Studies using epidemiological methods:
Mistakes you don't want to make

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Do you have a problem with that?

- Our aim was to compare gentamicin to ciprofloxacin as a single dose before prostatectomy.
- The main outcome was UTI in the week following the operation.
- We randomized patients to the 2 interventions in a 1:1 scheme.
- As both treatments are in use in our hospital in clinical practice we did not ask for patients' consent.
- Our sample size calculation was 200 patients, and we recruited 204.

Declaration of Helsinki

- In medical research involving competent human subjects, each potential subject must be **adequately informed** of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study.
- After ensuring that the potential subject has understood the information, the **physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent**, preferably in writing.

A problem with that?

- In Mordor resources are so poor that the great majority of HIV carriers and AIDS patients are not treated with anti-retroviral drugs.
- We have performed a RCT of our new drug vs placebo in HIV carriers.
- The patients gave their written informed consent.
- Primary outcome: the proportion of subjects with undetectable plasma viremia at 12 months.

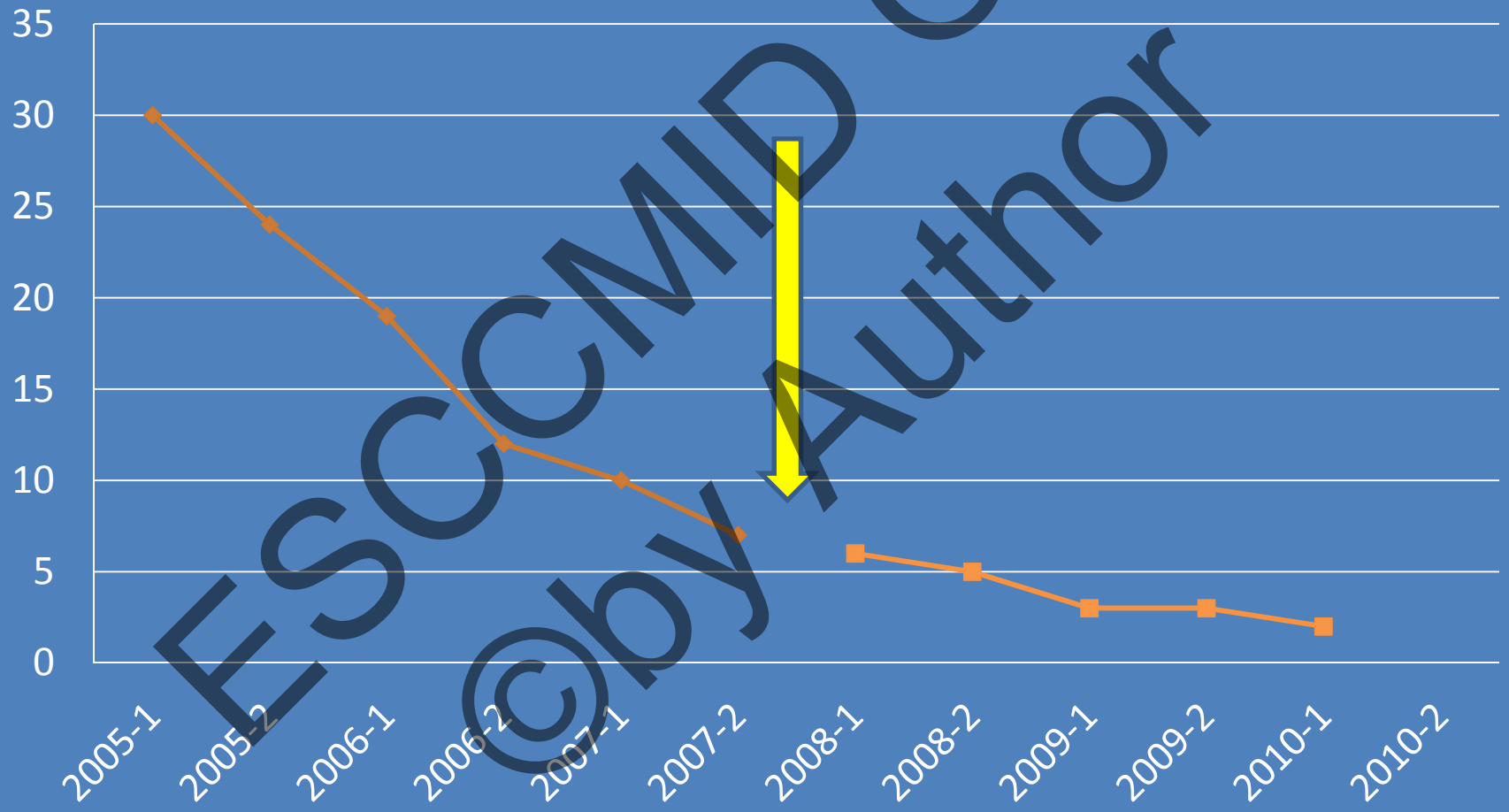
Declaration of Helsinki

- The benefits, risks, burdens and effectiveness of a new intervention must be tested **against those of the best current proven intervention**, except in the following circumstances:
  - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
  - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

A problem with that?

- In 2007 our hospital decided to introduce mithril-coated central venous catheters.
- Data on each insertion site infection and on patients' characteristics were collected to test whether the decision was justified and cost-effective.
- As the data were collected for the institution's purpose the patients were not asked for consent.
- For this paper we used anonymized data to compared rates of central line infections during 2005-2007 to 2008-2010.
- The rate in the first period was 10 per 1000 catheter days, and in the second period, 2 per 1000 catheter days, p=0.01.
- Mithril coated catheters are effective in reducing infections.

Rate of infection



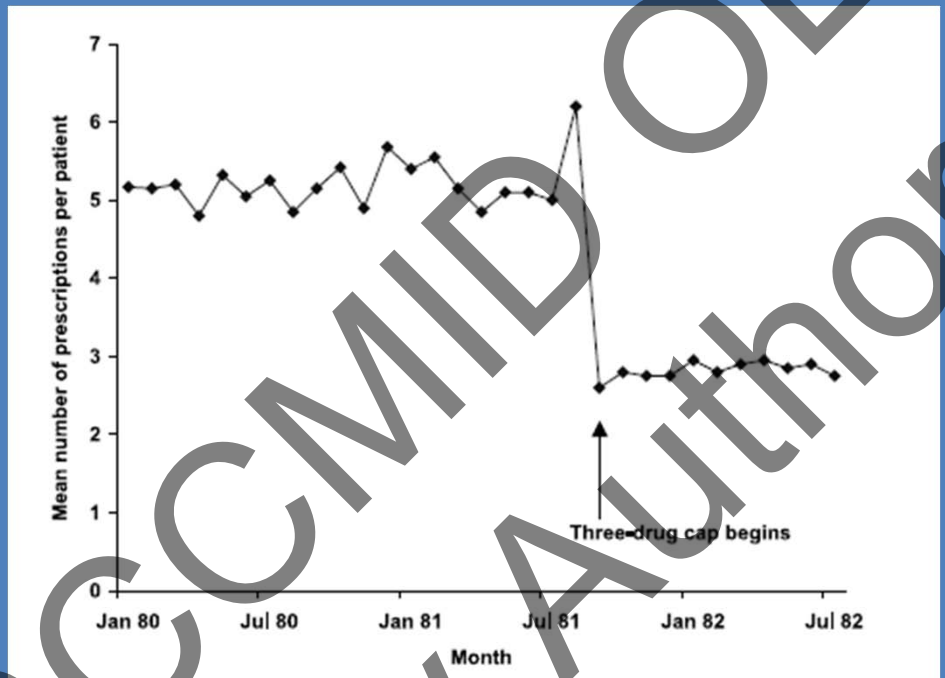
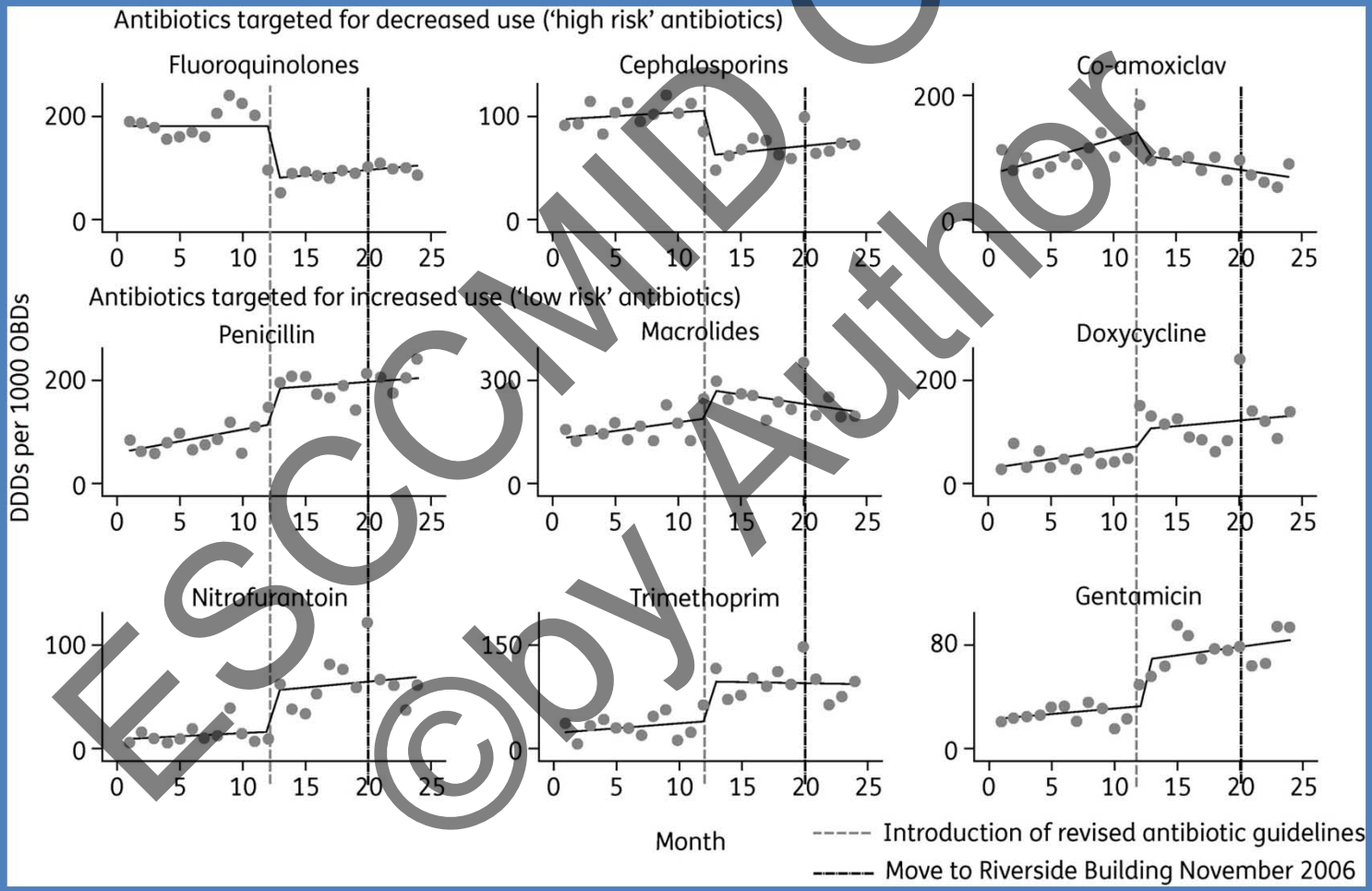


Fig. 1. Average number of constant-size prescriptions per continuously eligible Medicaid patient per month among multiple drug recipients (2).



A problem with that?

- In a cohort of 1011 patients admitted to the hospital, we found 22 carriers of MRSA.
- On univariate analysis, 18 factors were significantly related to carriage.
- These factors were entered into a stepwise logistic regression analysis.
- The resulting model was highly predictive of carriage, and can be used to reduce the number of screened patients.

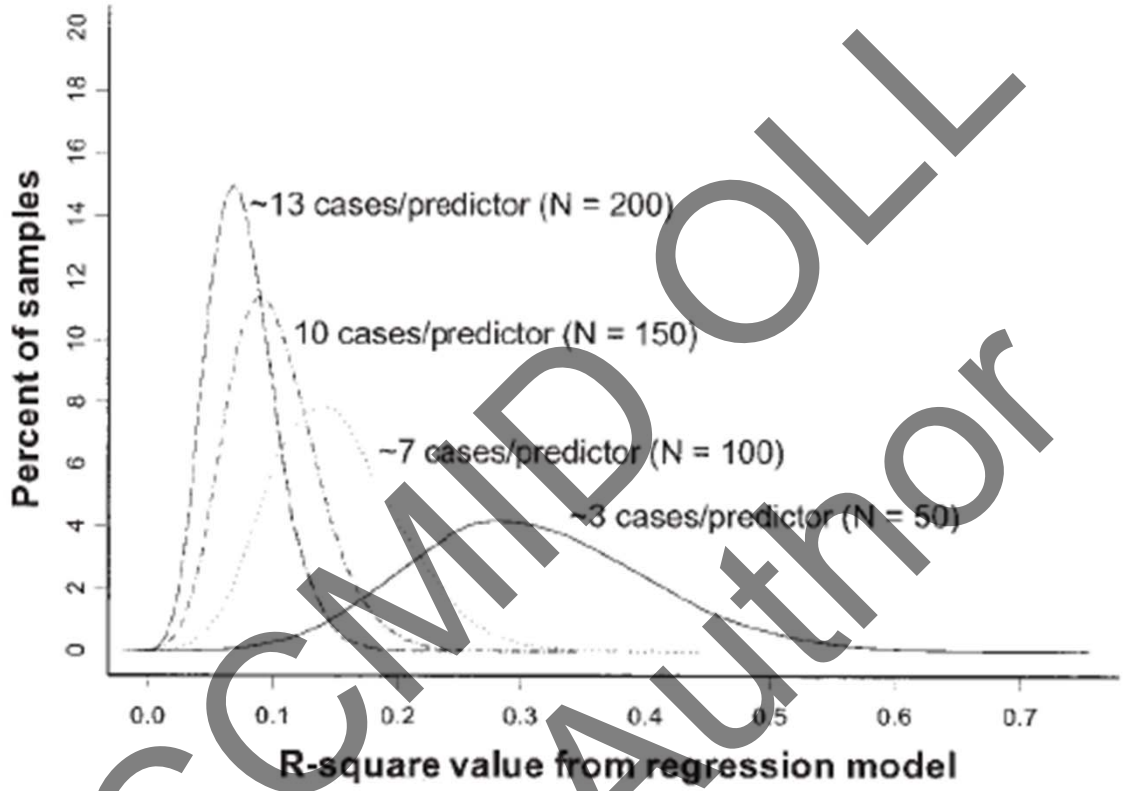


Figure 2. Pure noise variables still produce good R^2 values if the model is overfitted. The distribution of R^2 values from a series of simulated regression models containing only noise variables. The model contained 15 predictors, each consisting of randomly generated values, and a response variable, whose values were also randomly generated. Thus, the true model has an R^2 of 0. Four sets of 10,000 random samples were drawn, each of sample size $N = 50$, $N = 100$, $N = 150$, and $N = 200$. The smoothed frequency distribution of the R^2 values generated by each of the 10,000 models is plotted here for the 4 sample size conditions. Note that even when the number of cases per predictor is reasonably good (200/15=13.3), there are, solely because of the chance of the draw, a fair number of non-0 R^2 values. When there were only approximately 50/15=3.3 observations per predictor, the frequency of large R^2 values was quite high.

A problem with that?

- In a retrospective cohort study, the fatality rate of patients with pneumonia was 14% (79/562) in patients treated empirically with a beta-lactam alone vs 9% (67/750) in patients given a beta-lactam+macrolide, $p<0.01$.
- The difference remained significant when corrected for age, CURB-65, and underlying diseases.
- Combination is better than monotherapy with a beta-lactam

Propensity scores

- Propensity scores estimate the predicted probability (propensity) of use of a given drug or procedure in a particular subject, based on his or her characteristics when the treatment is chosen.
- Patients that were given the intervention are compared to these that were not by comparing variables known at the start of treatment.
- The variance that differ are combine into a score (usually using logistic regression analysis) and the score used to compare like to like.

Limitations of propensity scores

- We are not sure that variables of interest were really captured.
- Edges with no overlap.
- One score.

A problem with that?

- We tested the hypothesis that appropriate empirical treatment given within 12 hours reduces fatality rate of bacteremia.
- Fatality rate in inappropriate treatment group = 36% (277/767).
- Fatality rate in appropriate treatment group = 29% (73/252).
- On a logistic regression analysis, septic shock, age, pneumonia as source of bacteremia, congestive heart failure and acute renal failure emerged as independent predictors of a fatal outcome, but not appropriateness of treatment.

- Take care of the causal path

A problem with that?

- The new drug was as effective as the old drug. The present study aimed to look at the rate of serious adverse events.
- The efficacy of the new drug and comparator was similar.
- Serious adverse events were registered in 4 out of 80 patients on the new drug (5%) and in 1/76 patients on the comparator (1.3%); p=0.78, difference with no statistical significance.
- The new drug was as effective a the old one, and with a similar rate of serious side-effects.

- The study was not powered to show a difference in adverse side effects. A difference 1.3% →5% can be a major one.
- The proper sample size calculations should have been done.

Summary

- Make sure that our research is ethically correct.
- Read the ORION statement for before-after studies.
- Familiarize yourself with the terms of over-fitting and under-fitting.
- In non-randomized comparisons, be sure that the groups are comparable. Make correct use of propensity scores.
- Draw a causal path before data analysis.
- A proof that superiority was not shown is not a proof that equality exists.

Thank you