Knowledge and social norms shaping the discovery, use, and resistance trends of antimicrobial agents

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Theory of Knowledge
Knowledge

- Categories
- Cognition
- Judgments
- Ideas...

For instance, as in Kant’s Theory of Knowledge.

The real world do not necessarily adjust to the representation we have of it.

Scindere, Latin, from Greek skhizein "to cut, divide, split"
Knowledge

Individual
Academic incentive
Esthetics

Practical
Knowledge
(tekhne)

Conceptual
Knowledge
(episteme)

Scientific
Knowledge
(scientia)

For instance, as in Kant’s Theory of Knowledge

Scindere, Latin, from Greek skhizein “to cut, divide, split”
Richard Doll (1912-2005)
Smoking-health problems

Relevance of advancing knowledge addressing conceptual and applied issues

From applied to basic research!

Need of back-translational science!

Chalmers, I. et al. How to increase value and reduce waste when research priorities are set. Lancet 2014; 383:156
Chalmers, I. et al. How to increase value and reduce waste when research priorities are set. Lancet 2014; 383:156

From applied to basic research!
Need of back-translational science!

Richard Doll (1912-2005)
Smoking-health problems
Individual variability in finger-to-finger transmission efficiency of Enterococcus faecium clones


Sánchez Díaz et al., P1552. ECCMID 2014

Very scarce basic biology of hand washing!

Dynamics of conceptual and applied knowledge

Conceptual advances are absorbed by the gravity of applied knowledge.
The causal link of particular bacteria and infectious diseases

Etiological thinking

αἰτία, aitia, "cause"; and -λογία, -logia

Casimir Davaine (1812-1882)

Microbes are the cause of infections
The causal link of particular bacteria and infectious diseases

Etiological thinking

αἰτία, aitia, "cause"; and -λογία, -logia

Casimir Davaine (1812-1882)

Microbes are the cause of infections

But weak evidence of the effect of antibiotics on mortality in cholera infection (Das JK et al., BMC Public Health 2013)
Etiological thinking:
the classic simple causal chain in antibiotic resistance

- Pathogen
- Infection
- Antibiotic use
- Resistance
- Restrictions in antibiotic use
Etiological Thinking
The classic simple causal chain in antibiotic resistance

Cause

Effect and Cause

Effect and Cause

Effect and Cause

Effect and Cause...

Pathogen

Infection

Antibiotic use

Resistance

Restrictions in antibiotic use

Intervention

Interventions “on causes”

Intervention
Threats to causal inferences

**FALSE POSITIVE (Type I error)**

Infected patient → Antibiotic Prescription → Cure

Prescription is the **cause** of success

**FALSE NEGATIVE (Type II error)**

Infected patient → Antibiotic Prescription → Failure

Should exist a **cause** for negative result (resistance?)

**In fact..**

Infected patient → Antibiotic Prescription → Cure

“No” prescription is **not a cause** of success

**Interventions produce more causal feelings than non-interventions**

**In fact..**

Infected patient → Antibiotic Prescription → Failure

Prescription was a **cause** preventing severe infection (Invisible causal effect)
Infected patient

**Diagnosis:** cause A

Cure

**Antibiotic Prescription Targeting A**

Infected patient

**Diagnosis:** cause A

Cure

**Antibiotic is effective on A-infection**

Infected patient

**Diagnosis:** cause A

Failure

**Should exist a cause for negative result (A-resistance?)**

Infected patient

**Diagnosis:** cause A

Infected by cause B

Antibiotic Prescription Targeting A but acting on B

Cure

**Antibiotic is effective on A-infection**

Infected patient

**Diagnosis:** cause A

Infected by cause B

Antibiotic Prescription Targeting A but non-acting on B

Failure

**Antibiotic is non-effective on A-infection**

Infected patient

**Diagnosis:** cause A

Failure

**Antibiotic Prescription Targeting A**

**FALSE POSITIVE** (Type I error)

**FALSE NEGATIVE** (Type II error)
Threats to causal inferences

A cause frequently produce a multiplicity of effects, frequently with opposite signs

- Antibiotic consumption
  - Reduction of infections
  - Increase of resistant populations
    - Protection of susceptible populations ("cheaters")
    - Stability of the microbiota with lower colonization by novel resistant organisms
    - Increased fitness cost for pathogenicity and transmission rates?
  - Effects for the individual and groups
  - Stabilizing effect for resistance?

Reduction of infections

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Causes are frequently made of causes: difficulty to identify “single causes” for intervention.
It is agreed on all hands, that the qualities or modes of things do never really exist each of them apart by it self, and separated from all others, but are mixed, as it were, and blended together, several in the same object...

Georges Berkeley (1685-1752). *Introduction to the Principles of Human Knowledge*
Parameter causal space influencing Ab-resistance

- Density of colonized and colonizable hosts with Ab-R organisms;
- Population sizes of bacteria per host during colonization and infection
- Susceptibility to host colonization, age, nutrition, illness-facilitated colonization.
- Frequency of between-hosts interactions (as animal-human interaction)
  - Host natural and acquired immune response to colonizing organisms
- Ecological parameters of colonizable areas, including interaction with local microbiota
  and frequency and type of Ab-R commensals
  - Migration and dispersal of colonized hosts
- Antibiotic exposure: overall density of antibiotic use, type of antibiotics and mode of action,
  dosage and duration of therapy, adherence to therapy, selective concentrations, antibiotic
  combinations
- Mode of transmission of resistant organisms; transmission rates between hosts (antibiotic
  treated and not-treated, infected, and not-infected); time of contact between hosts
  - Exposure to biocides; hygiene, infection control, sanitation;
  - Food, water and water bodies contamination and host exposure
  - Environmental contamination with Ab-R selectors (as heavy metals)
  - Environmental contamination by resistant organisms, including sewage..

Different biological levels of causation

- Are molecular events somehow causally more important than events that occur at the scales of cells, organs or systems?
- And are there causally efficacious processes that can only be characterized at higher scales?

*Dennis Noble, 2011. A theory of biological relativity: no privileged level of causation. Interface Focus 2:55-64;*  
*Baquero F, Tedim AP, Coque TM. 2013. Antibiotic resistance shaping multi-level population biology of bacteria; Front Microbiol. 6:15*

The parameter space and the causal structure of antibiotic use and resistance change in different environments


Interventions should be targeted and evaluated at individual and local level
In complex systems, cause and effect are often distant in time and space
Selectivity

Attention-Publication of Confirmatory versus Disconforming tests

The result suggests:

Good shot person!

Plasmid P is associated to the dangerous clone C
Antibiotic resistance R is associated with the dangerous clone C
Clone C is highly frequent in this environment!

Interventions, including surveillance, against dangerous clone C to limit antibiotic resistance or virulence

Attention-Publication Confirmatory versus Disconforming tests

Selectivity
Selectivity

Attention-Publication  Confirmatory versus Disconforming tests

Plasmid P, or Antibiotic Resistance R, or Virulence gene V is associated with many other, eventually non investigated clones.
Overlooking random effects

- “Preventive antibiotic use reduces recidivism in acute exacerbations of chronic bronchitis”

<table>
<thead>
<tr>
<th>Before intervention</th>
<th>1</th>
<th>2</th>
<th>2</th>
<th>1</th>
<th>1</th>
<th>2</th>
<th>1</th>
<th>2</th>
<th>1</th>
<th>1</th>
<th>2</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>After intervention</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

1: exacerbation; 2: no exacerbation (6 months periods)

The intervention apparently worked!

In fact the result is that recidivism may be due to random inconsistencies, consequences of chance.
Overlooking random effects

Mirage correlations between three samples from a single run of a 2-species system; variables appear correlated, uncorrelated, and losing coherence.

Questionable inferences

“The introduction of accessible antibiotic therapy for citizens of an underdeveloped country decreases mortality by infectious diseases”

This introduction probably parallels improvements in sanitation, home and food accessibility, and general income level, greatly influencing transmission rates and susceptibility to infections.

Although McKeown’s analysis was flawed, his underlying ideas regarding the effects of poverty and economic wellbeing on health were essentially correct.

Veterans Affairs methicillin-resistant *Staphylococcus aureus* prevention initiative associated with a sustained reduction in transmissions and health care-associated infections.
“The introduction of accessible antibiotic therapy for citizens of an underdeveloped country decreases mortality by infectious diseases. This introduction probably parallels improvements in sanitation, home and food accessibility, and general income level, greatly influencing transmission rates and susceptibility to infections.

Although McKeown’s analysis was flawed, his underlying ideas regarding the effects of poverty and economic wellbeing on health were essentially correct.
t_0. A new mechanism of resistance: detection of a first outbreak related with a particular organism
t₁. A new mechanism of resistance: detection of the same resistant organism in other areas. Spread!
t\textsubscript{2}. A new mechanism of resistance: detection of the same resistant organism in other areas.

The order of discovery might wrongly suggest the spread trajectory.
Uncertainties in the elements of knowledge

The problem of defining biological units
• What is a bacterial species? What is a core genome?
• What is a clone? What is a ST-type?
• Are there “species” in plasmids, other MGEs?
• Are there biological units over the species?

The problem of defining biological traits
• What is antibiotic resistance?
• What is a resistance gene?
• What is a virulence gene?

The problem of representativeness bias (the problem of sampling)
• Biased collections of strains
• Biased collections of clones within species
• Biased collections of data in databases

“Practical” definitions are frequently deleterious to know the truth.
The quality of knowledge

“I figure there is a 40% chance of showers, and a 10% chance we know what we’re talking about.”

We can estimate the number of “resistance genes” in the soil or the intestinal microbiota resistome. Which is the meaning of such observations?

D’Costa et al., Science 2006
What are resistance genes?

- Genes encoding the outer membrane of *E. coli*, or AcrAB pumps protects this organism from macrolides, but they cannot be considered as having evolved in response to antimicrobials of anthropogenic origin.

- As these genes are “naturally present” in particular species (as acrAB pumps in *E. coli*, or *mexAB* in Pseudomonas), the detection of these genes in metagenomes only reveals the presence of such organisms in the sample.

- A gene encoding the target of an antibiotic that has been modified by mutation, or a wild gene harboring such mutation (producing intrinsic resistance) cannot be considered as resistance gene (only if transmissible!)

- A number of “resistance gene databases” includes as “resistance genes” those with sequence identity with “known· resistance genes as low as 50%. We estimate as candidates to be considered antibiotic resistance genes only those with >90% identity with known resistance genes involved in therapeutic failure.

*Martínez, JL. ICAAC 2013, and submitted manuscript 2014 (Martinez, Coque, Baquero)*
Genes (nodes; in gray) aligning >80% of their sequences with their match in a BLAST analysis (showing >50% identification and a BLAST score < 1 e−20) are directly connected.

*gyrA, gryrB, rpoB...* and many others
Uncertainties in the elements of knowledge

The problem of defining the pharmacodynamic parameters

- “Parametric reductionism” (Bruce Levin, 2013, 2014)
- MIC as the only pharmaco-dynamic parameter

**The “populational definition” of MIC**

Inhibited strains

Geometric antibiotic dilutions

Arithmetic antibiotic dilutions

**Martínez, Coque, Baquero** (submitted 2014)
Uncertainties in the elements of knowledge

The problem of defining “anti-infective drugs”

- “Drugs” beyond the individual?
- Faecal microbiome preparations as “drugs”?

Uncertainties: the acceptation in practice of imperfect knowledge

“Human reason is by nature architectonic”
Critic of Pure Reason, B502

Imperfect knowledge ensemble: not completely accurate and complete architecture

“Accepted block” of knowledge

If the block is applied in practice (social norms, recommendations) the acceptation as “truth” increases.

Broad (www.) dissemination of imperfect knowledge!

Practical Knowledge

- Practical knowledge in scientists
- Practical knowledge in prescribers
- Practical knowledge in patients and the society
- Practical knowledge in pharmaceutical industry
- Practical knowledge in regulatory agencies

Structural Determination of Practical Knowledge

As defined by the philosopher Mario Bunge, structural determination refers to "the process by which the behaviour of an individual (a molecule in a fluid, a person in a social group) is determined by the overall structure of the collection to which it belongs".

Social Norms

A social norm is a rule governing an individual’s behavior that third parties other than state agents diffusely enforce by means of social sanction for those who violate the norm and with rewards for those who follow it (Ellickson, 2001)
“Official recommendations”, “personal experience”, “uncertainties”, “external pressures to reduce prescribing”, “conflicts with patients”, “how to provide personalized care”, “occupational pressure”

Prescribers knowledge

Antwerp, Utrecht and Tromsø clinicians were most concerned with preventing resistance, trying to prescribe narrow-spectrum antibiotics, which are least likely to cause resistance, and believed that broader-spectrum antibiotics should be held in reserve for people who are most at risk.

Clinicians from Balatonfüred, Barcelona and Milan, generally stated they would use as first line the antibiotic that was most likely to cure the patient from the Outset, assuming that most infections are resistant to first-line antibiotics and therefore reported choosing newer, broader-spectrum, agents as empirical treatment.

A few clinicians (5% of the sample) thought that it would be helpful if they could have better access to local resistance data so that they could prescribe the narrowest-spectrum antibiotic that is most likely to be effective.

### Prescribers knowledge

<table>
<thead>
<tr>
<th>Outcomes for</th>
<th>Immediate treatment</th>
<th>Watchful waiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual</td>
<td>Satisfactory</td>
<td>Non-satisfactory</td>
</tr>
<tr>
<td>Group (prevalence R)</td>
<td>Non-satisfactory</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>Toxic effects</td>
<td>Non-satisfactory</td>
<td>Satisfactory</td>
</tr>
</tbody>
</table>

**Individual first**  **Society first**

**McCormick D.P. et al.** *Non-severe acute otitis media: a clinical trial comparing outcomes of watchful waiting versus immediate antibiotic treatment.* *Pediatrics* 115:1455, 2005
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_0$</td>
<td>1.2</td>
<td>Basic reproductive number for susceptible, S</td>
</tr>
<tr>
<td>$v_s, v_R$</td>
<td>0.1</td>
<td>Colonization for 10 days</td>
</tr>
<tr>
<td>$v_ST$</td>
<td>0.2</td>
<td>Colonization for 5 days</td>
</tr>
<tr>
<td>$t_{MAX}$</td>
<td>0.05 to 0.5</td>
<td>Maximum Prescription (treatments) Rate</td>
</tr>
<tr>
<td>$k_t$</td>
<td>0.15 or 0.05</td>
<td>$R$ when prescription (treatments) is half its maximum</td>
</tr>
<tr>
<td>$\mu$</td>
<td>$10^{-2}$ or $10^{-4}$</td>
<td>Rate of generation of resistance STR</td>
</tr>
<tr>
<td>$a_{ST}$</td>
<td>0</td>
<td>Effect of treatment on transmission</td>
</tr>
<tr>
<td>$a_R$</td>
<td>0.05</td>
<td>Effect of resistance on transmission (fitness cost)</td>
</tr>
</tbody>
</table>

**Prescription rates 5 %, $kt = 15\%$ and 5 %, $\mu = 0.01$**

**Prescription rates 5 %, $kt = 15\%$ and 5 %, $\mu = 0.0001$**

If prescriptions of A are avoided in patients harboring A-resistance, overall resistance rates do not evolve. Importance of knowledge about resistance!

Patient’s knowledge about “resistance”

Frequent **misinterpretation of antibiotic resistance as a property of the human body** rather than bacterial cells, preventing to understand transmission of resistant organisms and containment strategies

- Resistance as a “body reaction against antibiotic”
- Resistance as “becoming immune to the antibiotic”
- Resistance as “antibiotic damages the immune system”
- Resistance as “hospital acquisition of a resistant bug”
- Resistance as “something that losses potency when frequently used”
- Resistance if the “infection is caused by an organism different that for which it was prescribed”
- Resistance as “too strong illness to be managed by antibiotics”
- Resistance as “psychosomatic belief that antibiotics will not work”

Antibiotic resistance is much a societal problem as it is an individual one: if mass behavior change across the population does not occur, the problem of resistance cannot be mitigated at community level.
Antibiotic susceptibility is a limited common good, that is eroded by uncontrolled antibiotic use, aiming individual benefits, but with deleterious consequences for the community, and finally also for the individual. Because of that, social norms restrict the overuse of antibiotics.


Assessment of the effect of over-treatment of mild infection on the treatment of mild infections.

If only susceptible strains were treated


Mass antibiotic treatment programs might reduce morbidity and mortality from highly transmissible infections in certain communities. WHO endorses repeated non-specific mass antibiotic treatment as a key component of trachoma elimination programs.


Antibiotic susceptibility is a limited common good, that is eroded by uncontrolled antibiotic use, aiming individual benefits, but with deleterious consequences for the community, and finally also for the individual.

Garret Hardin, 1968

Growing prestige among younger clinicians resulting from “non-prescription attitude” might compensate the tragedy.

Increasingly anti-inflammation drugs (as ibuprofen) are substituting antibiotics in mild respiratory infections.


Dissemination and Evolution of Knowledge

“Social Mimetics”
The opinion (or research strategy) of a number of leading individuals contaminate the others.

Knowledge as an infectious process

Ehrlich P, Levin S et al., Evolution of Norms, PLoS Biology
Knowledge in Pharma: Classic Antibiotic Target Product Profile

- Broad spectrum. Indicated for a wide range of infections (RTI, genitourinary, ..Gram+ and Gram-)
- Active against all resistant strains selected by marketed compounds (new mode of action).
  Bactericidal.
- Available in both, oral and intravenous formulations. Once daily dosing
- Safe and very well tolerated (due to the target population, including children)
- Low cost (large number of different drug classes with generic products)

Marketing strategy:
“Empiric treatment of uncomplicated and complicated infections including community and hospital-acquired infections”

Kinetic stability: >100 μM
In vitro cytotoxicity: TC50>10 μM
MIC: <64 mcg/ml
Protein binding: more 10% free fraction
Chemical stability: <10% degradation/24 h
Neutropenic tight infection model: > 1 log reduction
Mutation frequency <10^-8

Past
Therapeutic Niche for clinical or preventive use and exploitation

Hit-to-Lead wastes

Increase in Research

Today
The expansion of knowledge and the expansion of interventions: inside the host

- Several targets in a cell
- Several phenotypes in a cell/population
- Several compartments within a host
- Several types of hosts within a group

Multi-targeted antimicrobial therapy; Combined therapy

Personalized Antimicrobial Therapy
The Tragedy of Overflowing Knowledge

Multiple Therapeutic Compartments

WHY NOT?
The expansion of knowledge and the expansion of interventions: outside the host

The classic view:
The group and the environment as cause of the individual infection

The other side of the coin:
The infected individual as cause of group and environmental sickness

The need of taking care of the sick “individual environment”
Country-specific antibiotic use practices impact the human gut resistome

Forslund et al., Genome Research 23:1163, 2013
Targeting multiple therapeutic niches along a multi-dimensional infective process.
Systems Biology and Multi-Compartmentalized Anti-Bacterial Strategies

- The National Institute of Allergy and Infectious Diseases recently initiated the Systems Biology Program for Infectious Disease Research.
- Bacterial pandemics remain, food and waterborne illnesses are frequent, multidrug-resistant microbes are on the rise, and the needed drugs and vaccines have not been developed.
- Intense research focus on individual genes and proteins typical of molecular biology—have not been sufficient to address these challenges.

Aderem A. et al., mBio 2(1):e00325-10, 2011

A stronger systems biology perspective must now focus on the interactions between drug, host, infectious bacteria and environment to foster the long-term success of antibiotic strategies

Dandekar T&M. Pharmacogenomics, 11, 2010

Multilevel Analysis of Infectious Diseases

Ana V. Diaz Roux and Allison E. Aiello
Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor

The J. of Infect. Dis., 191:S25, 2005
Global problems need **global** solutions (?)

**Antimicrobial resistance: a global response.** Richard D. Smith, Joanna Coast, Bull World Health Organ 2002 vol.80 n.2

**Antimicrobial resistance: global problems need global solutions**
Susan Maddocks; Med J Aust 2013; 198: 241


Global problems as ensembles of local problems requiring **local** solutions.

The resolution of local problems may result in global influences.

**Local solutions for global problems**
Giovanni Frazzetto, Friedrich Frischknecht, EMBO Reports 2003; 4:583

**Local Solutions to Global Problems: Policy Choice and Regulatory Jurisdiction**
Bushnell J et al., NBER Working Paper No. 13472, 2007 (climate change)

Global problems and local, particular solutions

Local, particular solutions of problems related with antibiotic use and antibiotic resistance require problems’ individualization

- **Individualization** of antibiotic use in particular patients
  Individualized therapy (Personalized therapy)

- **Individualization** of antibiotic use in the particular group

- **Individualization** of antibiotic use in particular areas and environments
Individualization and Complexity of Particular Knowledge

• Knowledge about conditions acting on individuals is extremely complex, as “individuality” results of unique patterns of influences.

• Because individuals (persons, groups, environments) are different, antimicrobial interventions should increase in complexity.

• As individuals are nested in successive hierarchical levels (bacteria inside patient, inside group, in society, inside environment) antimicrobial interventions should consider simultaneously all these levels.

The Temptation of Simplicity

- Easy to understand, to learn, to teach
- Easy to remember, “simple is elegant”
- Easy to be included in routine, familiarity, confidence, conservativeness
- Easy to test, to analyze statistically
- Easy to model, to predict
- Easy to control, to manage
- Easy to sell

Extracted and deeply modified from:
Fitzpatrick S (2013). Simplicity in the Philosophy of Science

William of Ockham
How to reconcile practicality and truth?

• Praxis might produce strong-cumulative biases preventing to know the reality.
• Praxis will contribute to fix wrong concepts, preventing the emergence and growth of knowledge of higher quality.

The current use of many definitions and criteria can be defined as
• over-simplification of explanation plus
• over-organization of applicability.

• But the development of Systematic indetermination might abort applications of science to praxis.
A plausible dynamics for knowledge

Deconstruction

- Re-visionary Attractors
- Conservatism Attractors

Ex unibus plurum

Reconstruction

Ex pluribus unum

An oscillator; also remembering Liang Yi (Taoism)

Collective versus individual thinking

Efficient cause

Collective thinking

Creativity
Innovation
Theory
Risk
Limited field

Individual thinking

Mediocrity
Conservatism
Practice
Safety
Broader field

Producing consensus knowledge: thinking inside the box
**Viscous** (slowly changing) **versus** **Fluid** (rapidly changing) **Norms and Behaviors**

- **A biological similitude**: *genetic variation* and compatibility of novelties with the *functioning of the entire genome* (for instance biological cost of antibiotic resistance):
  - **Balance between adaptability and conservatism**. Many “adopted” resistance genes persists even with a minimal adaptive value.
  - **Same dynamics in the emergence and maintenance of norms**. Many norms persist even after they appear to have outlived their usefulness.

Does it benefit society to have some behaviors and norms be fluid, while others are viscous, and, if so, which behaviors and norms can tolerate fluidity? What does this mean for the policy interventions that governments might make to alter behaviors? (Ehrlich and Levin 2005).

*Greater inclusion of social and behavioral scientists in periodic environmental policy assessments*

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The beginning of a time of great expectations

- Individual and collective knowledge start to merge because of growing involvement of **SMEs in drug discovery**.
- Individual **academic groups** start influencing the criteria for drug discovery of major pharma companies, as in the European Innovative Medicines Initiative.
- Novel **strategies to shorten the timelines required to bring a new antibiotic to market** (as the “four tiers” proposal)
- **Diversification and specialization of antimicrobial therapy**, including “targeted” of “precision” drugs for particular species, and clones.
- **Complexification** of antimicrobial therapy for very severe cases and severe epidemiological threats.
- Advances in design and reports (as CONSORT) of **trials**, analysis of **evidences**, **statistical** methods for multicausal processes, and **knowledge engineering**.

Rex JH. A comprehensive regulatory framework to address the unmet need for new antibacterial treatments Lancet Infect Dis. 2013.
“His talk was very racy and interesting, just like his writings, but he sometimes went on too long on the same subject. I remember a funny dinner at my brother's..... He laughed to scorn the idea that a mathematician, such as Whewell could judge, as I maintained he could, of Goethe's views on light..... As far as I could judge, I never met a man with a mind so ill adapted for scientific research.”


Science must have originated in the feeling of something being wrong

(Thomas Carlyle)

He was a “genetic historian”
The Re-visionary Imperative in antibiotic discovery, use, and fight against resistance

• Re-vision
• Re-flection
• Re-novation
• Re-placement
• Re-combination
• Re-consideration
• Re-search

Santiago Ramón y Cajal (1852-1934) Neurones
Overview

- Knowledge and causal thinking
- Threats to causal inferences
- Uncertainties in the elements of knowledge
- Practical knowledge and social norms
- Biological Relativism
- Compartmentalized-individualized knowledge; local solutions for global problems.
- The re-visionary imperative.
Acknowledgements

• Teresa M. Coque
• Bruce Levin
• Val Fernández-Lanza
• Rafael Cantón
• Jose-Luis Martínez
• Marc Lipsitch
• Andrés Moya
• Victor de Lorenzo
• Antonio Lazcano
• Juan-Carlos Galán
• Rosa del Campo
• Domingo Gargallo
• Javier Zamora
• All Bacteria happily populating the Earth
Certainly the same diagram applies for antibiotic use and antibiotic resistance.
# Global Surveillance

<table>
<thead>
<tr>
<th>Global?</th>
<th>Surveillance?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nations?</td>
<td>• S/I/R categories/species? Method?</td>
</tr>
<tr>
<td>• Regions?</td>
<td>• MICs/phenotypes/species? Method?</td>
</tr>
<tr>
<td>• Towns?</td>
<td>• Pathogens?</td>
</tr>
<tr>
<td>• Hospitals?</td>
<td>• Microbiome/Commensals?</td>
</tr>
<tr>
<td>• Community?</td>
<td>• Genetic Exchange Commun.?</td>
</tr>
<tr>
<td>• Travelers?</td>
<td>• Environmental?</td>
</tr>
<tr>
<td>• Healthy people?</td>
<td>• Clones? High-risk Clones?</td>
</tr>
<tr>
<td>• Animals?</td>
<td>• Plasmids? Phages?</td>
</tr>
<tr>
<td>• Food?</td>
<td>• Transposons, ICEs?</td>
</tr>
<tr>
<td>• Sewage?</td>
<td>• Integrons?</td>
</tr>
<tr>
<td>• Water bodies?</td>
<td>• R Genes? From resistome?</td>
</tr>
<tr>
<td>• Soil? Air?</td>
<td>• Proteins? Beta-lactamases?</td>
</tr>
</tbody>
</table>

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The tragedy of anticommons: scientists, companies are frequently reluctant to share their data

Paradoxically, epidemiology, the study of disease in populations, has largely been reduced to the study of individual-level risk factors for disease.

Multilevel or context analysis is one way to begin to restore a population or societal dimension to epidemiologic research (i.e., the idea that factors operating at the levels of groups or societies affect the health of individuals within them).

It challenges epidemiologists to develop models of disease causation that integrate macro- and micro-level determinants.
Table 13  Overview of the findings addressing the question: Does the published scientific literature support that there is a difference in outcome for patients with infections caused by the selected bacteria if they are resistant or sensitive to the relevant specific antibacterial drugs?

<table>
<thead>
<tr>
<th></th>
<th><em>Escherichia coli</em></th>
<th><em>Klebsiella pneumoniae</em></th>
<th><em>Staphylococcus aureus</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibacterial resistance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd generation cephalosporins</td>
<td>Yes (n=4)</td>
<td>Yes (n=4)</td>
<td>No (n=1)</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>No (n=1)</td>
<td>Yes (n=7)</td>
<td>No (n=1)</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Yes (n=3)</td>
<td>Unclear (n=3)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes (n=16)</td>
</tr>
<tr>
<td>MRSA</td>
<td>No (n=17)</td>
<td>ND</td>
<td>Yes (n=50)</td>
</tr>
<tr>
<td><strong>Outcome parameter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterium-attributable mortality</td>
<td>Yes (n=4)</td>
<td>Yes (n=4)</td>
<td>No (n=1)</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>Yes (n=11)</td>
<td>Yes (n=5)</td>
<td>Yes (n=3)</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>No (n=3)</td>
<td>No (n=3)</td>
<td>Unclear (n=3)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Admission to ICU</td>
<td>No (n=1)</td>
<td>Yes (n=1)</td>
<td>ND</td>
</tr>
<tr>
<td>Post-infection LOS</td>
<td>No (n=3)</td>
<td>Yes (n=4)</td>
<td>No (n=1)</td>
</tr>
</tbody>
</table>

ICU, intensive care unit; LOS, length of stay; MRSA, methicillin-resistant *Staphylococcus aureus*; n, evaluated number of studies; ND, no data.

<sup>a</sup> Data in two studies were inconsistent and a third study could not be included in the analysis.

<sup>b</sup> A small study found that there was not a significant increase in the risk of health-care facility transfer for patients with carbapenem-resistant *K. pneumoniae* infections; however, patients enrolled in this study may have come from long-term care facilities at the time of study enrollment, so this result may not be directly attributable to *K. pneumoniae*.