

**Imperative to develop vaccines for children,
pregnant women, the immunocompromised
« HCTs in vulnerables: can we break the rules? »
Dominique Ploin, Hôpitaux de Lyon, France**





Disclaimer

- ✓ The views and opinions expressed in the following slides are those of the individual presenter and should not be attributed to the PDCO nor the European Medicines Agency (EMA) nor the IRB of Sud-Est III.
- ✓ I am employed by Hôpitaux de Lyon (80%) and the French regulatory agency (20%), and have no interest to disclose.

Imperative to develop vaccines for children?

✓ **Out of 9 million deaths in children <5y, 5 million deaths related to infect diseases**

✓ Pneumonia	1.6	Diarrhea	1.4
✓ Malaria	0.7	Neonatal sepsis	0.5
✓ Others	0,7	AIDS	0.2
✓ Meningitis	0.2	Pertussis	0.2
✓ Measles	0.1	Green sections #70%	

2008 Worldwide causes of child mortality
Black RE et al, on behalf of WHO and UNICEF
Funding WHO, UNICEF, BM Gates Foundation

Imperative to develop vaccines for pregnant women?

- ✓ Classically, NO; most vaccine done before:
 - ✓ Tetanus, rubella, pertusis, etc: recapture+++
 - ✓ Zika to develop+++
- ✓ Becomes YES:
 - ✓ Flu vaccine coverage to maintain, & improve
 - ✓ YES: specific needs uncovered to date
 - ✓ Group B streptococcus, RSV
 - ✓ Future Zika recapture for unvaccinated pregnant ♀

Imperative to develop vaccines for the immunocompromised?

- ✓ Specific studies required:
 - ✓ asplenic patients, cancer patients, HIV patients, hematopoietic stem cell recipients, inflammatory bowel diseases patients, psoriasis patients, primary immunocompromised patients, inflammatory rheumatic diseases patients, and solid organ transplant recipients
 - ✓ Dose ranging: dose/shot, N° of boosters
 - ✓ Follow-up the immune response

**Imperative to develop vaccines for
children, pregnant women,
the immunocompromised.**

→ HCTs in the vulnerables: so what?

Does anyone have a dream?

Wishable? Possible?

HCTs? Syphilis

I reviewed the historical human challenges:

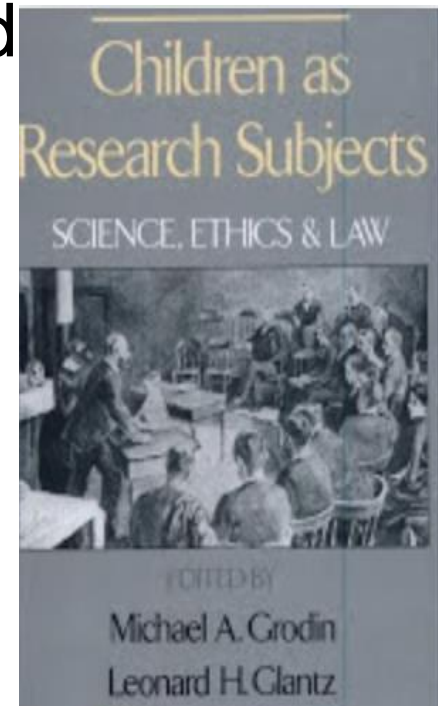
- ✓ In Lyon, a junior and a senior doctor from the Hotel-Dieu published in 1859 the case of a young child inoculated with the pus from syphilitic patient during a consultation for tinea capitis; he developed syphilis and thus, the “experiment was a success”.
- ✓ So did in Hawaii Dr Fitch 1892, with 6 leprous girls < 12y...

Pierre-Charles Bongrand

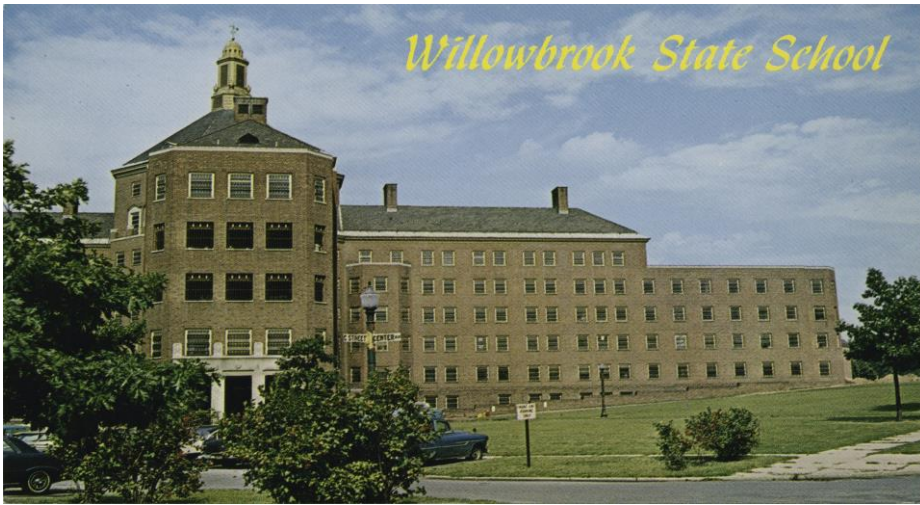
L'expérimentation sur l'homme

sa valeur scientifique et sa légitimité

© IgrPress.fr, 2011



Willowbrook State School



HCTs? Hepatitis

- ✓ I remembered the story of Dr Krugman who challenged children with hepatitis A and B virus in the Willowbrook studies.
- ✓ How Dr Saul Krugman observed 2 kinds of HV, challenged the children, then vaccinated (boiled plasma/water).
- ✓ Observation, interpretation, concept, nerve

Going back to the precise story

- ✓ In Lyon, the 1859-publication was brought to the justice court and both doctors from Lyon were “condemned” and (lightly) blamed for lack of consent for care.
- ✓ Despite some justifications and a dazzling success, SK was denounced by Dr Beecher

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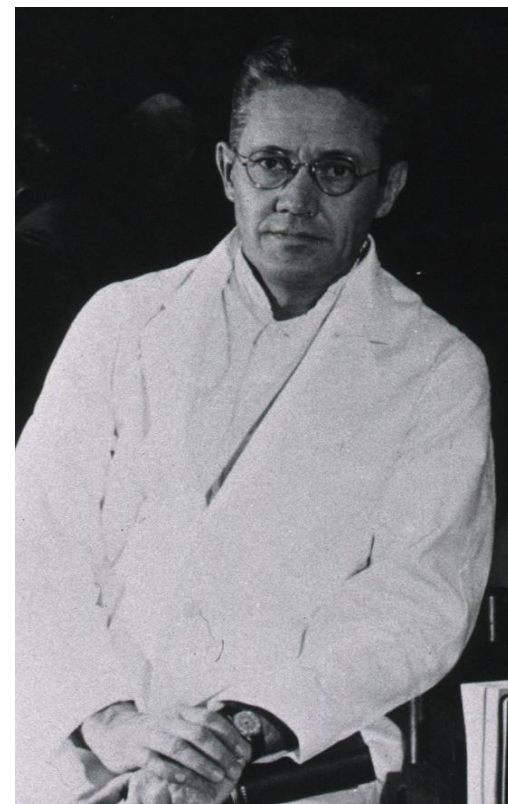
Reprinted from pages 1354-1360.

SPECIAL ARTICLE

ETHICS AND CLINICAL RESEARCH*

HENRY K. BEECHER, M.D.†

BOSTON



Could we try again now?

Getting current advice and opinions

« I have some good friends that propose sharing with us ambitious and rigorous pediatric protocols to recruit your patients or your children for challenge with malaria, cholera, dengue... would you agree to consider and to sign? »

- ✓ In my pediatric department...
- ✓ In my IRB...
- ✓ Our nurses...
- ✓ The chair of the Regional Ethic Committee...

Do we have strong guidelines?

Declaration of Helsinki

(1964, 1975, 2000, 2004, 2008, 2013)

✓ Vulnerable Groups and Individuals: Medical research with a vulnerable group is **only justified** if the **research is responsive to the health needs or priorities of this group** and the **research cannot be carried out in a non-vulnerable group**. In addition, this group should stand to **benefit from the knowledge, practices or interventions that result from the research**.



Strong guidelines?



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- ✓ REGULATION (EC) No 1901/2006 on medicinal products for paediatric use

Article 1

- ✓ This Regulation lays down rules concerning the development of medicinal products for human use in order to meet the specific therapeutic needs of the paediatric population, **without subjecting the paediatric population to unnecessary clinical or other trials** and in compliance with Directive 2001/20/EC.

Strong guidelines?



- ✓ **Human Challenge Trials for Vaccine Development: regulatory considerations**
- ✓ **© World Health Organization 2016**
- ✓ ...It is for the reason of the need for truly informed consent that consideration of conducting **human challenge studies in children, or in any other vulnerable population which would have diminished capacity to give informed consent, would not be deemed acceptable at this time.**

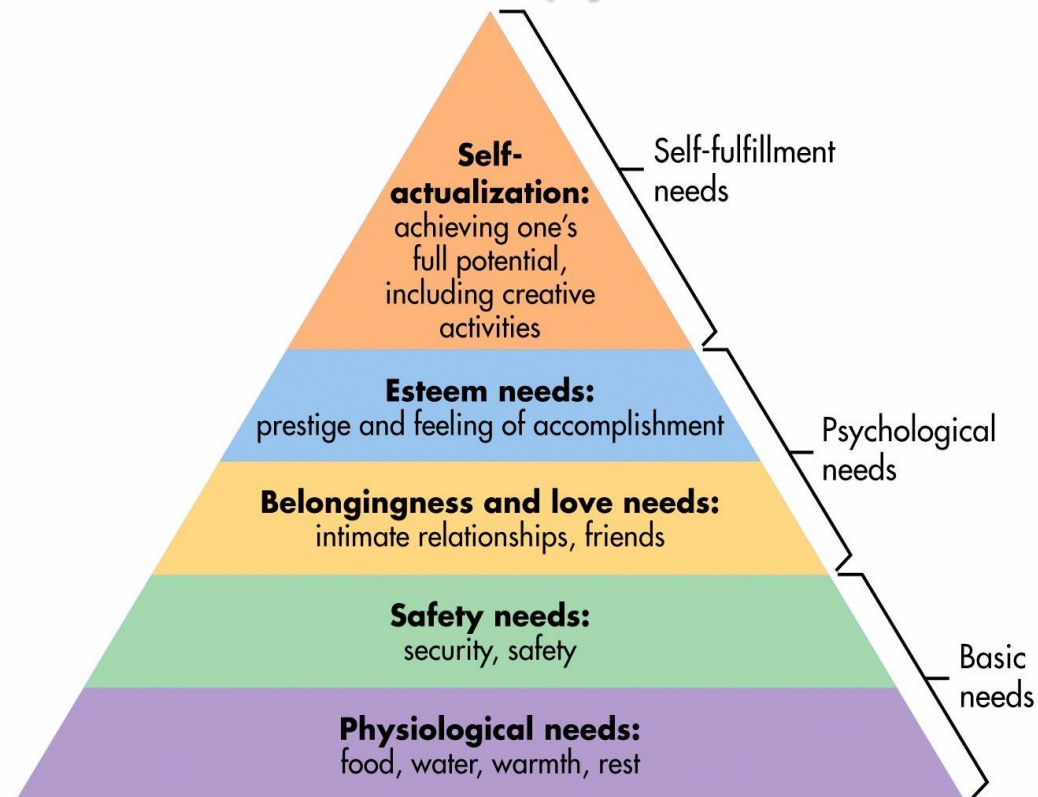
Strong guidelines?

Convention on the Rights of the Child
General Assembly resolution 20 Nov 1989



- ✓ Article 27: States Parties recognize the right of every child to a standard of living adequate for the child's physical, mental, spiritual, moral and social development.
- ✓ Article 28: States Parties recognize the right of the child to education...

Better reading
with Maslow's pyramid?



So what?

- 1) There is a need...**
- 2) Let's combine
the tools**

Let's go back to the Agencies



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Reflection paper on the use of extrapolation in the development of medicines for paediatrics

Draft

To be released
October/November 2017

**Leveraging Existing Clinical Data
for Extrapolation to Pediatric Uses
of Medical Devices**

**Guidance for Industry and Food
and Drug Administration Staff**

Document issued on June 21, 2016.
This document will be in effect as of September 19, 2016.

July 2000 - ICH E11: Clinical Investigation Of Medicinal Products In The Pediatric Population

- When a medicinal product is studied in pediatric patients in one region, the intrinsic (e.g., pharmacogenetic) and extrinsic (e.g., diet) factors that could impact on the extrapolation of data to other regions should be considered.

- **Extrapolation of efficacy from adult to children and from older children to the youngest**

2006: EU paediatric Regulation:

- High quality, ethical research into medicines for children
- Increase availability of authorised medicines for children
- Improved information on medicines

Without subjecting children to unnecessary studies

2013: EMA Concept paper on extrapolation of efficacy and safety in medicine development

‘Extending information and conclusions available from studies in one or more subgroups of the patient population (source population(s)), or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information (types of studies, design modifications, number of patients required) to reach conclusions for the target population, or condition or medicinal product.’

EMA Extrapolation Framework

- Set out **a structured approach** to be followed for each extrapolation exercise to improve interactions with stakeholders and to standardise the decision making.
- **Supports an explicit and systematic approach to extrapolation which sets out i) when, ii) to what extent, and iii) how extrapolation can be applied and validated.**

The original framework proposed in the Concept Paper has been refined and methodological approaches and decision criteria for extrapolation have been proposed.

How does that work?



Biost Com.

PK Com.

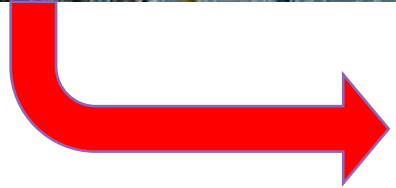
Ped Com.

PV Com.

MA Committee

Entry

Mod Sim Com.



Scientific Advice

Situations

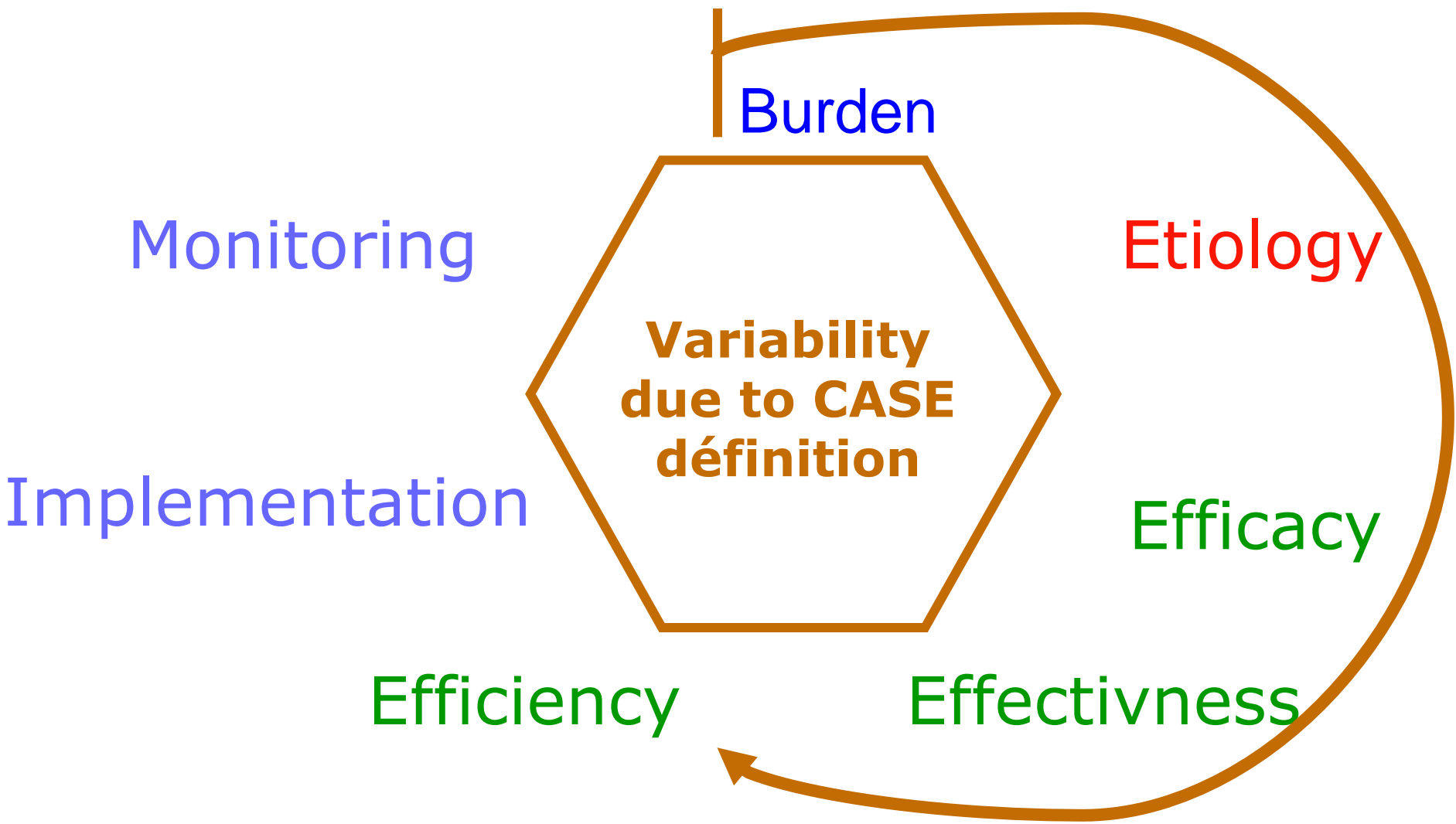
- ✓ Ebola vaccine: adult challenge? Children challenge?
 - ✓ Existing models and data
 - ✓ Extrapolation plan: studies in source & in target populations → PK, PD, PK/PD, POP-PK/PD, PB-PK/PD
 - ✓ Modeling and simulation studies
 - ✓ Follow-up post licensure, check expected/observed
- ✓ Shigella vaccine: challenge done in adult. Children?
 - ✓ Extrapolation plan: studies in source & in target populations → PK, PD, PK/PD, POP-PK/PD, PB-PK/PD
 - ✓ Studies to perform in children, but no challenge
 - ✓ Modeling and simulation studies
 - ✓ Follow-up post licensure, check expected/observed

THM

- ✓ HTCs and Extrapolation complementary and can synergically empower developments
- ✓ Define ASAP an extrapolation plan, and **check it ASAP through SA at an early stage**
- ✓ Pressure not only early step of development (efficacy/effectiveness) but also implementation by HCP and lay population
- ✓ Be confident with Dr Beecher and the talking cricket: they are + safeguard for ethics
- ✓ Maintain pressure for security & ethics

- ✓ In terms of market, the pediatric population is for once, the main target; pediatricians must and will be contributive, as vaccines are prone to be much more effective and efficient care than all actual curative care

Thank you for your attention



Burden

Etiology

**Variability
due to CASE
définition**

Efficacy

Effectiveness

Efficiency

Implementation

Monitoring