The Ethics of Antimicrobial Use, AMS and Antibiotic Resistance

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The Pillars of Ethics

- Autonomy
- Non-maleficence
- Beneficence
- Justice

Garau J. Clin Microbiol Infect 2006; 12(suppl. 5): 16-24 (after Beauchamp and Childress)

Uncertainty and the Ethics of Allergy Care

- Uncertainty is a situation faced by physicians and/or patients in which there is a lack of confidence about the optimal course of action
- Two types of uncertainty plague medicine and are especially evident in the practice of allergy
  - Evidentiary uncertainty – limitation of medical knowledge.
  - Existential uncertainty – is an articulation of the inherent "not knowing" that accompanies the medical condition
- Knowledge gaps persist because high-quality evidence is lacking

Nickels AS et al. Ann Allergy Asthma Immunol 2015; 114: 3-5

Uncertainty and the Ethics of Allergy Care

He who loves practice without theory is like the sailor who boards ship without rudder or compass and never knows where he may be cast.

attributed to Leonardo da Vinci

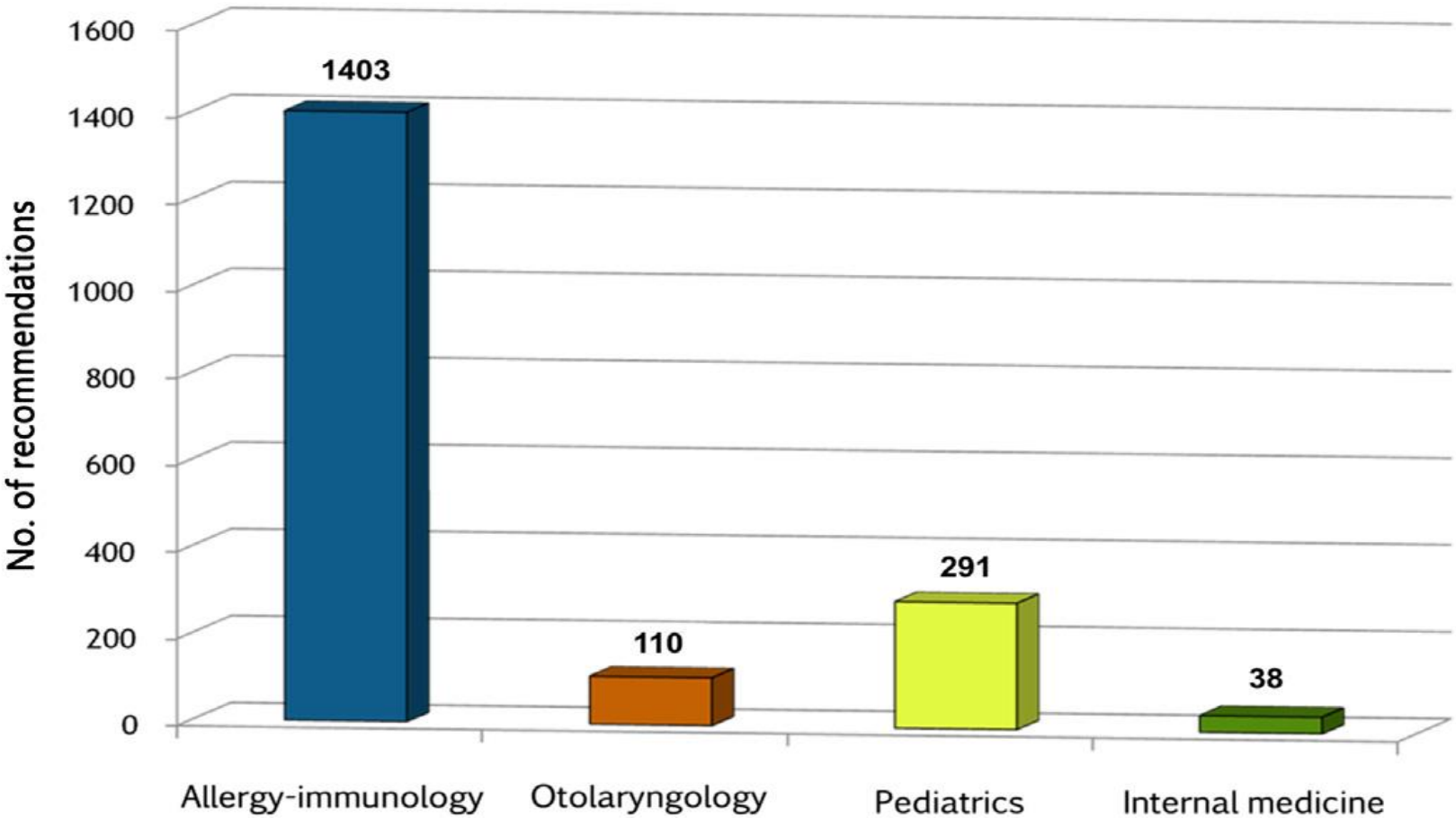
Banks T et al. Ann Allergy Asthma Immunol 2014; 113: 193-197

Practice Parameters and Recommended Data

- Study to assess the level of evidence underlying the recommendations in allergy-immunology, otolaryngology, paediatrics and internal medicine
- Analysed the practice parameters that guide these specialities that appeared in 2012
- Strengths of recommended data was compared after making adjustments for differences in rating scales
- Evidence from controlled trials was lower in the subspeciality fields compared with the primary care fields

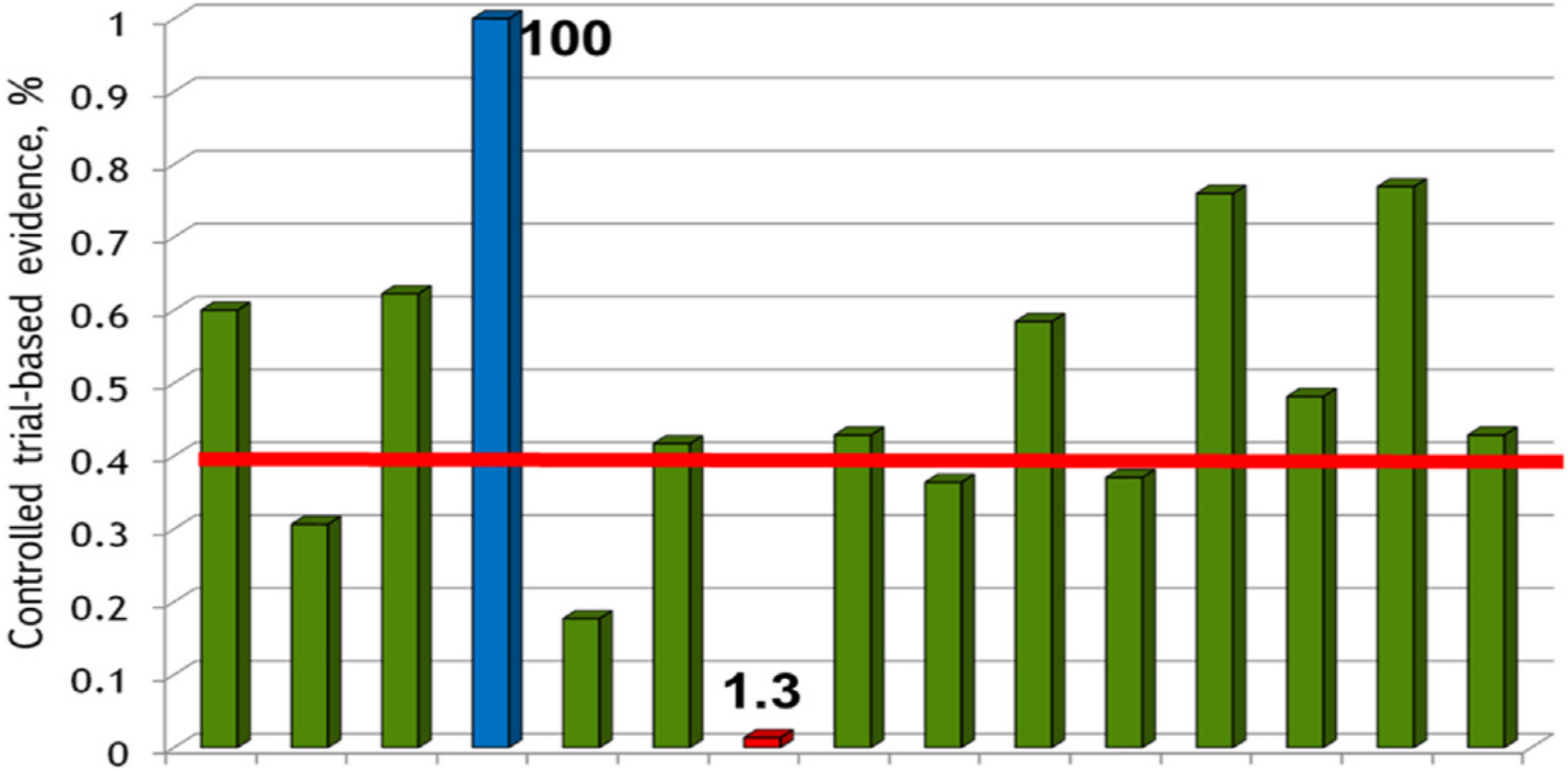
Banks T et al. Ann Allergy Asthma Immunol 2014; 113: 193-197

Number of Recommendations



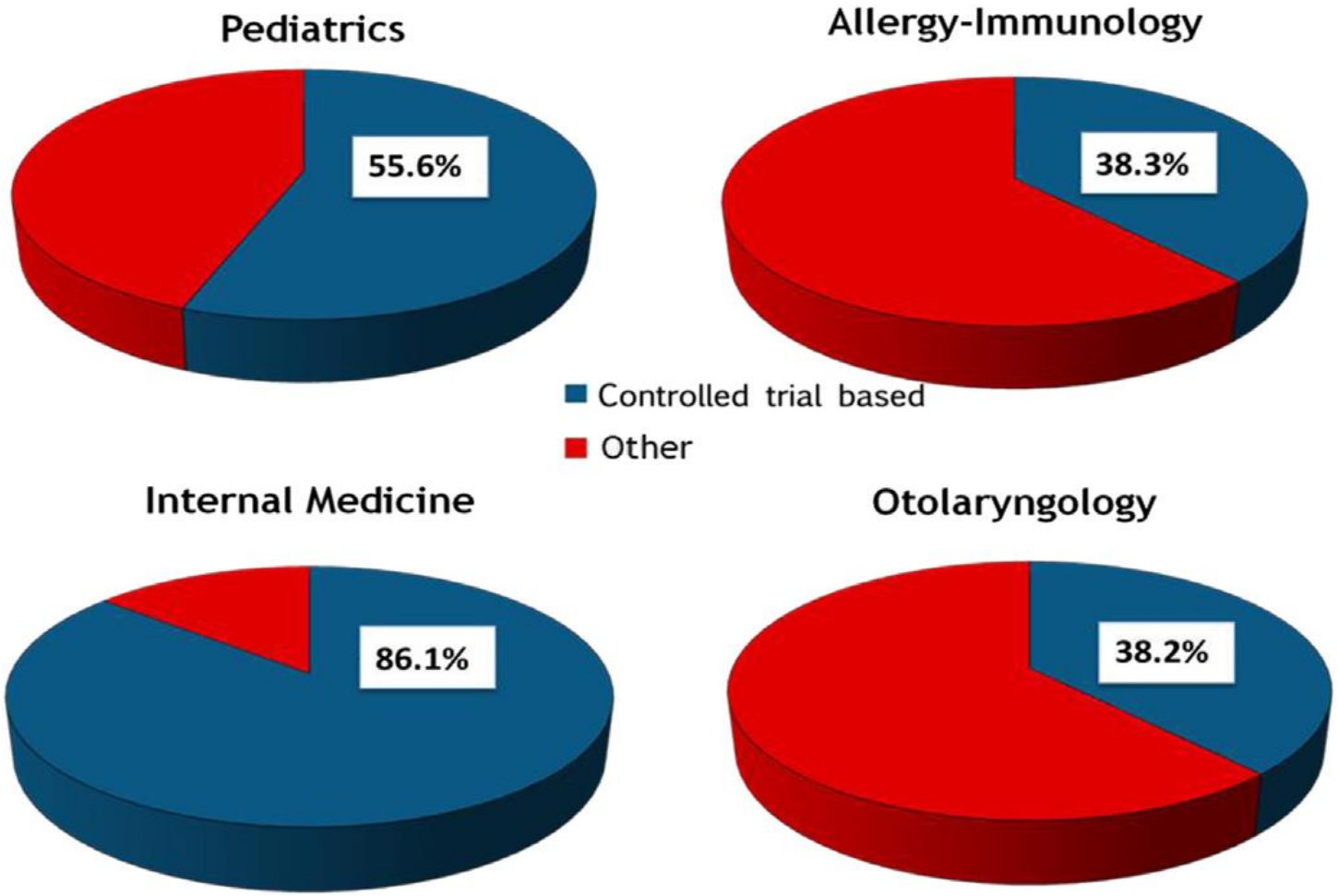
Banks T et al. Ann Allergy Asthma Immunol 2014; 113: 193-197

Percentage of Controlled Trial-based Evidence



Banks T et al. Ann Allergy Asthma Immunol 2014; 113: 193-197

Controlled Trial-based Recommendations



Banks T et al. Ann Allergy Asthma Immunol 2014; 113: 193-197

Antibiotics in Acute Rhinosinusitis

- Overall 90% of adults seen in USA with acute rhinosinusitis get an antibiotic
- Recent research suggest that antibiotics may not always be needed, with most mild-moderate infections being able to get better without antibiotics, avoiding their use and associated risk of antibiotic resistance
- Judicious use is now recommended by many agencies that have published guidelines including the American Academy of Allergy, Asthma, and Immunology, the American College of Allergy, Asthma, and Immunology, and the Joint Council of Allergy, Asthma and Immunology

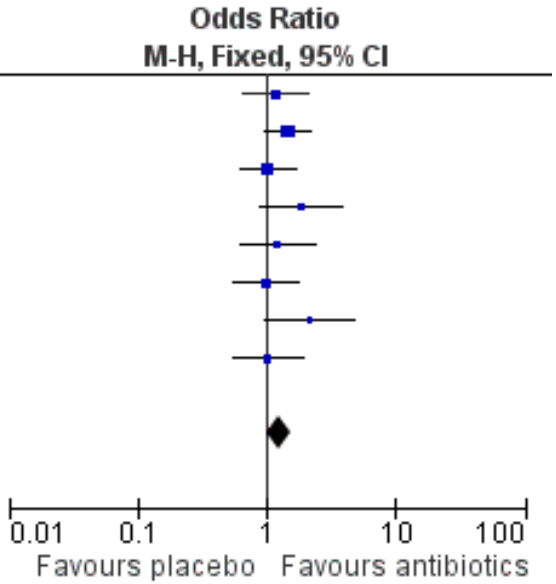
http://www.webmd.com/allergies/antibiotics?print=true

Antibiotics versus Placebo – Overall Treatment Effects

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bucher 2003	95	124	93	126	13.0%	1.16 [0.65, 2.07]
De Sutter 2002	73	189	59	195	21.5%	1.45 [0.95, 2.21]
Kaiser 2001	76	133	75	132	19.5%	1.01 [0.62, 1.65]
Merenstein 2005	32	56	25	60	6.2%	1.87 [0.89, 3.90]
Norrelund 1978	40	71	33	64	9.2%	1.21 [0.62, 2.39]
Stalman 1997	56	94	55	92	13.6%	0.99 [0.55, 1.78]
Varonen 2003	70	85	39	57	5.0%	2.15 [0.98, 4.74]
Williamson 2007	75	101	80	108	12.0%	1.01 [0.54, 1.88]
Total (95% CI)		**853**		**834**	**100.0%**	**1.25 [1.02, 1.53]**
Total events	517		459			

Heterogeneity: $Chi^2 = 5.28$, df = 7 (P = 0.63); $I^2 = 0\%$

Test for overall effect: Z = 2.16 (P = 0.03)



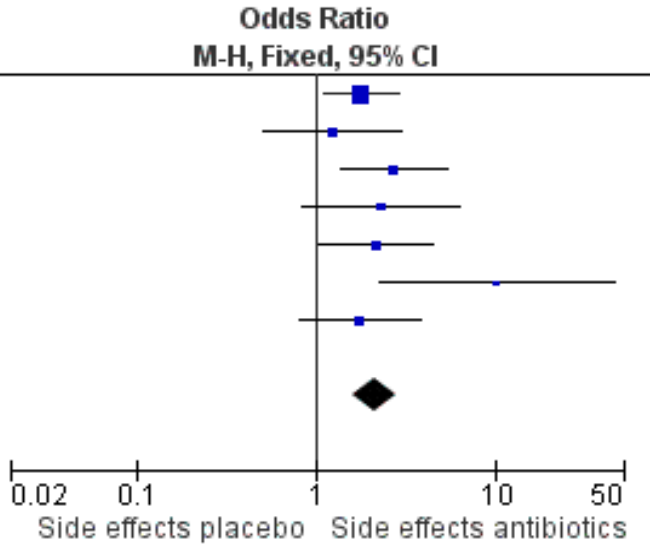
Lemiengre MB et al. Cochrane Database of Systematic Reviews 2012; Issue 10. Art No,: CD006089

Antibiotics versus Placebo – Side Effects

Study or Subgroup	Antibiotica Events	Antibiotica Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
De Sutter 2002	55	189	37	195	35.8%	1.75 [1.09, 2.82]
Garbutt 2012	13	81	10	74	12.2%	1.22 [0.50, 2.99]
Kaiser 2001	32	133	14	132	14.8%	2.67 [1.35, 5.28]
Merenstein 2005	13	56	7	60	7.2%	2.29 [0.84, 6.24]
Norrelund 1978	31	71	17	64	14.0%	2.14 [1.04, 4.43]
Stalman 1997	17	94	2	92	2.3%	9.94 [2.22, 44.37]
Varonen 2003	32	82	13	48	13.9%	1.72 [0.79, 3.74]
Total (95% CI)		**706**		**665**	**100.0%**	**2.10 [1.60, 2.77]**
Total events	193		100			

Heterogeneity: $Chi^2 = 6.86$, df = 6 (P = 0.33); $I^2 = 13\%$

Test for overall effect: Z = 5.29 (P < 0.00001)



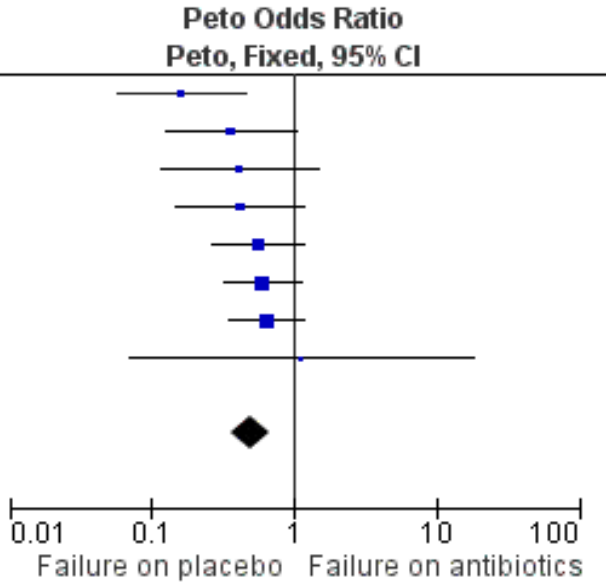
Lemiengre MB et al. Cochrane Database of Systematic Reviews 2012; Issue 10. Art No,: CD006089

Antibiotics versus Placebo – Treatment Failure

Study or Subgroup	Antibiotic Events	Antibiotic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Kaiser 2001	1	135	14	134	8.9%	0.16 [0.06, 0.45]
Varonen 2003	6	89	10	60	8.7%	0.36 [0.12, 1.03]
Stalman 1997	3	98	7	94	6.0%	0.41 [0.12, 1.47]
Garbutt 2012	5	85	11	81	9.1%	0.42 [0.15, 1.16]
Bucher 2003	11	125	19	127	16.6%	0.56 [0.26, 1.19]
De Sutter 2002	16	202	26	206	23.7%	0.60 [0.32, 1.14]
Meltzer 2005	18	251	27	248	25.7%	0.64 [0.35, 1.17]
Williamson 2007	1	113	1	127	1.2%	1.12 [0.07, 18.17]
Total (95% CI)		**1098**		**1077**	**100.0%**	**0.49 [0.36, 0.66]**
Total events	61		115			

Heterogeneity: Chi² = 6.55, df = 7 (P = 0.48); I² = 0%

Test for overall effect: Z = 4.54 (P < 0.00001)



Lemiengre MB et al. Cochrane Database of Systematic Reviews 2012; Issue 10. Art No,: CD006089

Ethics and Infectious Diseases

- Infectious diseases have caused more morbidity and mortality than any other single cause, including war
  - Black death killed 1/3 of European population in 14th century
  - TB has killed 1 billion people (1850 – 1950)
  - 1918 ‘flu killed between 20 – 100 million people
  - Smallpox killed 300 – 500 million people during the 20th century alone
  - New infectious diseases are emerging in recent decades (HIV/AIDS, Ebola, SARS, Avian Influenza, H1N1, H7N9, MERS)
  - Antibiotics have saved ~80 million lives since 1940s

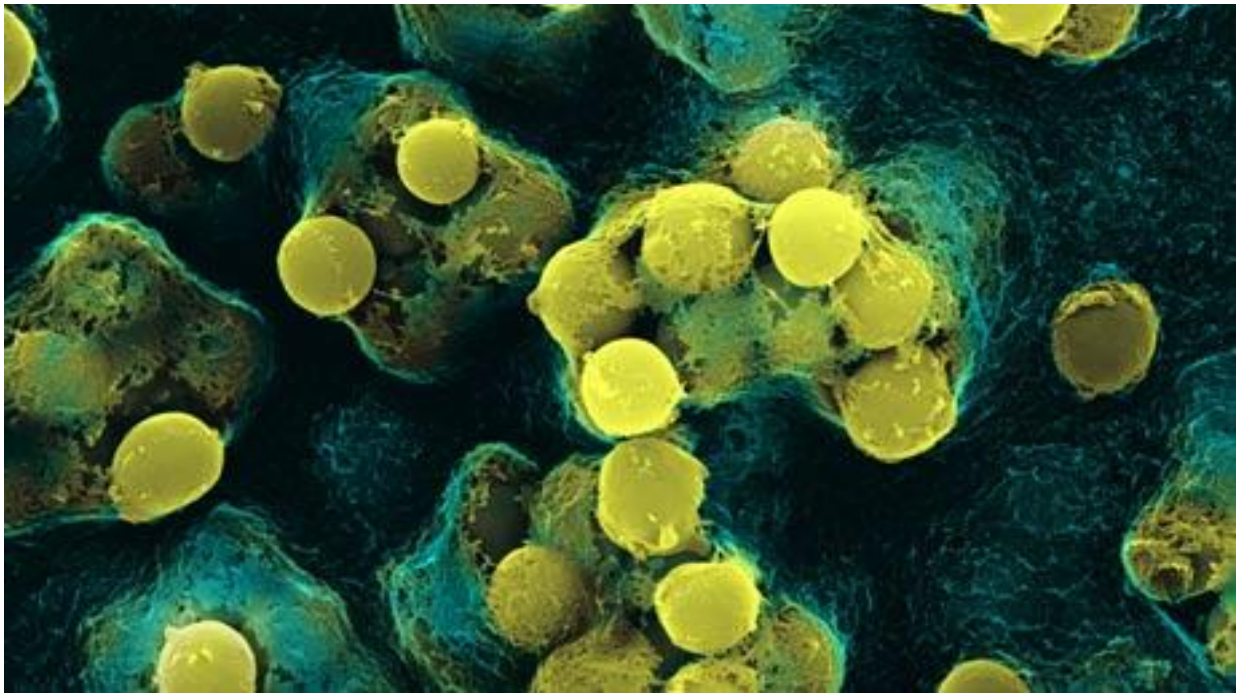
Selgelid MJ. Public Health 2009; 123: 255-259

Ethics and Infectious Diseases

- Infectious diseases raise difficult ethico-philosophical questions
  - surveillance, mandatory treatment, isolation/quarantine, vaccination
- The topic is closely connected to the topic of justice
  - malnutrition, sanitation, water, overcrowding, access to care, education (poverty)
- May promote fear, panic, stigmatization, discrimination, emotional and irrational decision making and policies
- Pose a threat to security of countries

Selgelid MJ. Public Health 2009; 123: 255-259

So are you Ready for A World Without Antibiotics?



Sarah Boseley. The Guardian 12 August 2010

So are you Ready for A World Without Antibiotics?

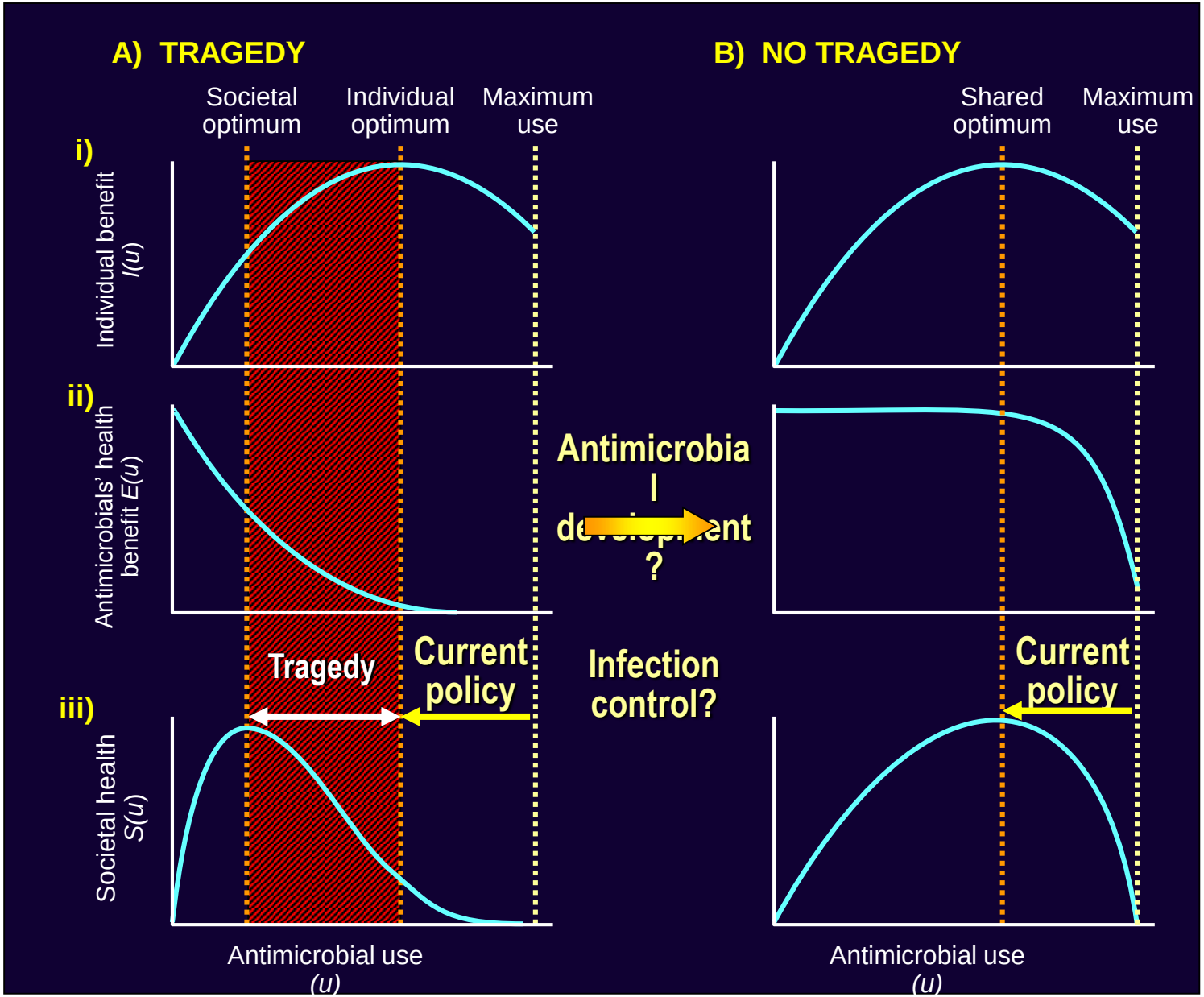
- Antibiotics are the bedrock of modern medicine
- In the near future we are going to have to live without them once again
- And it's going to be nasty
- 65 years ago David Livermore's paternal grandmother died following an operation to remove her appendix – she succumbed to a series of infections that the pre-penicillin world had no drugs to treat

Sarah Boseley. The Guardian 12 August 2010

The Potential for a Tragedy - Antibiotics

- Appropriate antibiotic use presents a dilemma
- Can benefit individual patients but carry a cost to societal health by selecting resistant strains
- Mirrors what Hardin termed *"the tragedy of the commons"* – putting too many cows in a pasture will destroy it by overgrazing [overpopulation, shared fisheries] [driving a car – tax on carbon emissions]
- Protecting the antimicrobial commons, and hence the collective best interest, may require society sometimes to act against individual patient's best interests – serious ethical concerns

Foster et al. Plos Medicine 2006; 3: 0177-0180



Foster et al. Plos Medicine 2006; 3: 0177-0180

The Ethics of Prescribing Antibiotics

- Driving a car releases carbon dioxide which takes the world closer to global warming
- In such a situation there is often a call for taxes so that the person gaining the benefit pays costs equivalent to the damage they cause
- We are currently not paying the true costs of antibiotics and this encourages them to be used profligately

http://blog.practicalethics.ox.ac.uk/2010

The Ethics of Prescribing Antibiotics

- If there was a world-wide tax (“sin tax”) on antibiotics we may stop using them for viral infections and depending on the size of the tax may use them only for severe bacterial infections thus prolonging their length of activity
- The problems with “sin taxes” is that they may place the most unfair burden on the poorest
- They could be made “revenue neutral” or progressive so world’s poorest people are joint beneficiaries of the tax

http://blog.practicalethics.ox.ac.uk/2010

So, What is the Challenge?

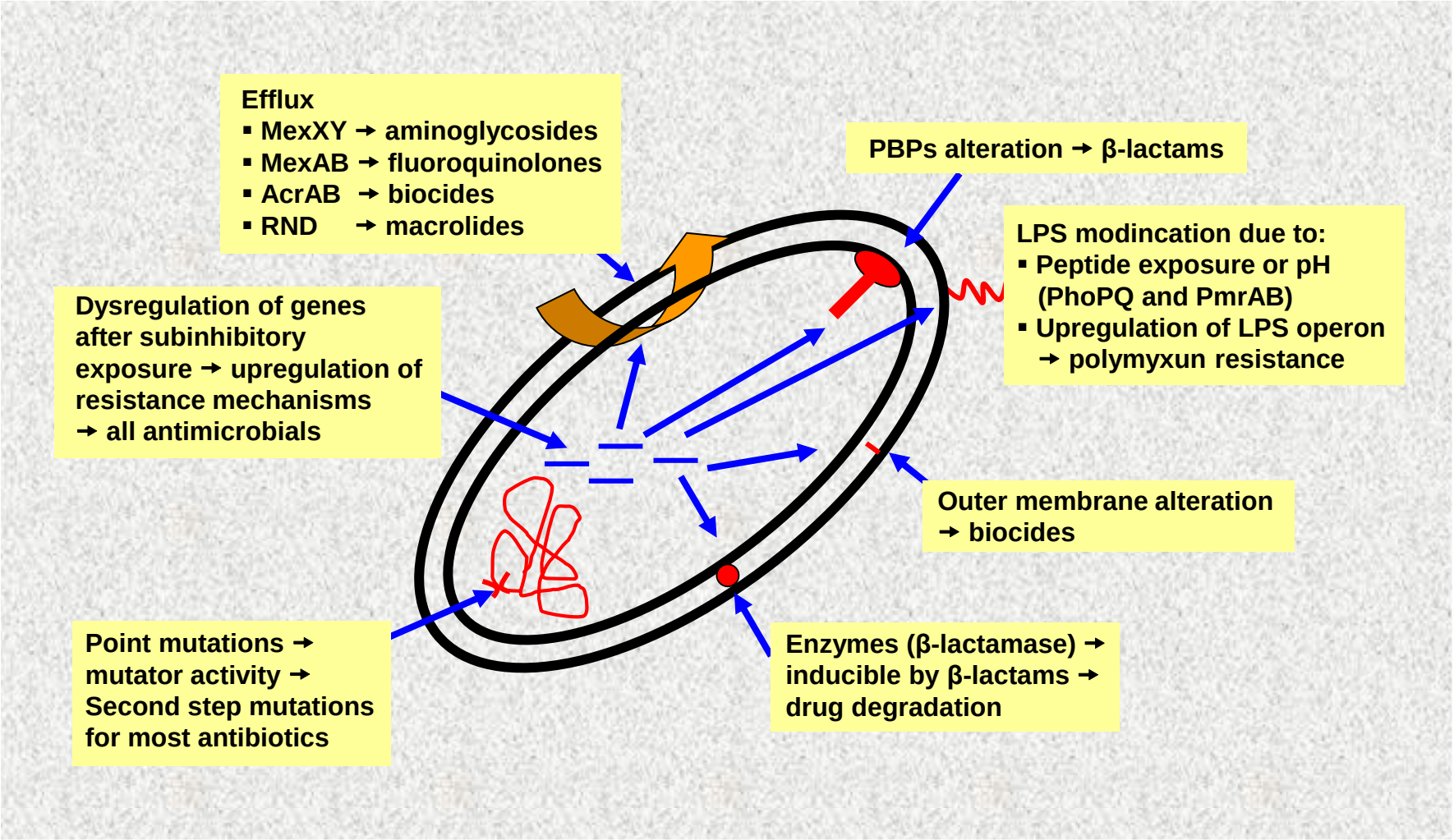
Christian Torres. Nature Medicine News 2010

Worldwide Impact of Resistance

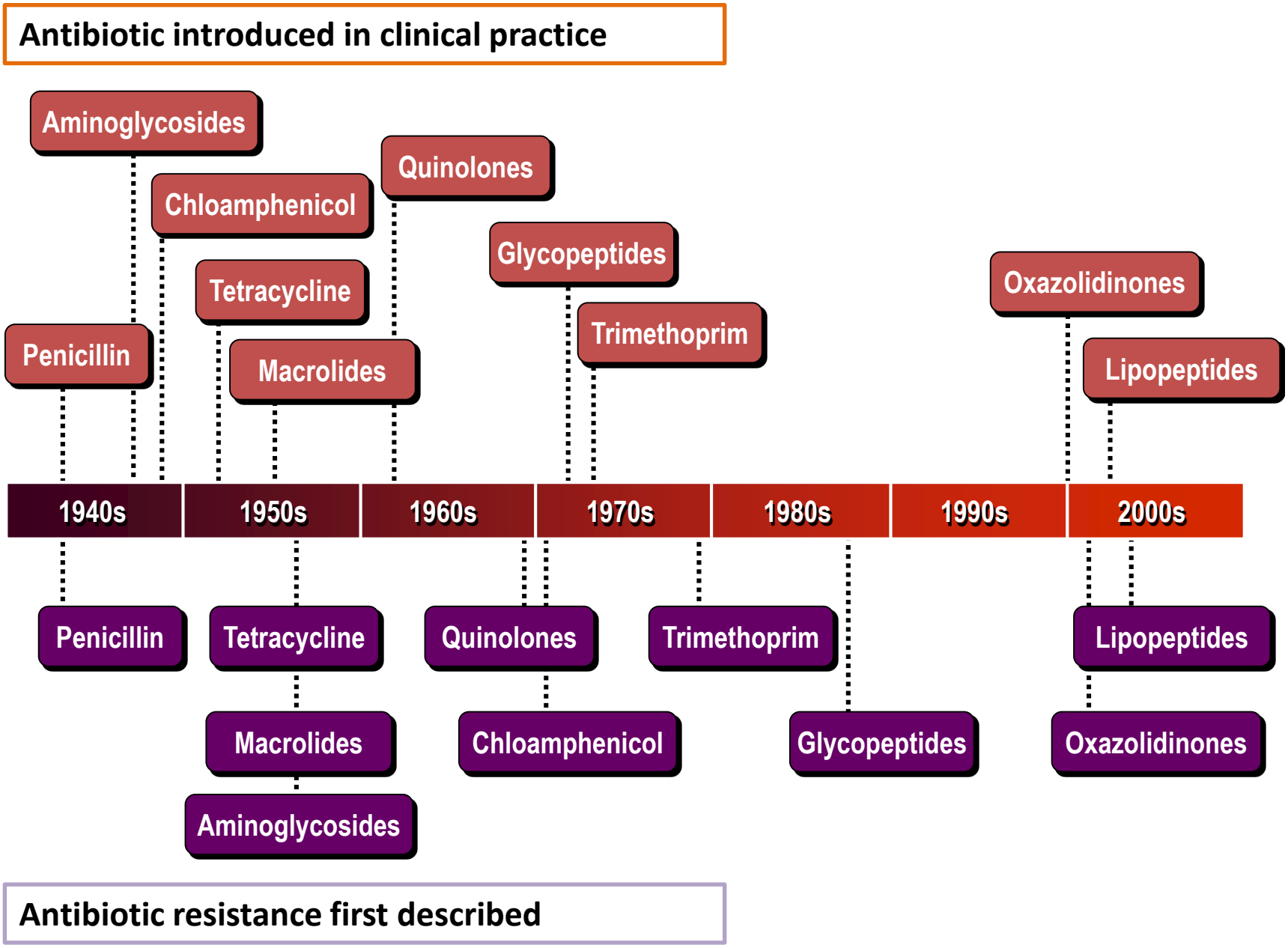
- Worldwide burden of deaths from antimicrobial-resistant infections is estimated to be more than 700,000, mainly in low and middle income countries
- In high income countries annual deaths from antibiotic-resistant pathogens are estimated at 23000 in the USA and 25000 in Europe
- The excess costs of antibiotic-resistant infections is $20 billion/year
- O'Neill report indicates that by 2050 there will be 10 million deaths per year and costs of $100 trillion

Anonymous. Lancet Infect Dis 2016; 16: 1085

Mechanisms of Antimicrobial Resistance



Fernandes L et al. Drug Resistance Updates 2011



TRENDS in Pharmacological Sciences

IDSA
Infectious Diseases Society of America

Bad Bugs, No Drugs

As Antibiotic Discovery Stagnates ...
A Public Health Crisis Advances

And……..No ESKAPE

And …….. No ESKAPE!

- ***E**nterococcus faecium*
- ***S**taphylococcus aureus*
- ***K**lebsiella pneumoniae*
- ***A**cinetobacter baumanii*
- ***P**seudomonas aeruginosa*
- ***E**nterobacter* spp.

Boucher et al. Clin Infect Dis 2009; 48: 1-12

Why Antibiotic Resistance is an Ethical Dilemma

- There are ethical issues with accelerating antibiotic resistance
- **Firstly**, emergence of MDR and XDR infections accelerates the ethical challenges in treating infectious diseases – isolation against one's will is a trade off between respect for individual autonomy and public good
- **Secondly**, fighting antibiotic resistance raises ethical questions about fair distribution of resources around the globe and while antibiotic use must be reduced in many countries around the globe, many people do not have ready access to effective antibiotics in the first place

http://www.reactgroup.org

Littman J et al. Int J Antimicrob Agents 2015; 46: 359-361

Why Antibiotic Resistance is an Ethical Dilemma

- **Thirdly**, the extensive use of antibiotics in farming and need for AMS raises ethical concerns about wellbeing and appropriate treatment of farm animals and by the way we produce meat, but current farming practices are often only lucrative because the use of antibiotics keep infection rates low
- This comes at cost of animal welfare and consumer safety when DR infections are transmitted in food
- F**ourthly**, we have a moral obligation to future generations to protect the effectiveness of antibiotics and not leave a post-antibiotic world behind
- Need to acknowledge these ethical issues and incorporate them into public discussion and policy

http://www.reactgroup.org

Littman J et al. Int J Antimicrob Agents 2015; 46: 359-361

What Are the Solutions to Antibiotic Resistance?

- Stimulate antibiotic development with incentives
  - Extent patent life
  - Better approval processes
  - Purchase commitments
  - Tax credits
- Use antibiotics more wisely
  - Impact on resistance development
  - Reduce pharmacy costs and toxicity
  - Reduce acquisition of potentially pathogenic bacteria

Gould IM. Int J Antimicrob Agents 2009; 34: S2-S5

What about Antibiotic Stewardship?

- Whereas antibiotic resistance is inevitable, current rate and spread is not
- Challenge is to reduce total consumption of antibiotics as the only sure way to delay development of resistance
- Stewardship programs may be restrictive or educational
- Tend to encourage homogeneity in prescribing because of restricted formularies

Gould IM. Int J Antimicrob Agents 2009; 34: S2-S5

What is Resonsible Antibiotic Stewardship?

- AMS is often referred to as “judicious use” of antibiotics
- “Judicious use” challenges use to be scientific in our approach to patient care
- We must be able to communicate our decision not only to the patient but also to the general public
- Risk analysis is a fundamental component of “judicious use” but risk management and risk communication are also required

http://blogs.usda.gov/2015

What about Antibiotic Stewardship?

- Reassess and increase the level of education to medical students
- Life-long re-education of prescribers
- Should prescribing only be possible by heath professionals who have been certified as competent, probably after undergoing educational training?
- Gone are the days when all doctors can prescribe what they like, when they like!

Gould IM. Int J Antimicrob Agents 2009; 34: S2-S5

The Ethical Dilemmas of Antibiotic Restriction

- Antibiotic restrictions present difficult choices and ethical considerations for physicians, patients and payers
- **Physicians** must choose between welfare of the patient and directives of healthcare system to restrict antibiotic use [impact on their autonomy]
- These may be supported by incentives or penalties, causing a conflict of interest
- **Patients** have an expectation of best care, but are often unaware of antibiotic restriction policies and therefore not fully informed about their treatment [lack of full informed consent]

Garau J. Clin Microbiol Infect 2006; 12(suppl. 5): 16-24

The Ethical Dilemmas of Antibiotic Restriction

- For **payers** the reduction of volume of antibiotics used or use of less expensive agents are attractive targets for cost saving
- [What about the **pharmaceutical industry**]
- Only recently are we starting to understand the consequences of restricting antibiotics on costs and outcomes
- Balancing the risks of treatment with not treating with antibiotics is complex
- Suboptimal therapy that fails to eradicate the bacterial infections puts the patient at risk of poor outcome, adverse events and antibiotic resistance

Garau J. Clin Microbiol Infect 2006; 12(suppl. 5): 16-24

The Ethical Dilemmas of Antibiotic Restriction

- Failure to treat where the risk of poor outcome exceeds the risk of an adverse event is not only unethical but also unacceptable
- The key to rational antibiotic prescribing is to identify those patients who need antibiotic therapy and to optimise treatment to achieve the fastest bacterial and clinical cure

Garau J. Clin Microbiol Infect 2006; 12(suppl. 5): 16-24

Futility in Medical Care

- In clinical care it is important to distinguish between futile and marginal treatments
- Futile treatments are those that hold no prospect of achieving the intended outcome
- Bioethicists have largely abandoned the notion of futility after efforts to develop a clinically serviceable definition proved fruitless
- In reality, few treatments hold zero prospect of achieving the desired result
- Those that do rarely lead to clinical dilemmas

Niederman MS et al. Crit Care Med 2010

Futility in Medical Care

- Example is ventilated patient on 100% Fi02 and 15 cm PEEP who remains hypoxic
- Because, in its most narrow sense, the goal of mechanical ventilation is to achieve satisfactory oxygenation, and it has not been able to do so in this example case, the ventilation may be considered “futile”
- However, these situations of “physiological futility” are seldom troubling situations in ICU

Niederman MS et al. Crit Care Med 2010

Futility in Medical Care

- The challenges are where the effect of the intervention are uncontested but the benefit of the intervention are unclear
- Example is a cardiologist not wishing to place a intra-aortic balloon pump in a patient with cardiogenic shock, not because it will fail to raise BP, at least for some time, but because no remedial benefit to the pump failure is possible or because the patient has poor clinical status – e.g. anoxic encephalopathy
- Futility should be viewed in the overall context of the patient and not just from a physiological perspective

Niederman MS et al. Crit Care Med 2010

Futile Care can Harm Others

- Conceivably at some stage antibiotic use could create completely resistant bacteria for which no other therapeutic resource exists
- Antibiotic allocation is not a zero-sum game as it occurs with typically limited resources
- This is potentially exponential and many studies indicate that mortality from ICU infection increases with inappropriate therapy and this is more likely to occur with MDR pathogens
- Antibiotics are among the least refused therapies

Niederman MS et al. Crit Care Med 2010

Futile Care can Harm Others

- Antibiotics are therefore atypical in this regard
- Their continued use in situations in which they no longer provide tangible medical benefit cannot be justified because of potential harm to others
- This type of futile care cannot be justified
- Physicians and patients have ethical obligations to desist from such marginal and symbolic use of futile interventions because of quantifiable collective harm

Niederman MS et al. Crit Care Med 2010

Antibiotic Misuse - Examples

- Using antibiotics for non-bacterial infection
- Administering an antibiotic “just in case”
- Wrong empiric antibiotic choice
- Underdosing antibiotics
- Using an antibiotic that does not penetrate to site of infection
- Using a second line antibiotic when a first line should be used

Gary Skankey, University of Nevada School of Medicine 2011; powerpoint presentation on Google

Antibiotic Misuse - Examples

- Using a broader spectrum than necessary
- Continuing multiple antibiotics when pathogen known
- Continuing antibiotics past the point of resolution
- Administering an antibiotic in response to a culture when there is no evidence of infection

Gary Skankey, University of Nevada School of Medicine 2011; powerpoint presentation on Google

Reasons for Antibiotic Misuse

- Fear of Malpractice suits
- Lack of confidence in ones ability to diagnose infection
- Poor understanding of antibiotic PK/PD and spectrum of activity
- Lack of knowledge of sensitivity patters (antibiogram) of the local community

Gary Skankey, University of Nevada School of Medicine 2011; powerpoint presentation on Google

Reasons for Antibiotic Misuse

- Erroneous concept that antibiotics are safe even if used when not needed
- Too busy or too lazy to try and confirm a diagnosis and blindly starting antibiotics
- Patients expect a prescription
- Pressure from imposed clinical pathways to start an antibiotic within a short period of time

Gary Skankey, University of Nevada School of Medicine 2011; powerpoint presentation on Google

Problems Faced in South Africa

- Questionnaire study involving patients and GPs
- Assess patients views and expectations regarding need for antibiotics and compare with doctors perception of this expectation
- Durban Metropole, KZN, South Africa, 2001
- Ethics approval was obtained from the University
- GPs provided services in first world setting to patients of all race groups
- Completed questionnaires from 11 practicing GPs and 330 patients met inclusion criteria and were assessed

Hoffman D et al. SA Fam Pract 2003; 45: 20-24

RSA Study - Questions to Patients/Parents

	Yes	No	Don't know
Are you/your child currently taking any medication?	29%	71%	-
Do you feel that antibiotics will help this illness?	47%	4%	49%
Do you expect the doctor to give you antibiotics?	83%	17%	-
Will you ask the doctor for an antibiotic today?	48%	52%	-
Does over-use of antibiotics hold dangers to the community?	27%	11%	63%

Hoffman D et al. SA Fam Pract 2003; 45: 20-24

RSA Study - Questions to Doctors

	Yes	No
Was an antibiotic expected by the patient?	60%	40%
Was an antibiotic indicated for his condition?	76%	24%
Was an antibiotic prescribed to the patient?	81%	19%
Did you feel pressurised to prescribe an antibiotic?	16%	84%

Hoffman D et al. SA Fam Pract 2003; 45: 20-24

“[The physician] is under great pressure to prescribe the ‘newest’, ‘best’, ‘broadest’, antibiotic preparation, prescribe it for any complaint whatever, quickly, and preferably without worrying too much about specific etiologic diagnosis or proper identification of the drug”

Earnest Jawetz 1956

The following facts are true?

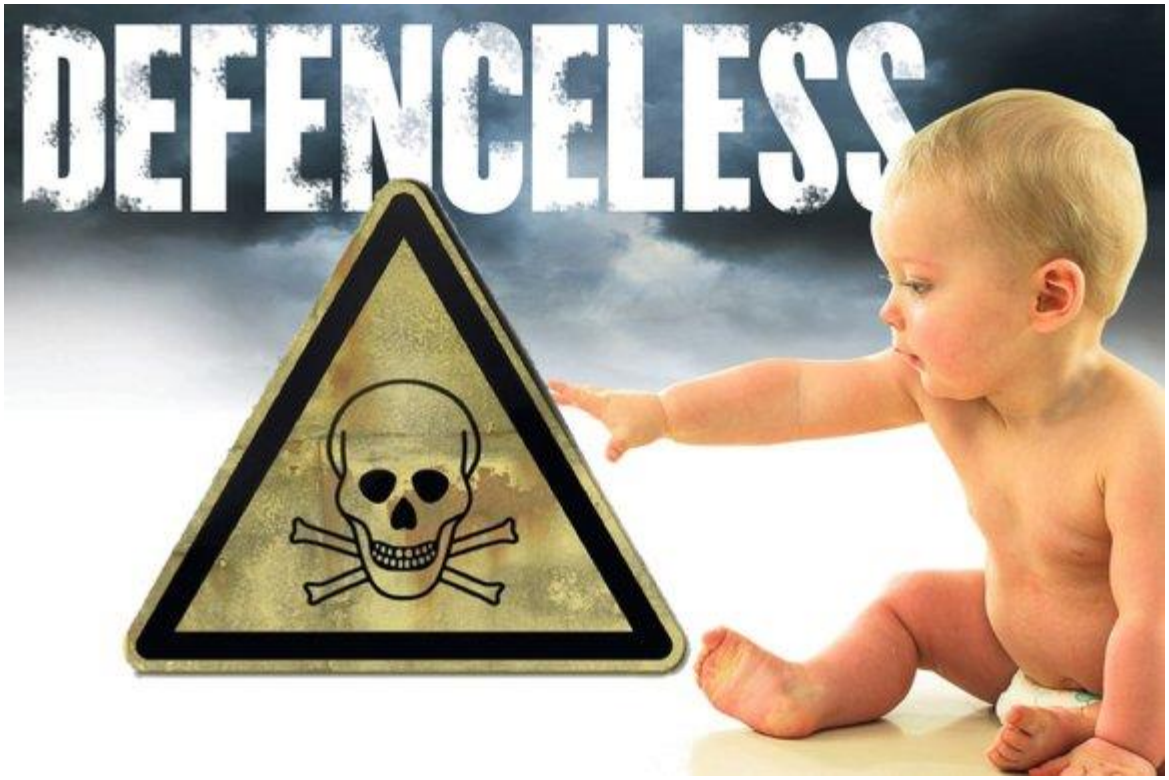
1. Antibiotic use has saved 80 millions lives since the 1940s
2. Antibiotic resistance predates antibiotic use
3. Even appropriate antibiotic use promotes resistance
4. Restrictive AMS programs work better than purely educational ones
5. All of the above

After Antibiotics: What Happens when the Drugs don't Work?

- Transplant surgery becomes virtually impossible
- Removing a burst appendix becomes a dangerous operation once again
- Pneumonia becomes once more "the old man's friend"
- Gonorrhoea becomes hard to treat
- Tuberculosis becomes incurable

Sarah Boseley. The Guardian 12 August 2010

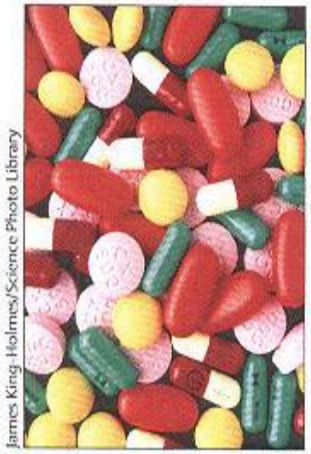
The Drugs Don’t Work



Sally Davies. The Sunday Times 15 September 2013

The Drugs Don’t Work

Antibiotic resistance: a final warning



James King-Holmes/Science Photo Library

For the **CDC report on antibiotic resistance** see http://www.cdc.gov/drugresistance/threat-report-2013/

For more on the **Get Smart About Antibiotics Week** see http://www.cdc.gov/getsmart/campaign-materials/week/overview.html

For more on the **meeting of the Strategic Technical Advisory Group on antimicrobial resistance** see http://www.who.int/drugresistance/stag/en/index.html

On Sept 16, the US Centers for Disease Control and Prevention (CDC) released its report *Antibiotic Resistance Threats in the United States, 2013*—their first ever report on this subject. From the outset the tone is clear: in his foreword, Tom Frieden, director of the CDC, states that "antimicrobial resistance is one of our most serious health threats. Infections from resistant bacteria are now too common". The stated aim of this report is to increase awareness of the threat resistance poses and to encourage immediate action to address this threat.

To put the problem of resistance into perspective the report presents some sobering statistics. The CDC estimates that antibiotic-resistant organisms are the cause of infections in more than 2 million people each year in the USA. Of these people, more than 23 000 die as a consequence of their infections. The CDC stresses that these are conservative estimates and so the true numbers are probably much higher.

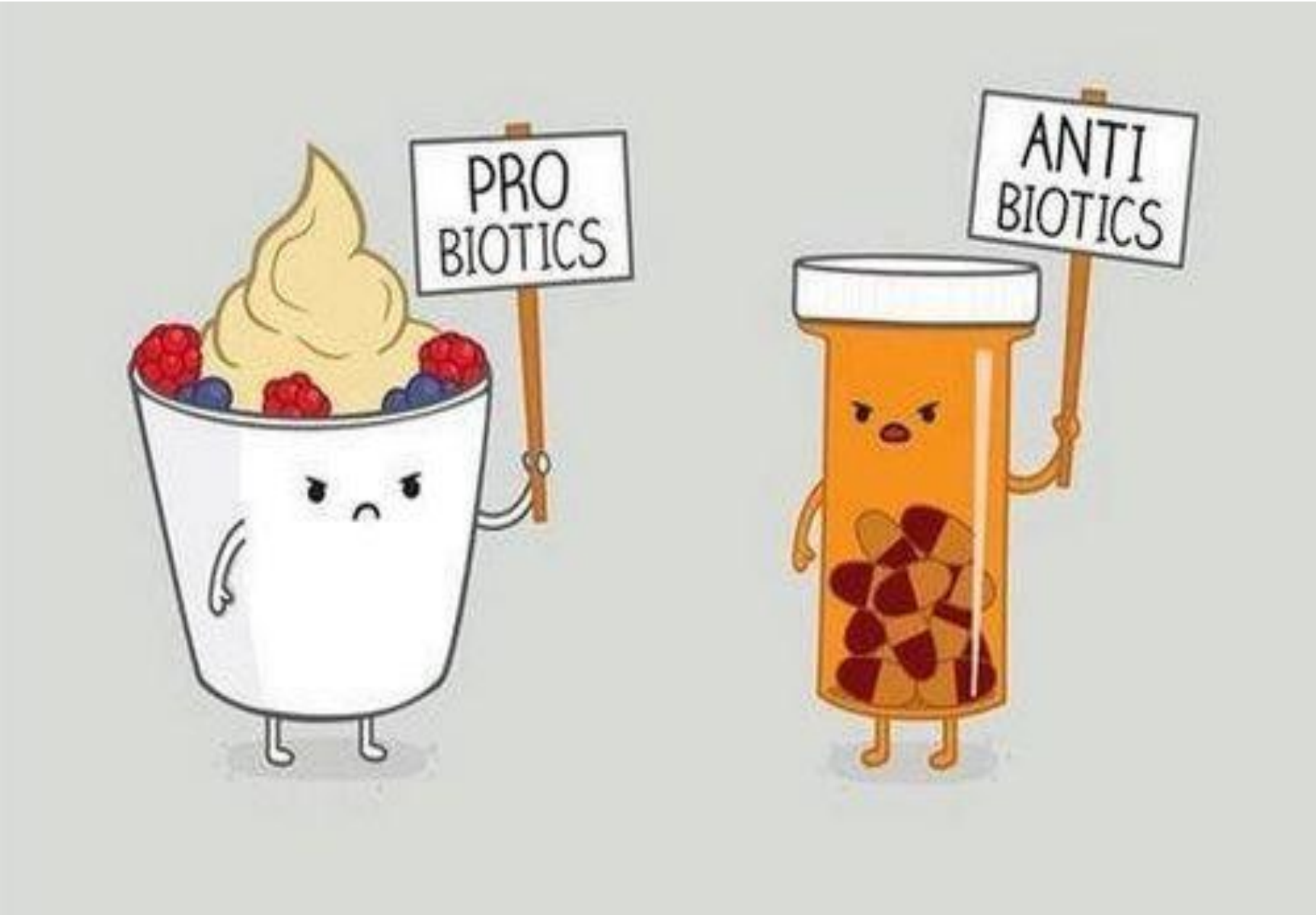
To further promote the risks posed by antimicrobial resistance the CDC will be holding its annual *Get Smart About Antibiotics Week* on Nov 18–24. This campaign will promote the appropriate use of antimicrobials across the USA and will coordinate with similar campaigns in Australia, Canada, and Europe. To coincide with these events, *The Lancet Infectious Diseases* will be publishing its commission on antimicrobial resistance.

Raising the profile of the problem of antimicrobial resistance is always welcome, but it begs the question of why we are still facing an issue identified decades ago? The report itself presents a timeline of emerging resistance, showing that reports date back to 1943. We are rapidly approaching the point when antimicrobial resistance will be nothing short of a catastrophe. And for the many thousands in the USA and elsewhere, the world's response is already too late. However, momentum on this issue seems to be building. On Sept 19–20, there was a meeting of WHO's Strategic Technical Advisory Group on antimicrobial resistance, with the purpose of identifying the key issues and options that will feed into a new global strategy. Hopefully, this will be more than the strong words we have become used to and will herald the beginning of robust action. ■ *The Lancet*

Conclusions of Talk

- Antibiotic misuse and overuse is driving antimicrobial resistance
- Antibiotic overuse and misuse is driven by clinician fear of litigation, patient pressure, clinical pathways and lack of confidence in ability to diagnose infection
  - Antibiotics are a clinicians security blanket
- It can be curbed by educating clinicians on making a proper diagnosis of infection, understanding appropriate empiric antibiotic choices

Gary Skankey, University of Nevada School of Medicine 2011; powerpoint presentation on Google



Google Pictures