substantial uncertainty about the relative value of one treatment versus another. Studies in which intervention and control are thought to be non-equivalent violates the uncertainty principle.

Methods We examined the quality of 136 published randomised trials...

Findings ... However, when the analysis was done according to the source of funding, studies funded by non-profit organisations maintained equipoise favouring new therapies over standard ones (47% vs 53%; p=0.608) to a greater extent than randomised trials supported solely or in part by profit-making organisations (74% vs 26%; p=0.004).

Interpretation The reported bias in research sponsored by the pharmaceutical industry may be a consequence of violations of the uncertainty principle. Sponsors of clinical trials should be encouraged to report all results and to choose appropriate comparative controls.

Back to Antiseptics…

The CLEAN Trial

Skin antisepsis with chlorhexidine–alcohol versus povidone iodine–alcohol, with and without skin scrubbing, for prevention of intravascular-catheter-related infection (CLEAN): an open-label, multicentre, randomised, controlled, two-by-two factorial trial

Lancet 2015; 386: 2069–77

- Published AFTER more widely recognised that CHX-ALC vs. PVI-ALC better comparison
- Sponsored by CHX-ALC company; CR-BSI pot. serious outcome
- Comparators: CHX 2% IPA 70% versus PVI 5% EtOH 69%
- **Decades of microbiol. testing** indicate:
  - CHX >> PVI persistency on skin (relevant for catheters)
  - IPA >> EtOH microbicidal activity
- **Did the company know?** – Impossible to not know!
- **Was there equipose** – Don’t think so!
Possible Approaches/Solutions (1)

- Investigators should be aware of likely competitor imbalances.
- Pre-trial non-RCT information should be disclosed (e.g. appendix).

(1) Consider pre-trial microbiological testing when applicable:
- Easy for antiseptics
- To disclose in trial protocol

(2) Plan for interim analyses and early termination in trial protocol when necessary to test 'imbalanced' competitors

(3) Consider outcome-adaptive randomisation
Possible Approaches/Solutions (2)

(4) Consider 'stepped-wedge' trial design

- Suitable when logistical challenges
- E.g. vaccine supply limited

(5) Consider non-RCTs and historical controls when biol. plausibility very strong and likely outcomes dramatic

(6) Consider complex trial designs with RCT and non-RCT elements

- Shortest time to roll-out or rejection


Possible other solutions I may have overlooked (?)
Conclusions

• Investigators need to be aware of equipoise problem & trial imbalances
  • Pre-trial results should be disclosed/discussed/cited
  • Should be incorporated in trial protocols & standards
• Controversies/different opinions re. equipoise remain
• We need a more holistic & inclusive approach to evidence assessment, incl. scientific & lab approaches
• Industry-sponsored trials likely remain a problem
  • Important funding source
  • But unrealistic to expect 'perfect' conduct
• Scientific/medical community needs to retain a critical attitude towards equipoise & lack thereof