Ethical dilemmas in antibiotic treatment

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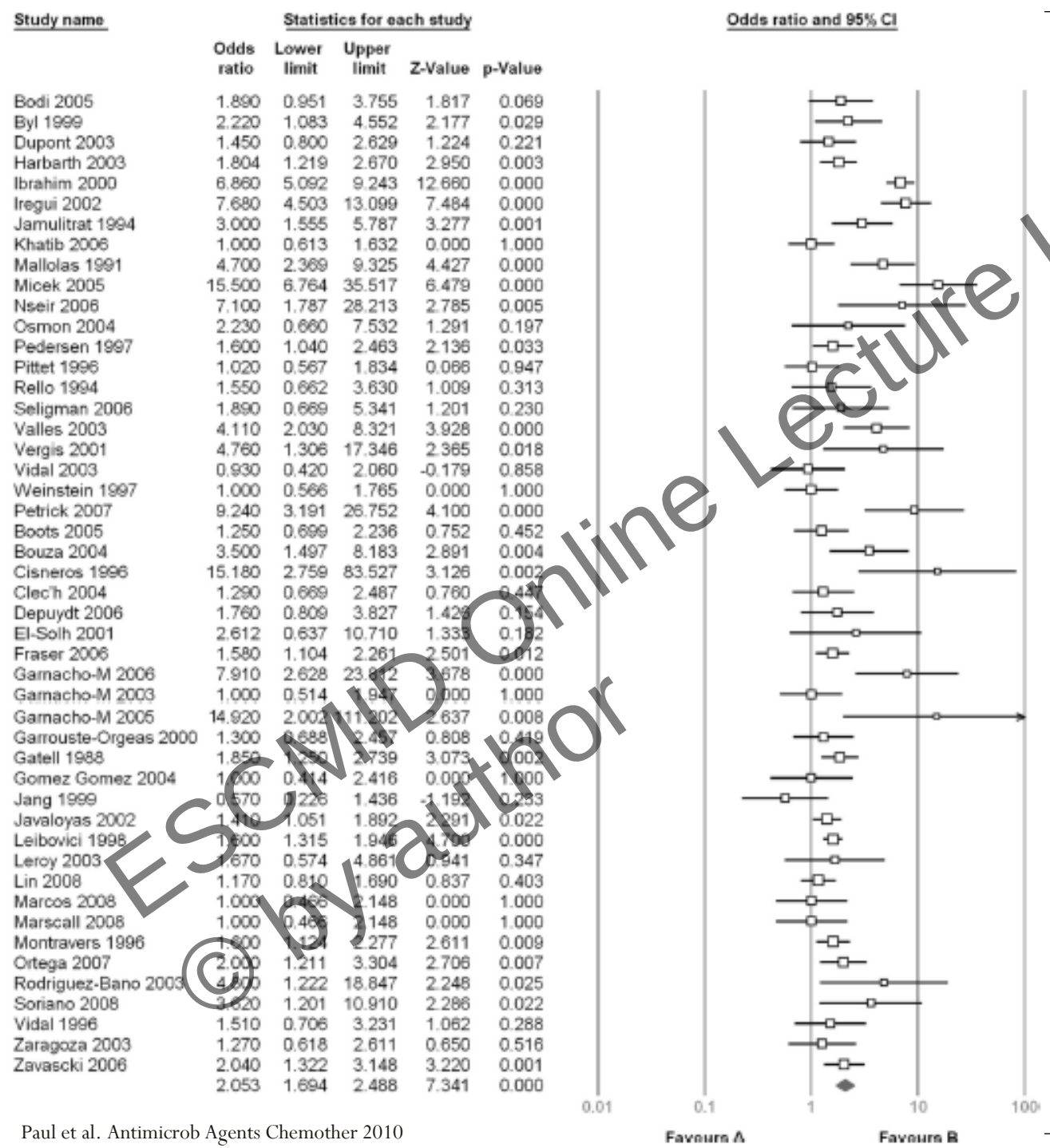
Empirical antibiotic treatment

- Almost all antibiotic treatments started in hospitals are started empirically: the pathogen and its susceptibilities to antibiotics are unknown.
- About 30%-50% of definitive antibiotic treatments are empiric.
- We are prescribing treatment according to probabilities.
- Appropriate empirical antibiotic treatment (i.e. matching the in-vitro susceptibility of the pathogen) affords better chances for survival and uneventful recovery to patients with a moderate to severe bacterial infection.
- We (practitioners all over the world) almost never prescribe empirical antibiotic treatment with maximum coverage to these patients, although it can be done.
- In part this is due to miscalculations, but in part it is done to slow the rapid rise in resistance.

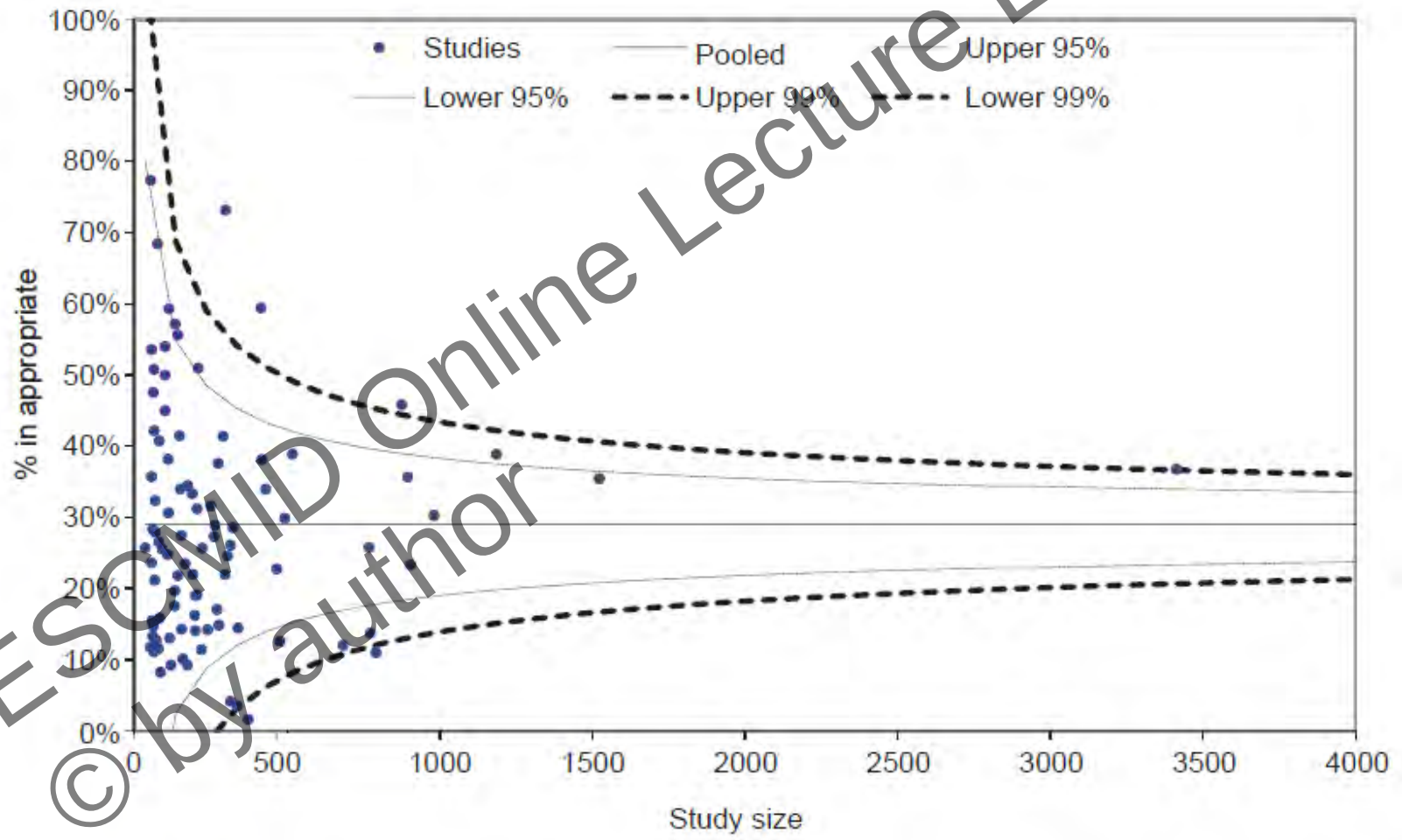
Association of appropriate empirical antibiotic treatment and all-cause mortality



OR of inappropriate empirical treatment for mortality 2.05 (95% CI 1.69-2.49)

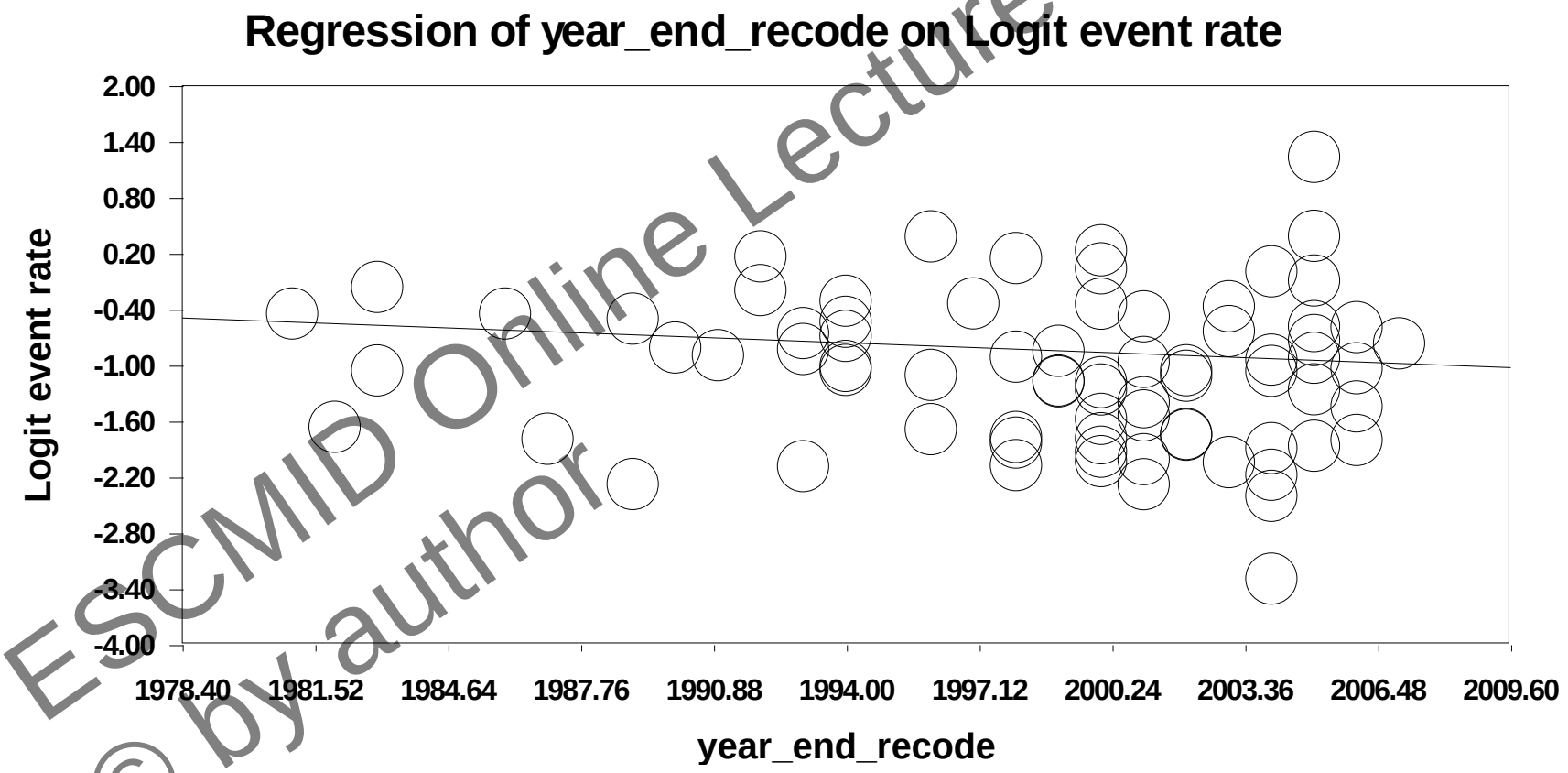
Paul et al. Antimicrob Agents Chemother 2010

Rates of inappropriate empirical antibiotic treatment in the published literature



Kariv et al. Clin Microbiol Infect 2012: 92 studies, 27, 628 patients, 1977- 2007

Are we improving with time?



Mixed effect meta-regression, slope -0.01 (-0.03-0.01, p=0.23

The ethical dilemmas:

We prescribe less than maximum treatment for the present patient in order to benefit future patients. It raises 2 ethical dilemmas:

- Current, identified patients at risk are given less than maximum treatment in order to benefit future, unidentified patients;
- The present patient is not informed of the choices and the patient's consent is not given, although the choice of antibiotics might have grave consequences for the patient's health and chance of survival.

Should we balance a benefit to future, unknown patients with the harm to the present patient?

- The Georgetown mantra of bioethics: beneficence, non-maleficence, autonomy, and justice.
- 'Justice between generations' (Rawls J. A Theory of Justice. Cambridge, MA, USA: Belknap Press of Harvard University Press, 1971.)
- '…when a person takes something from nature and makes it his own property, one is allowed to do so only where there is enough, and as good left in common for others' (John Locke's Second Treatise of Government)
- Medical professionalism: The fair distribution of healthcare resources is one of the principles of professionalism, and commitment to just distribution of finite resources is one of its commitments. (ABIM Foundation, ACP-ASIM Foundation, European Federation of Internal Medicine. Medical professionalism in the new millennium: a physician charter. Ann Intern Med 2002; 136: 243–6.)
- Utilitarian theories and models: cost utility and cost benefit among them.

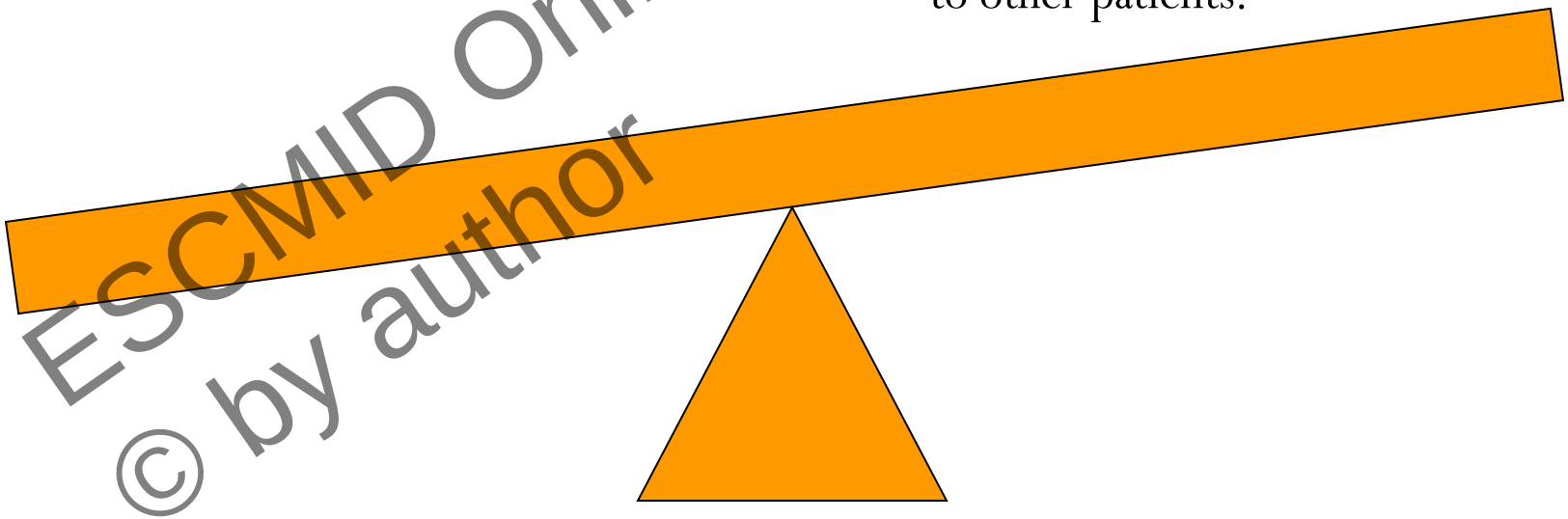
Utilitarian theories: The most benefit for all people:

Cost-effectiveness or cost-utility or cost benefit analysis

Benefits: better survival;

less morbidity: QALYs

Costs: direct, side-effects, ecological cost: to patient, to other patients.



Immanuel Kant:

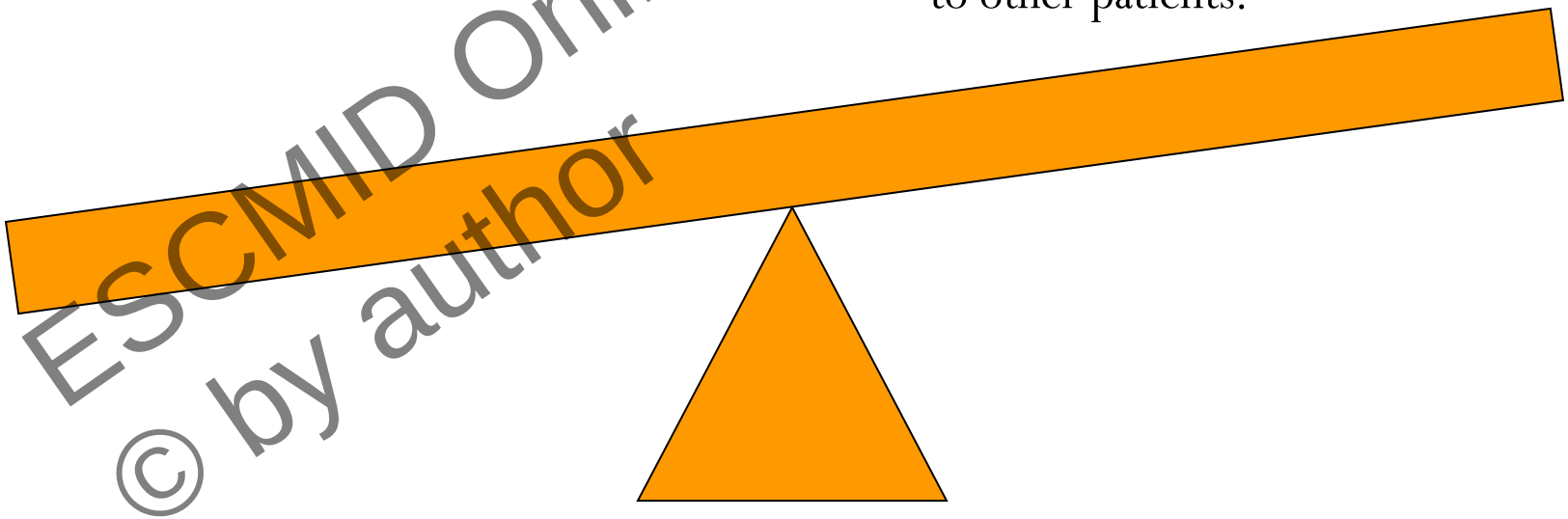
"Act in such a way that you treat humanity, whether in your own person or in the person of any other, never merely as a means to an end, but always at the same time as an end."

42 years old patient with severe infection

Benefits: better survival;

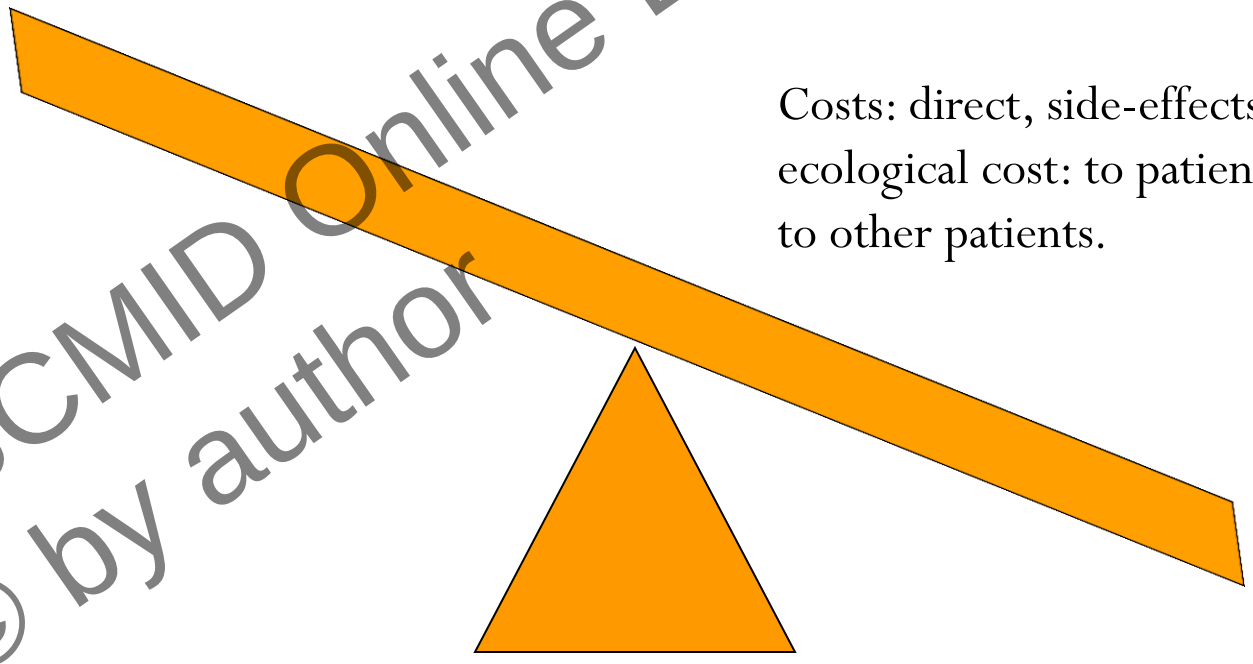
less morbidity: QALYs

Costs: direct, side-effects,
ecological cost: to patient,
to other patients.



80 years old healthy patient with severe infection:

Few QALYs



Costs: direct, side-effects, ecological cost: to patient, to other patients.

Autonomy, consent:

Isaiah Berlin:

'I wish my life and decisions to depend on myself, not on external forces of whatever kind. I wish to be the instrument of my own, not other men's act of will. I wish to be a subject, not an object; to be moved by reasons, by conscious purposes which are my own, not by causes which affect me, as it were, from outside.'

Autonomy, consent:

- I see no viable solution in which the consent of the patient for balancing one's rights against rights of other people is asked for .
- Decisions on the collective (guidelines, decision support systems) are part of the solution. The better they are, the better the solution.
- Ignoring autonomy goes against the fiber of the modern bioethical discourse, where the autonomy principle is almost always paramount.

Autonomy, consent:

- Autonomy is the foremost protection against the abuses of medical research that started the modern bioethical discourse.
- We are dealing with clinical practice and not with research.

Informed consent, research:

The Helsinki Declaration, 2013:

- Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary.
- …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, post-study provisions 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.

GCP rules: very detailed and structured written informed consents.

Impressions from pragmatic randomised controlled trials we are running (1):

- Trials of old antibiotics: TMP/SMZ vs vancomycin for severe MRSA infections; colistin vs. colistin+meropenem for Gram (-) severe infections susceptible only to colistin.
- Septic patients, even when '*compos mentis*' are in no shape to read pages of explanation and weigh "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, post-study provisions and any other relevant aspects of the study".
- Almost a mockery of the informed consent concept.

Impressions from pragmatic randomised controlled trials we are running (2):

- The Research Ethics Board did not authorize us to recruit patients who could not sign an informed consent into the TMP/SMZ trial.
- It created huge differences between potential and actual participants; and endangered external validity.

Informed consent in trials of old antibiotics in septic patients:

- Not really informed; creates a huge problem of external validity.
- Opinions are voiced that in some comparative effectiveness trials informed consent is not needed.
- Personal, absolute autonomy (informed consent) is the foremost guardian against the abuses of human rights disguised as medical research.
- Solutions?

Summing up

- Future patients have rights. Prescribing antibiotics we should weigh their rights against the rights of present patients.
- A quantitative balance can be achieved using cost benefit or cost utility analysis; but these have moral limitations, common to all utilitarian models, that have to be solved.
- In clinical practice it's unpractical to ask for consent of the present patient with a severe infection to limit treatment brcause of future patients, and the autonomy principle is breached.
- Decisions on the collective are part of the solution.
- Are we justified in infringing on the patients' autonomy in comparative effectiveness trials of old antibiotics?