TREAT: a system for decision support in antibiotic treatment and for antibiotic stewardship: a case study

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Disclosure:

I was the initiator and one of the original developers of TREAT.

I am on the scientific advisory board of TREAT Co.; a non-paying position.

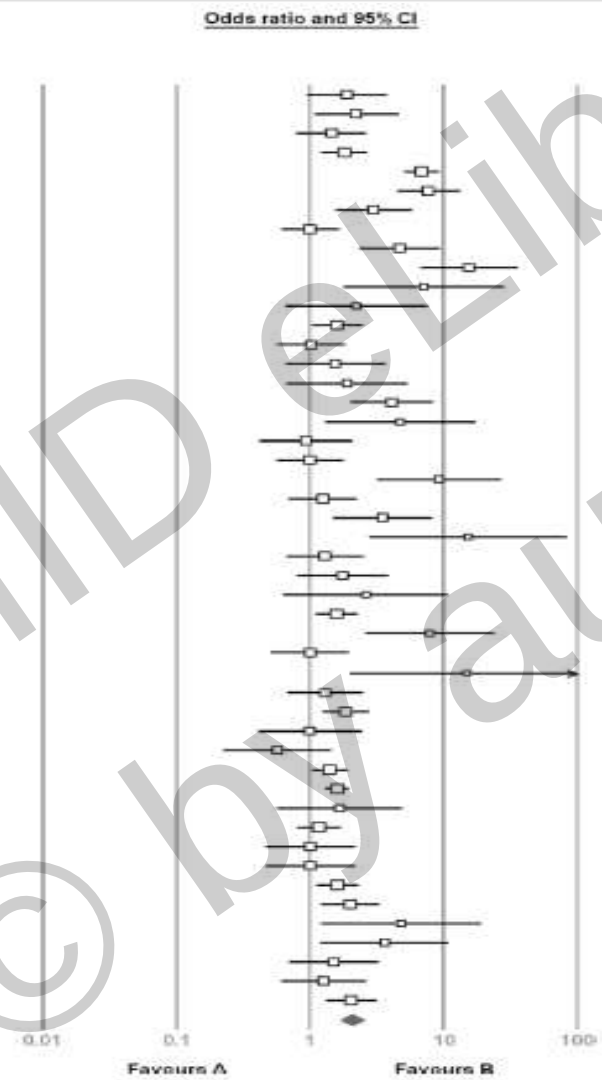
Early empirical antibiotic treatment is often wrong and harms patients

- 1988-1998: 3413 patients with bloodstream infections in my hospital.
- 1255 (37%) were given inappropriate empirical antibiotic treatment.
- Fatality rate:
  - Appropriate empirical antibiotics: 20%
  - Inappropriate: 34%
  - aOR: 1.6, 95% CI: 1.3-1.9

Leibovici L et al. J Intern Med 1998;244:379.

Association of appropriate empirical antibiotic treatment and all-cause mortality

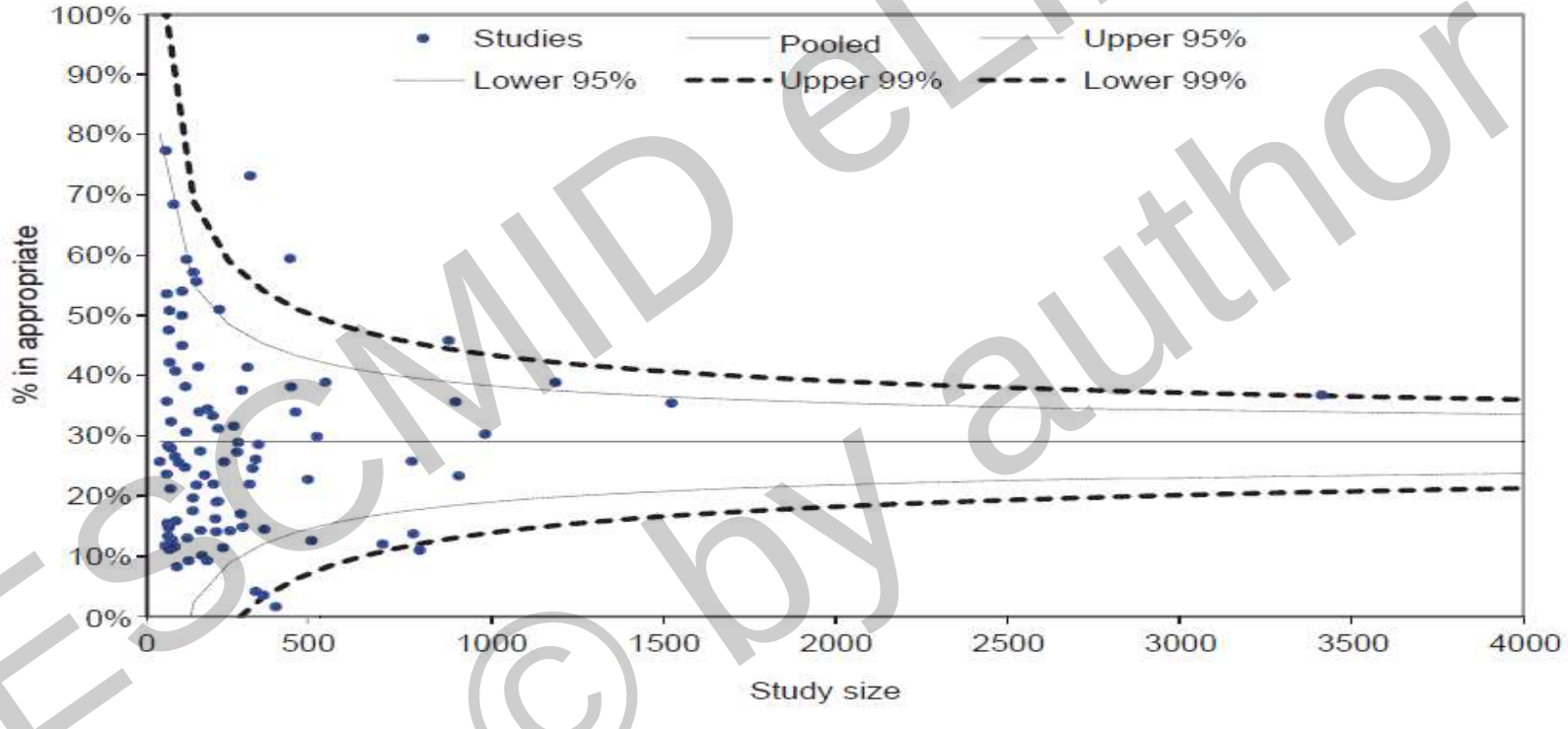
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Bodi 2005	1.890	0.951	3.755	1.817	0.069
Byl 1999	2.220	1.083	4.552	2.177	0.029
Dupont 2003	1.450	0.800	2.629	1.224	0.221
Harbarth 2003	1.804	1.219	2.670	2.950	0.003
Ibrahim 2000	6.860	5.092	9.243	12.660	0.000
Iregui 2002	7.680	4.503	13.099	7.484	0.000
Jamulitrat 1994	3.000	1.555	5.787	3.277	0.001
Khatib 2006	1.000	0.613	1.632	0.000	1.000
Mallolas 1991	4.700	2.369	9.325	4.427	0.000
Micek 2005	15.500	6.764	35.517	6.479	0.000
Nseir 2006	7.100	1.787	28.213	2.785	0.005
Osmon 2004	2.230	0.680	7.532	1.291	0.197
Pedersen 1997	1.600	1.040	2.463	2.136	0.033
Pittet 1996	1.020	0.567	1.834	0.066	0.947
Rello 1994	1.550	0.662	3.630	1.009	0.313
Seligman 2006	1.890	0.669	5.341	1.201	0.230
Valles 2003	4.110	2.030	8.321	3.928	0.000
Vergis 2001	4.760	1.306	17.346	2.365	0.018
Vidal 2003	0.930	0.420	2.060	-0.179	0.858
Weinstein 1997	1.000	0.566	1.765	0.000	1.000
Petrick 2007	9.240	3.191	26.752	4.100	0.000
Boots 2005	1.250	0.699	2.236	0.752	0.452
Bouza 2004	3.500	1.497	8.183	2.891	0.004
Cisneros 1996	15.180	2.759	83.527	3.126	0.002
Clec'h 2004	1.290	0.669	2.487	0.760	0.447
Depuydt 2006	1.760	0.809	3.827	1.426	0.154
El-Solh 2001	2.612	0.637	10.710	1.333	0.182
Fraser 2006	1.580	1.104	2.261	2.501	0.012
Garnacho-M 2006	7.910	2.628	23.812	3.678	0.000
Garnacho-M 2003	1.000	0.514	1.947	0.000	1.000
Garnacho-M 2005	14.920	2.002	111.202	2.637	0.008
Garrouste-Orgeas 2000	1.300	0.688	2.457	0.808	0.419
Gatell 1988	1.850	1.250	2.739	3.073	0.002
Gomez Gomez 2004	1.000	0.414	2.416	0.000	1.000
Jang 1999	0.570	0.226	1.436	-1.192	0.233
Javaloyas 2002	1.410	1.051	1.892	2.291	0.022
Leibovici 1998	1.600	1.315	1.946	4.700	0.000
Leroy 2003	1.670	0.574	4.861	0.941	0.347
Lin 2008	1.170	0.810	1.690	0.837	0.403
Marcos 2008	1.000	0.466	2.148	0.000	1.000
Marscall 2006	1.000	0.466	2.148	0.000	1.000
Montravers 1996	1.600	1.124	2.277	2.611	0.009
Ortega 2007	2.000	1.211	3.304	2.706	0.007
Rodriguez-Bano 2003	4.800	1.222	18.847	2.248	0.025
Soriano 2008	3.620	1.201	10.910	2.286	0.022
Vidal 1996	1.510	0.706	3.231	1.062	0.288
Zaragoza 2003	1.270	0.618	2.611	0.650	0.516
Zavascki 2006	2.040	1.322	3.148	3.220	0.001
	2.053	1.694	2.488	7.341	0.000



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

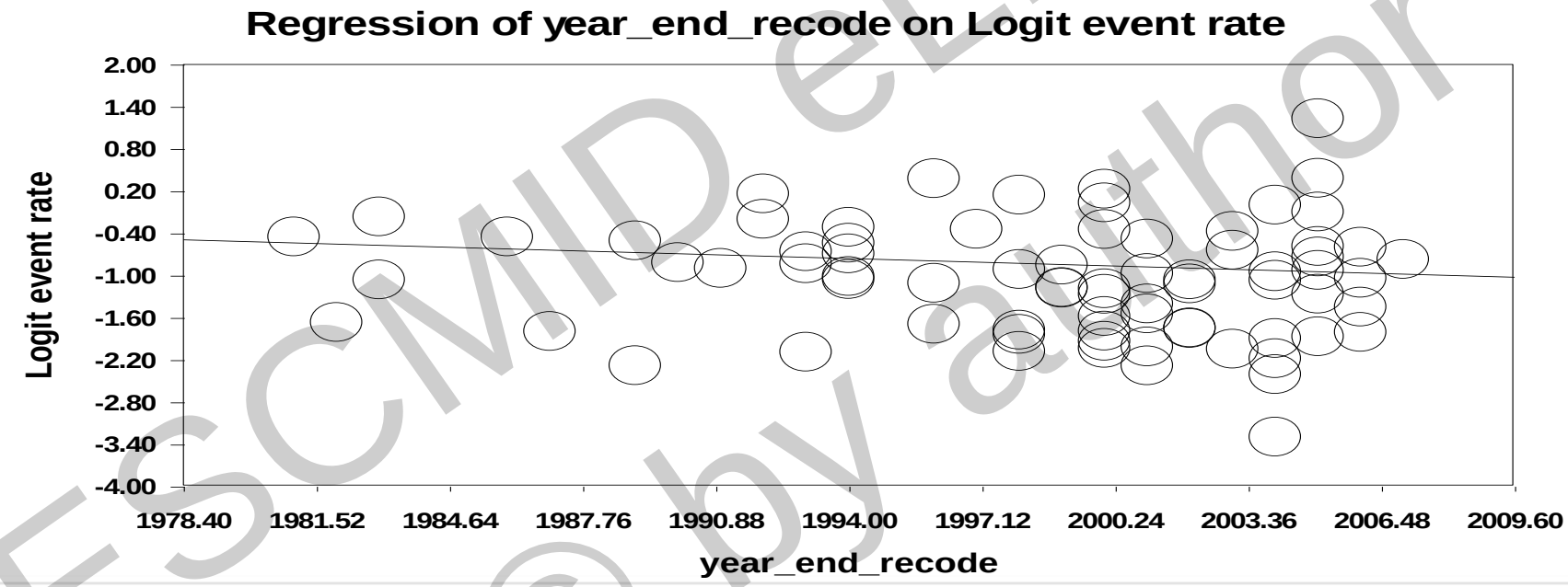
Paul et al. Antimicrob Agents Chemother 2010

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

Superfluous and unnecessary antibiotic treatment

- About 50% of antibiotic courses are either unnecessary (no bacterial infection) or too broad spectrum.
- Antibiotic treatment is special:
  - There is no other instance where treatment of an individual affects other people
  - There is no other treatment that consumes itself
  - There is no intervention in medicine as effective as antibiotic treatment

About 95% of early antibiotic treatments and 65% of definitive treatments are empirical

- We are doing badly.
- Data exists and might be better used, e.g.:
  - Leibovici L et al. Clinical index to predict bacteraemia caused by staphylococci. J Intern Med. 1993;234:83.
  - Gransden W et al. Risk factors and a clinical index for diagnosis of Pseudomonas aeruginosa bacteremia. Clin Microbiol Infect. 1995;1:119.

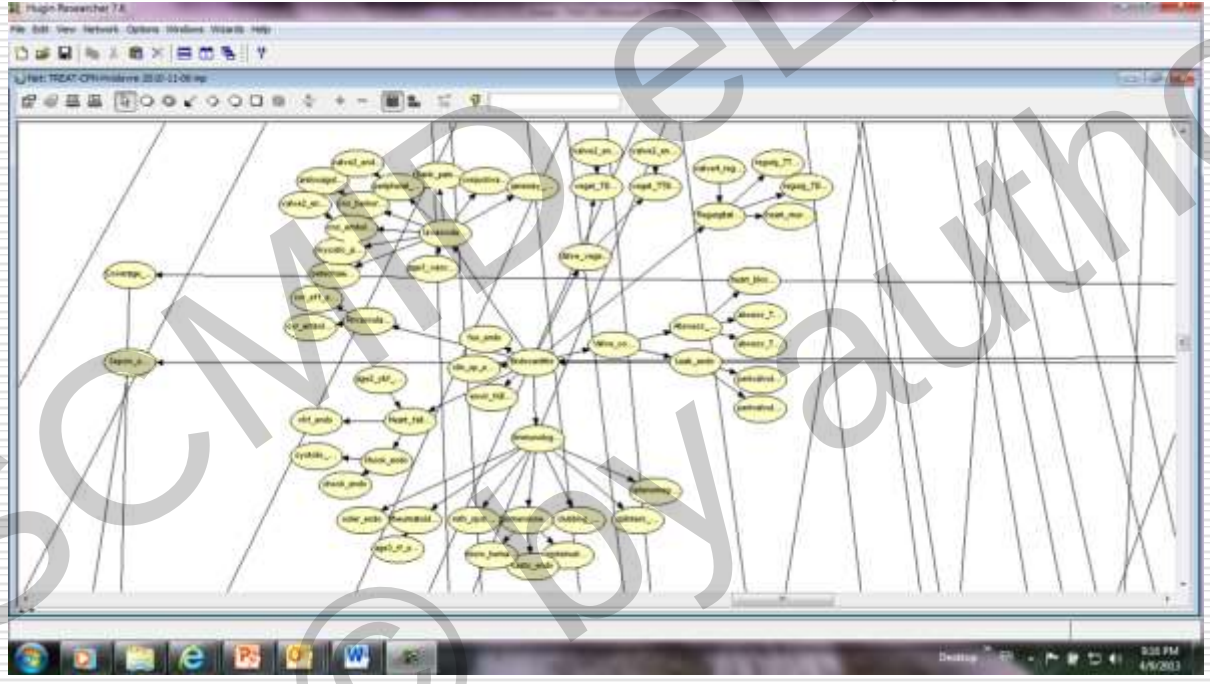
Decision support system

- Can intervene in the myriads of interactions of prescribing antibiotics.
- Decisions on the collective: weighs in the same model the benefit to the present patient vs harm to future patients.
- Uniform, equalitarian considerations.

The logical core: CPNs' advantages

- Qualitative knowledge integrated into the network's structure
- Quantitative data into probabilities.
- Allows for combination of data from different datasets.
- Allows for missing data.
- Explicit definition of universal vs. local factors.
- Allows for local and temporal calibration.
- Allows for addition of new knowledge and new data.
- Functionality transparent.

Endocarditis model:



Output

- Probability of infection, source of infection and pathogen probabilities
- Coverage of specific antibiotics and antibiotic combinations (expressed as proportion of eradicated infection)

Cost-benefit model

- Benefit
  - Appropriate antibiotic reduces mortality odds by ~1.6
  - Reduces hospital stay by ~2 days
- Cost
  - Direct drug, administration and monitoring costs
  - Adverse events costs
  - Ecological costs
  - Penalty

Proof that it works

- Observational studies → akin to phase I and II in drug trials
- Randomized controlled trial:
  - cluster randomization
  - 14 wards of medicine: Rome, Freiburg, Petah-Tiqva

Randomized controlled trial

- Cluster (=department) randomized trial
- Included 2,326 patients in Israel, Germany, Italy
- Departments of medicine, infectious diseases, and specialized medical department

Intervention

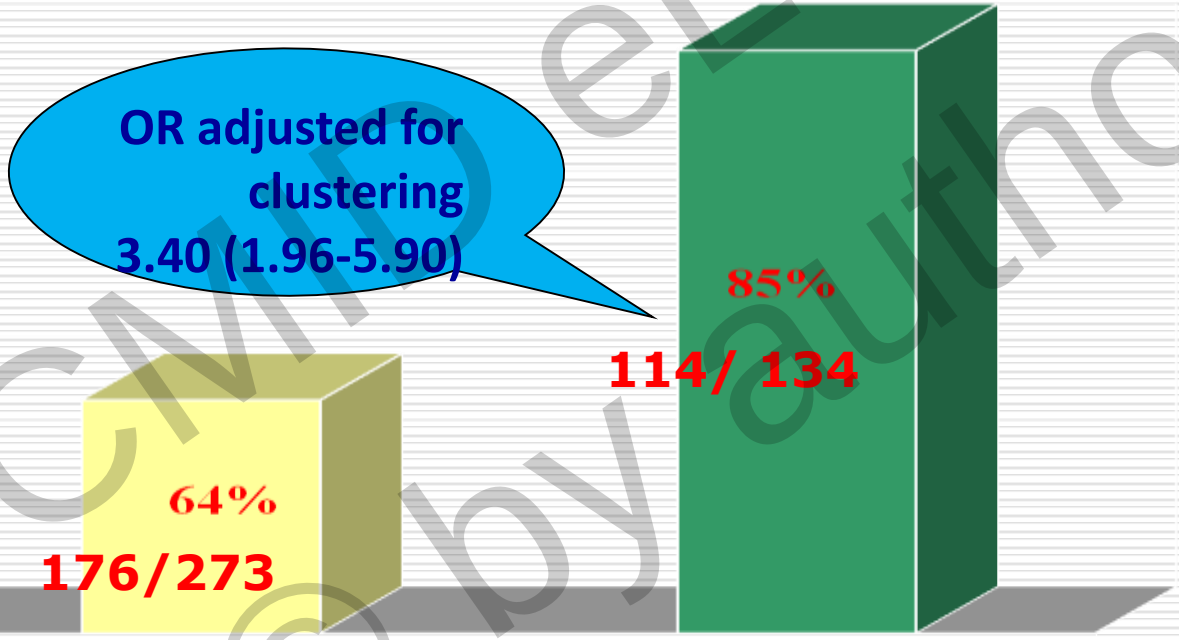
TREAT system installed and used. Advice optional.

Control

Local guidelines distributed. Antibiotic use monitored

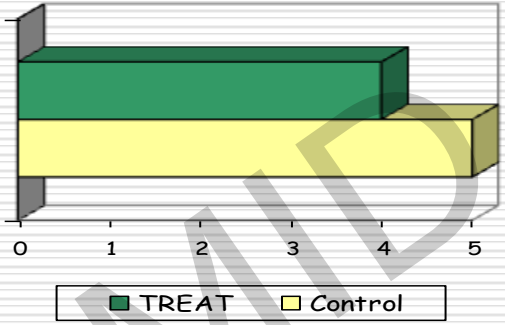
Paul, Leibovici et al. J Antimicrob Chemother 2006

Appropriate empirical treatment



Secondary outcomes
intention to treat

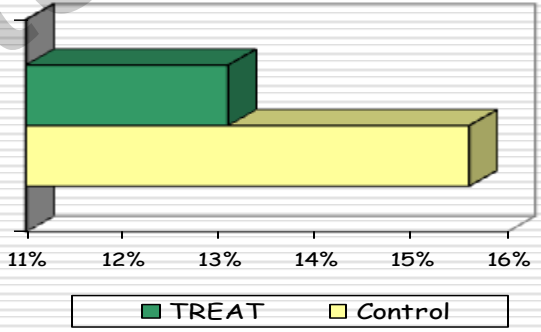
Mean hospital stay



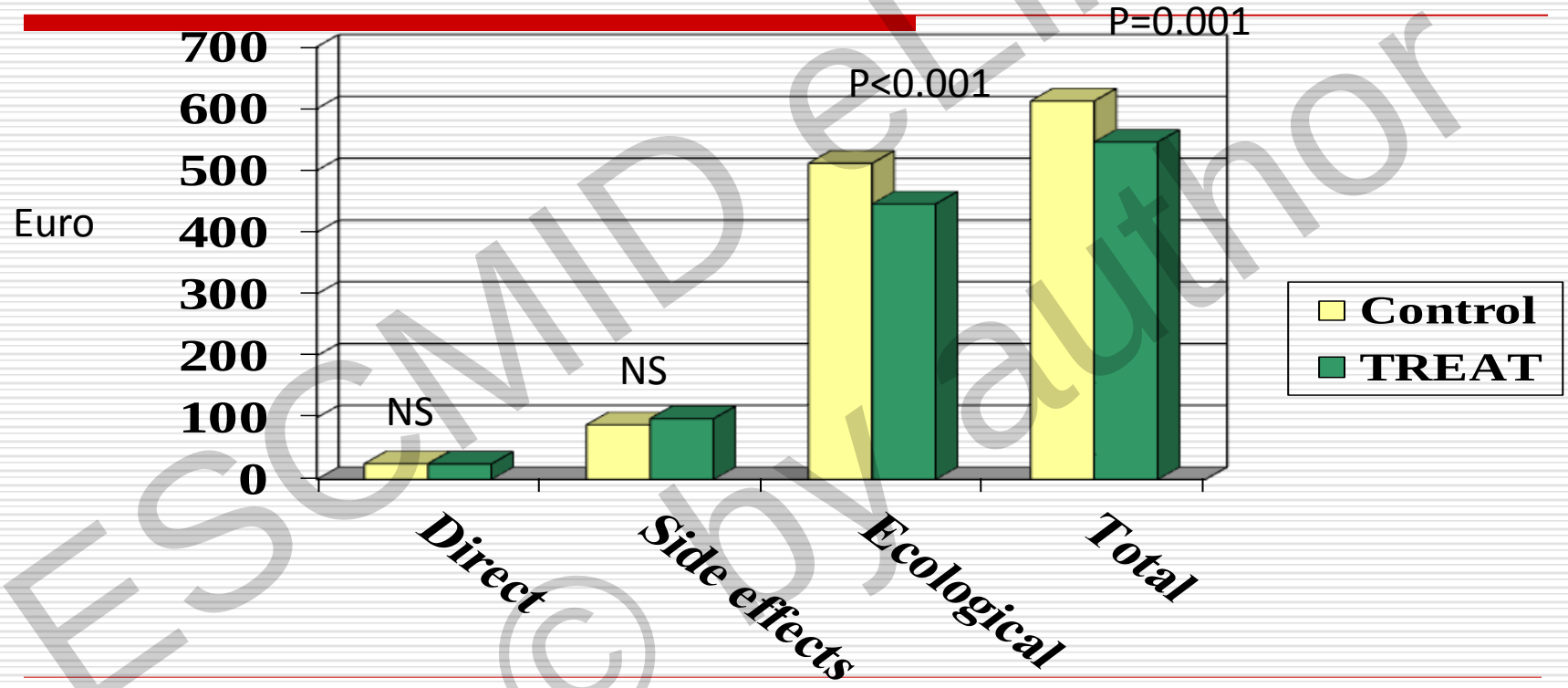
P=0.014

P=0.327

all-cause 30-day mortality

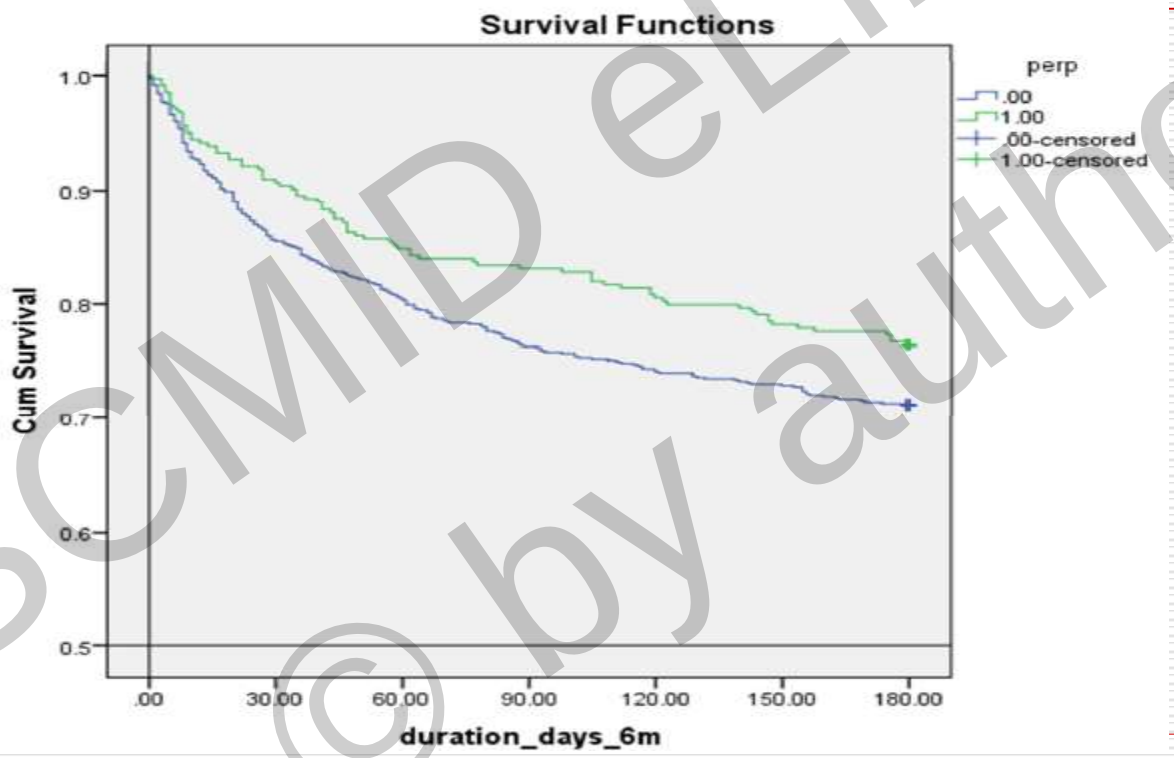


Antibiotic costs



Paul, Leibovici et al. J Antimicrob Chemother 2006

Long-term follow-up: survival, the whole group



Leibovici et al. J Antimicrob Chemother 2013

Judex decides to go commercial: TREAT company established

- Interfaces with hospital databases
- New graphical interface
- New functionality for antibiotic stewardship
- Standard procedures for local calibration.

In my hospital:

- The hospital administration is convinced.
- But does not have the money to install it (in reality: lower priority than a surgical robot and other gadgets).
- Time passes.
- I enlist the help of a philanthropic foundation (the Hurvitz Foundation)

What is done

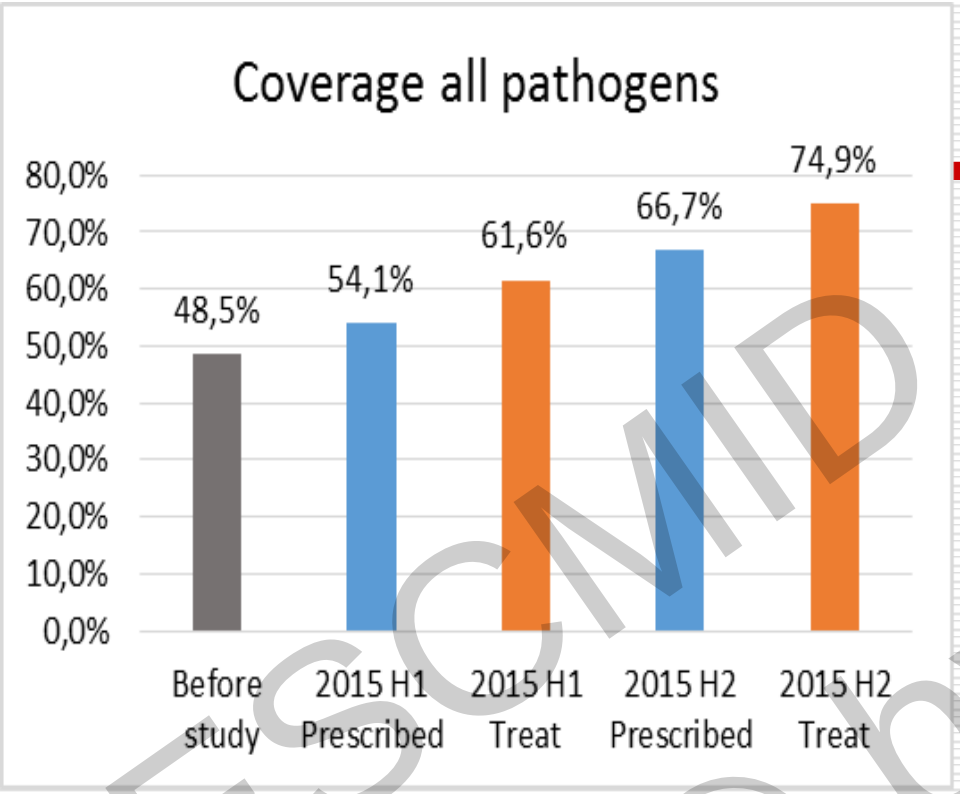
- A central committee on antibiotic stewardship is activated.
- Partners: Infectious Diseases Unit; Pharmacy; clinical units; hospital administration.
- The system is connected to the hospital databases and triggered from the electronic patient file.
- It is calibrated to the hospital:
  - Local distribution of pathogens and their susceptibility.
  - Local formulary.
  - Local preferences.

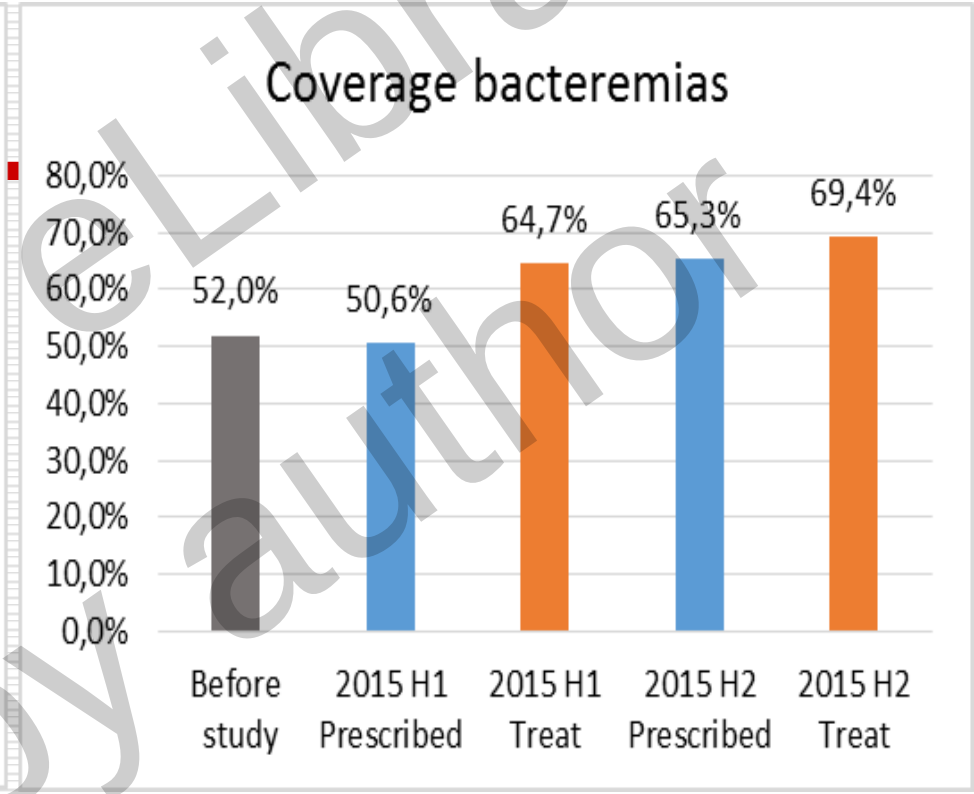
Works in the departments of medicine since 1.1.2015:

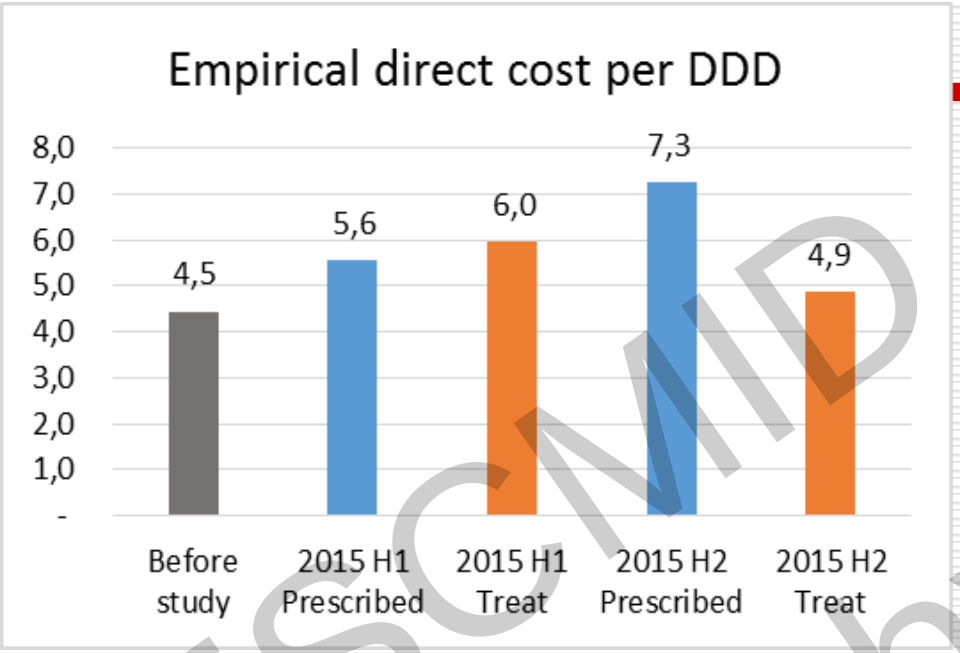
- Is activated from a link in the patient electronic file which opens the patient's data in the TREAT interface
- The physician has to fill in some details on medical history, signs and symptoms (mean interaction <4 min).
- An advice is generated but no direct link to the prescription module.

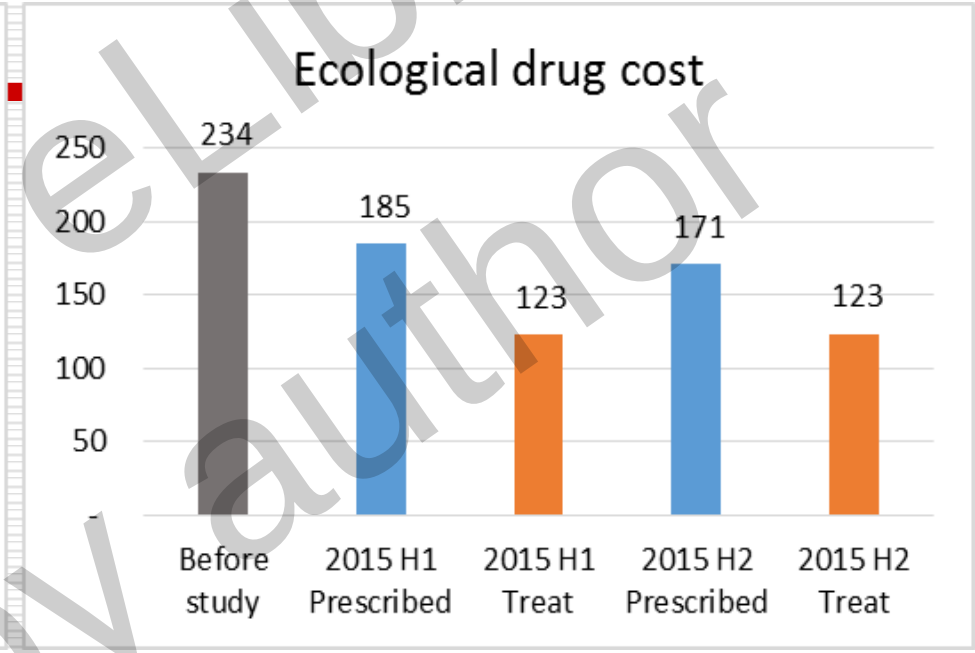
Beilinson 2015-2016, 6 departments of medicine+acute geriatrics

- Before: 2703 patients, MDI:45%
- 2015: 2612 patients; MDI: 42%
- %usage: ~50%
- %compliance: ~50%

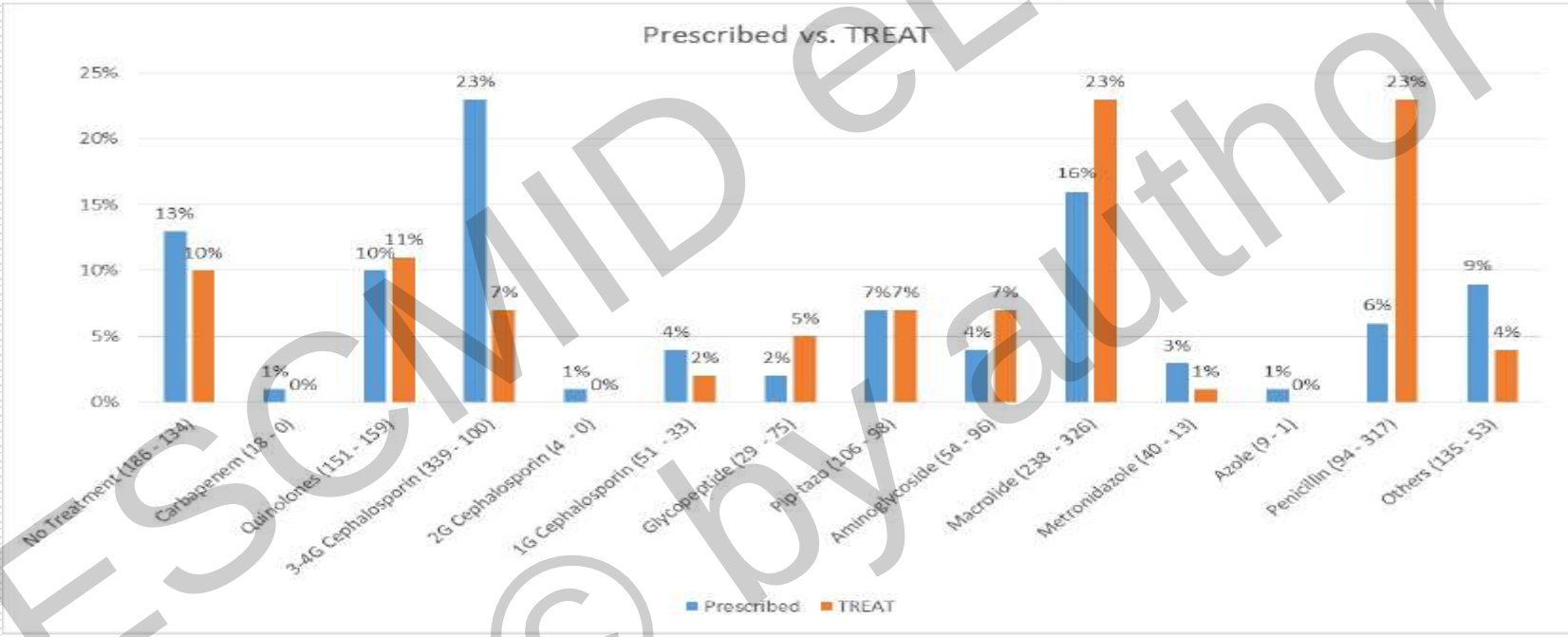




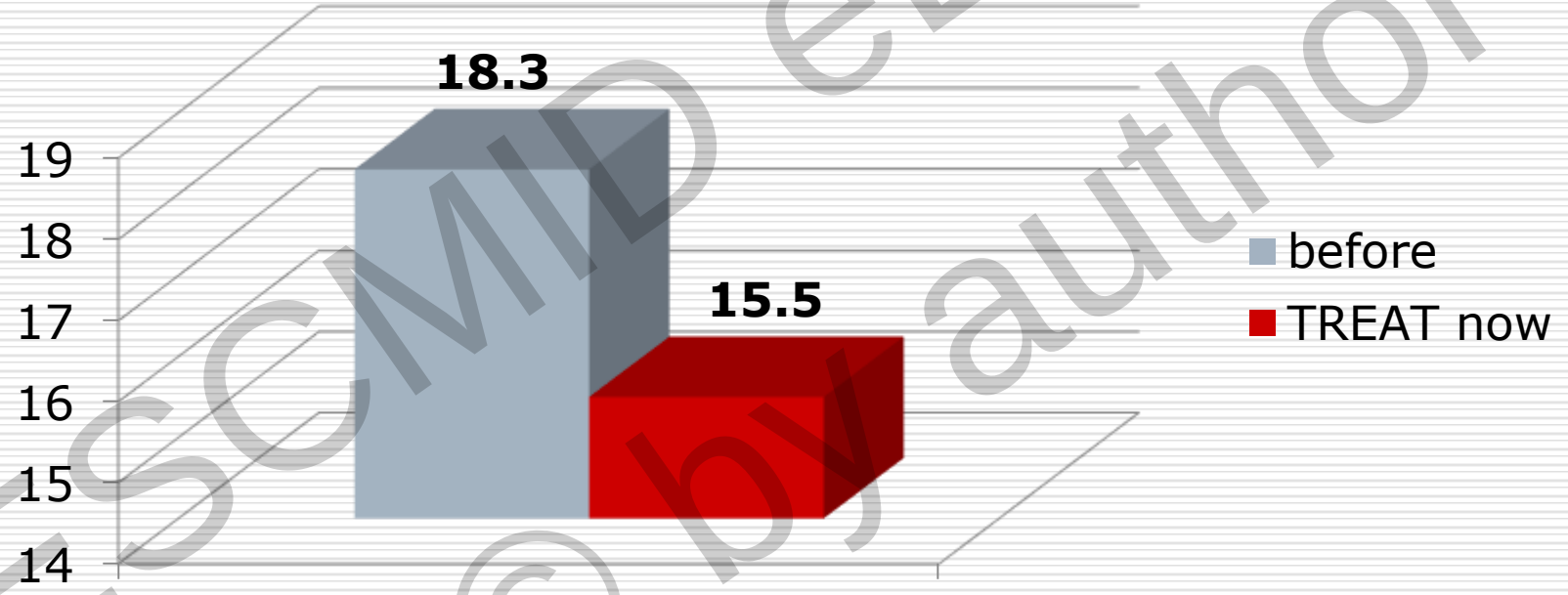




Empirical antibiotic treatment, before vs after:



30 day fatality rate, TREAT now vs before



2016:

- For the first time since 1990 a reduction in antibiotic consumption hospital wide; in the lines expected from the TREAT influence (less 3d gen cephalosporins, more aminoglycosides and penicillins).
- TREAT stewardship interface serves for audits in the surgical departments.

Problems:

- Needs continuous reminders, which demands a dedicated person. A certain method for reminder works for a limited time.
- Needs continuous updating of the content.
- Why did you not use it for this patient?
  - Did not have the time
  - The patient is too complicated
  - The senior physician/I don't believe in computerized decision support.
  - Not according to departmental practice.
  - Incorrect diagnosis or advice
    - Usually because of a wrong input

Do cDSSs work?

- Overall TREAT performance, both in RCT and in real life, was impressive:
  - Higher percentage of appropriate empirical antibiotic treatment.
  - Less use of 'bad' broad spectrum antibiotics
  - Better survival
  - Reduced hospital stay
- Very difficult to maintain it in its present form.
- **Solution: complete integration into the patient electronic file: no DSS interface.**

We need DSS for antibiotic treatment:

- The only solution that intervenes in the myriad physician-patient interactions on antibiotic therapy.
- The only fair, ethical solution to the balance between the present patient and future patients.

Thank you