CLINICAL FIELD TRIALS FOR DRUGS AND VACCINES

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Treatments should be adopted "not because they ought to work, but because they *do* work."

Optimism Bias

If you are certain you are right
and if you can convince the patient [client] that you are right,
then whether you are right or not,
often makes little difference.

Richard Asher, 1972

Experimental Studies

- Evaluation of treatment effects (the clinical trial) comes as close to a laboratory experiment as you can get in clinical epidemiology

Deciding on the Best Therapy

Three ways to pick a therapy

- *1. Induction*

Logically arrive at the therapy that *seems to work* or *ought to work*

- on the basis of retrospective analyses of
- your own uncontrolled clinical experience,
- that of others,
- or the extension of current concepts of disease mechanisms

Deciding on the Best Therapy

Three ways to pick a therapy

- *2. Seduction* (or *abdication*)

Accept a treatment on faith

- On the basis of recommendations from academics, consultants, colleagues, advertisements, or drug reps

Deciding on the Best Therapy

Three ways to pick a therapy

- *3. Deduction* (or hypothetico-deduction)

Select the therapy that *successfully withstands formal attempts to demonstrate their worthlessness*

Deciding on the Best Therapy

Three ways to pick a therapy

- *3. Deduction* (or hypothetico-deduction)

Select the therapy that *successfully withstands formal attempts to demonstrate their worthlessness*

- On the basis of prospective analyses of formal randomized clinical trials designed to expose worthless or dangerous treatments

Inductive Choices

- Historical controls:
- Judge something is more efficacious because it works better than former clinical experience

- Over 20% of more recent controls (randomized not to receive the tx) exhibited more than 20% better survival than controls from older studies who could not receive the new treatment

Inductive Choices

- Comparing groups that were compliant to groups that were less compliant (eg. heart medications)

		Patients	% mortality
Compliance	< 80%	882	26%
	> 80%	1813	16%

Risk reduction = (0.26 - 0.16) / 0.26 = 38% (p > 0.001)

Inductive Choices

- Compliance seems to have a major impact on survival

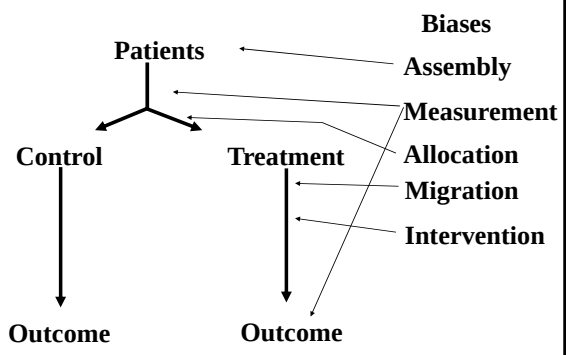
- Except that these were patients that were in the placebo group!
- Better compliance resulted in improved survival regardless of whether it was treatment or placebo

In addition to asking whether it is ethical in the light of current knowledge to plan a randomized trial in which some ... will not be offered the new measure,

it is also necessary to ask whether it is ethical not to plan a randomized trial

since failure to do so may subject the population as a whole to the perpetuation of an ineffective program

Hill 1952



Concepts to consider

- Experimental units
- The smallest independent grouping of individuals that could receive a different treatment given the randomization process
  - Assumes: independent units
  - Treatment effect separated from pen or tank effect ?

Allocation

- Formal randomization
  - Primary advantage over prospective cohort studies
  - Often impossible to account for effects of all known extraneous factors in cohort studies
- Randomization used to protect against systematic differences in treatment and control groups
  - Balances confounding variables, provides validity for the statistical tests

Randomization

- Coin toss
- Drawing numbers from a hat
- Random number generators
- Allocation within matched units

Follow up Period

- Differential management or assessment of outcomes must be avoided
- Blinding techniques reduce this bias
- Double-blind (manager *and* investigator) are useful
  - Sham / placebo treatments necessary

Outcome Measurements

- Practical importance to animal +/- owner
  - What about Ab titres when not proven to be related to protection for vaccine?
- Should include productivity as well as morbidity or mortality
- Blind assessment of outcomes important

Analyzing Effect

- Simple statistical tests suffice in most trials
  - Eg. t-test or Chi-square tests
- Consult statistical advice before starting trial

Clinical field trial summary ISSUES

- 1. Randomization
- 2. Blinding
- 3. Mortality versus infection
- 4. Unit of concern
- 5. Cost versus benefit

1. Randomization

- Need equivalent probability of outcomes distributed across study subjects
  - Outcomes of exposure, infection, growth, disease, mortality
  - Distribute confounders across study groups
- Rarely done in aquaculture field trials
  - Need control of production decision, but don't own fish

2. Blinding

- Everyone potentially adds bias (usually subconsciously)
  - Owners, managers, workers, vets, researchers
- Blinding can remove the ability to differentially manage part of study population
- Rarely done in aquaculture field trials
  - Requires agreement that decisions applied without prior knowledge

3. Mortality/disease versus infection

- Policy is to depopulate *before* mortalities increase
  - Prevents observations of impact of management (vaccine) change on clinical outcome
  - Already concluded in observational studies that no significant difference in probability of depopulation when vaccinated (cf non-vaccinated)

4. Unit of concern

- BMA vs site vs cage vs fish
  - Herd immunity challenges
  - Not all units exposed, need exposure to see difference
  - Sufficient units to detect a difference in outcomes
    - Insufficient areas
    - Sites: essentially *all* sites would need to be blinded and randomized
    - Cages: large number of cages blinded / randomized – not practical
    - Individual fish: you must be joking

Clinical Vaccine Field Trial

- Necessity?
  - No observed difference in depopulations
  - Anecdotal reports that cages NOT vaccinated were turning ISA positive later than vaccinated cages at same site
    - Not a valid comparison!
  - Control was not keeping up (prior to genotyping)

Unit of concern

- Sites vs cages vs fish
- Individual fish were chosen
  - all other levels were less logistically practical
  - Uniquely identified with PIT tags

Summary of clinical field trial considerations:

- 1. Randomization is important (but rarely done)
- 2. Blinding is important (but rarely done)
- 3. Mortality versus infection important consideration
- 4. Unit of concern must be considered