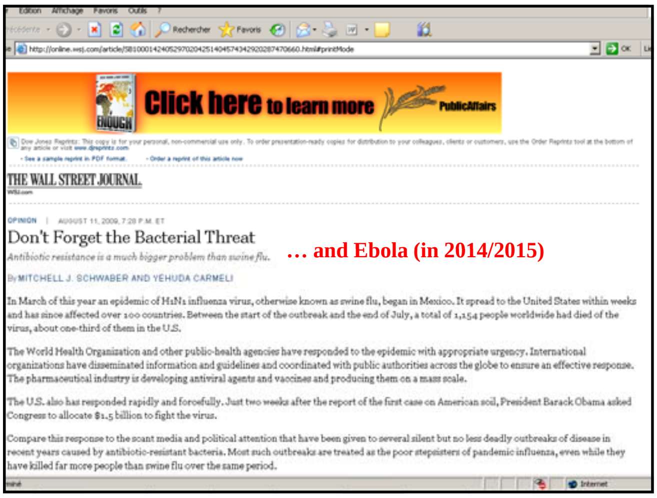
Why should we care about multi-resistant bacteria? Clinical impact and public health implications

Prof. Stephan Harbarth
Infection Control Program
Geneva, Switzerland



THE WALL STREET JOURNAL.

OPINION | AUGUST 11, 2009, 7:28 P.M. ET

Don't Forget the Bacterial Threat

Antibiotic resistance is a much bigger problem than swine flu.

By MITCHELL J. SCHWABER AND YEHUDA CARMELI

In March of this year an epidemic of H1N1 influenza virus, otherwise known as swine flu, began in Mexico. It spread to the United States within weeks and has since affected over 100 countries. Between the start of the outbreak and the end of July, a total of 1,154 people worldwide had died of the virus, about one-third of them in the U.S.

The World Health Organization and other public-health agencies have responded to the epidemic with appropriate urgency. International organizations have disseminated information and guidelines and coordinated with public authorities across the globe to ensure an effective response. The pharmaceutical industry is developing antiviral agents and vaccines and producing them on a mass scale.

The U.S. also has responded rapidly and forcefully. Just two weeks after the report of the first case on American soil, President Barack Obama asked Congress to allocate $1.5 billion to fight the virus.

Compare this response to the scant media and political attention that have been given to several silent but no less deadly outbreaks of disease in recent years caused by antibiotic-resistant bacteria. Most such outbreaks are treated as the poor stepsisters of pandemic influenza, even while they have killed far more people than swine flu over the same period.

… and Ebola (in 2014/2015)

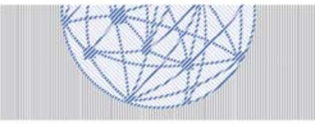
WORLD ECONOMIC FORUM

Insight Report

Global Risks 2013
Eighth Edition

have such modern medical successes bred a sense of hubris – excessive confidence that science will always come to the rescue?

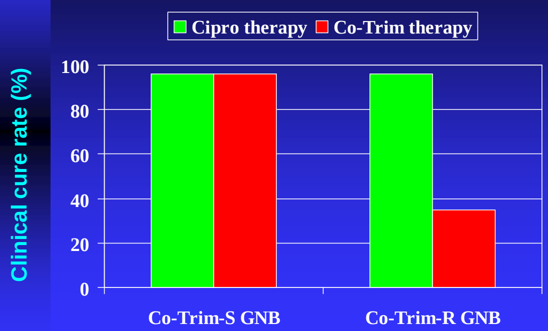
While viruses may capture more headlines, arguably the greatest risk of hubris to human health comes in the form of *antibiotic-resistant bacteria*. We live in a bacterial world where we will never be able to stay ahead of the mutation curve. A test of our resilience is how far behind the curve we allow ourselves to fall.



What are clinical implications of AMR?

- Treatment failure due to wrong choice
  - Increased morbidity and mortality

Cure Rates -- Pyelonephritis



Talan et al. JAMA 2000; 283: 1583-90

USA TODAY — Deadly MRSA Infection

- C. H. (71) first woman elected lieutenant governor in South Dakota.
- She had suffered a spinal fracture and 3 broken ribs Oct. 8 while sailing the Adriatic Sea.
- She underwent surgery in Zagreb, Croatia on Oct. 10, then was hospitalized Oct. 19 during a stop in Switzerland on her way back to the US.
- She suffered pneumonia, a bacterial blood infection, and a series of strokes, which claimed her life in Lausanne, Switzerland on October 25, 2007.

Impact of antibiotic resistance on in-hospital mortality

Pathogen	OR	95 % CI	*P*
VRE	2.1	1.0 - 4.4	.04
Pseudomonas spp	3.0	1.2 - 7.8	.02
Enterobacter spp	5.0	1.1 - 22.9	.01

Carmeli et al, Arch Intern Med 1999; 159: 1127-1132
Cosgrove et al, Arch Intern Med 2002; 162: 185-90
Carmeli et al, Arch Intern Med 2002; 162: 2223-2228

ANTIMICROBIAL RESISTANCE - Global Report on surveillance

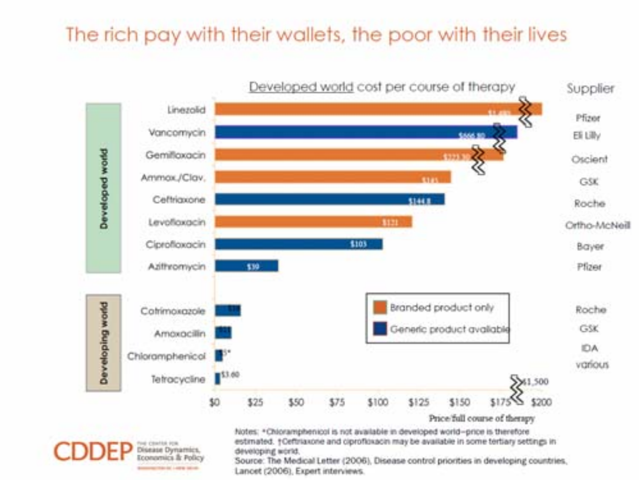
Table 13 Overview of the findings addressing the question: Does the published scientific literature support that there is a difference in outcome for patients with infections caused by the selected bacteria if they are resistant or sensitive to the relevant specific antibacterial drugs?

	Escherichia coli		*Klebsiella pneumoniae*		*Staphylococcus aureus*
Antibacterial resistance					
	3rd generation cephalosporins	Fluoroquinolones	3rd generation cephalosporins	Carbapenems	MRSA
Outcome parameter					
Bacterium-attributable mortality	Yes (n=4)	No (n=1)	Yes (n=4)	No (n=1)	Yes (n=46)
30-day mortality	Yes (n=11)	Yes (n=5)	Yes (n=7)	Yes (n=3)	Yes (n=16)

WHO report 2014

What are clinical implications of AMR?

- Treatment failure due to wrong choice
  - Increased morbidity and mortality
- Use of more toxic, less efficacious and more expensive alternatives
  - Example *Staphylococcus aureus*: Vancomycin/Linezolid (MRSA) vs. Oxacillin/Cephalosporins (MSSA)



What are clinical implications of AMR?

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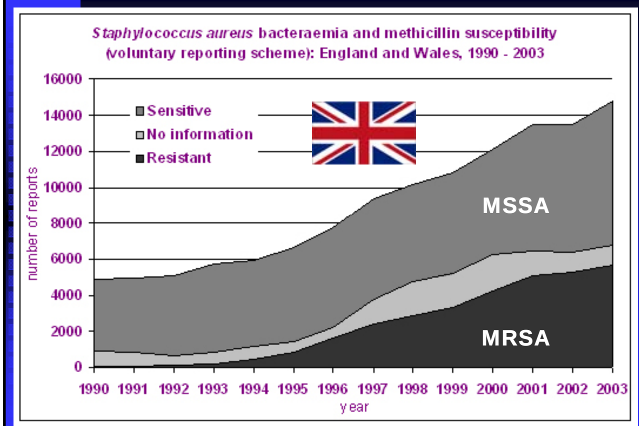
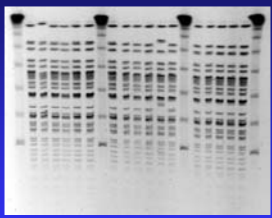
- Use of more toxic and less efficacious alternatives
- Added burden of nosocomial infections



Acinetobacter Outbreak, Lausanne

- **Index patient**
  - Severe burn injuries, transfer from Bali (Oct 2002)
  - Multi-R *Acinetobacter* at admission
- **Outbreak**
  - Spread to 2 patients
  - 6 months later: 6 new cases
  - Closure of the burn unit
- **Environnement**
  - Widespread contamination: 16/161 (10%) positive swabs

Patients *Environnement*



► Environmental cleaning & disinfection
► Complete replacement of all disposable material

Zanetti G et al. Infect Control Hosp Epidemiol 2007; 28: 723-25

Economic burden of MDROs

- **Increased direct costs** of providing care to MDRO-infected patients;
- **Antibiotic treatment costs** for therapy or empiric coverage of MDRO;
- **Indirect costs** to patients, caregivers, & diminished quality of life;
- **Infrastructure and productivity costs** of surveillance, screening and isolation.

Direct costs of MRSA-infections

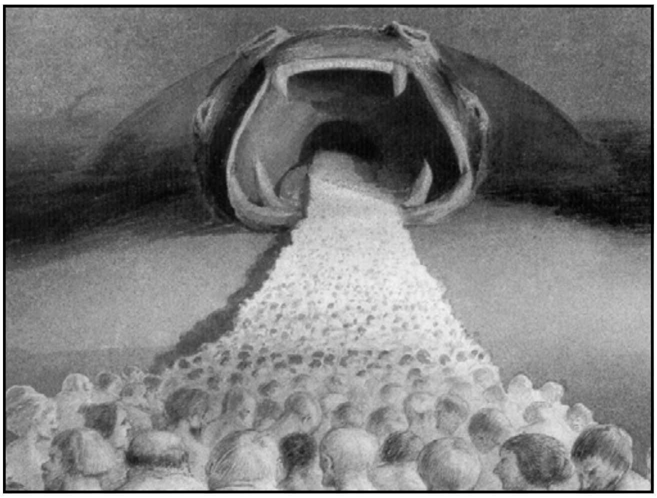
Study	Type of study (n, MRSA patients)	Type of MRSA-infection	Control group	Attributable costs
Abramson, 1999	Matched cohort study, 8 patients	bacteremia	Uninfected patients	27 080 $
Chaix, 1999	Matched cohort study, 27 patients	mixed	Uninfected patients	9 275 $
Kim, 2001	Chart review, 20 patients	mixed	Uninfected patients	14 360 $
Rubin, 1999	Ecologic study, 2,780 patients	mixed	MSSA	2 500 $
Engemann, 2003	Matched cohort study, 121 patients	surgical site infection	MSSA	13 900 $
Kopp, 2004	Matched cohort study, 36 patients	mixed	MSSA	3 713 $
Cosgrove, 2005	Cohort study, 96 patients	bacteremia	MSSA	6 900 $

What are clinical implications of AMR?

- Treatment failure due to wrong choice
  - Increased morbidity and mortality
- Use of more toxic alternatives
- Added burden of nosocomial infections
- Possibility of no alternate agents (e.g. VRSA, XDR-Tb, pan-resistant *Acinetobacter* spp, colistin-resistant NDM & KPC)

ANTIBIOGRAMMES	(28)x1 Candida albicans	(29)x1 Pseudomonas aeruginosa	(30)x1 Pseudomonas aeruginosa	(31)x1 Proteus mirabilis	(35)x1 Pseudomonas aeruginosa
Amoxicilline				RESIST.	
Co-amoxiclav				RESIST.	
Piperacilline		RESIST.	RESIST.	RESIST.	RESIST.
Piperac.+tazob		RESIST.	RESIST.	RESIST.	RESIST.
Cefoxitine				S	
Cefuroxime				RESIST.	
Ceftazidime		RESIST.	RESIST.	RESIST.	RESIST.
Ceftriaxone				RESIST.	
Cefepime		RESIST.	RESIST.	RESIST.	RESIST.
Imipenem		RESIST.	RESIST.	S	RESIST.
Meropeneme		RESIST.	RESIST.		RESIST.
Aztreonam		RESIST.	RESIST.	RESIST.	INTERM.
Amikacine		RESIST.	RESIST.	RESIST.	RESIST.
Gentamicine		RESIST.	RESIST.	RESIST.	RESIST.
Tobramycine		RESIST.	256 R		RESIST.
Norfloxacine		RESIST.	RESIST.	INTERM.	RESIST.
Ciprofloxacine		RESIST.	RESIST.	S	RESIST.
Co-trimoxazole				RESIST.	
Fosfomycine			INTERM.	RESIST.	INTERM.
Furanes				RESIST.	
Polymyxine B		S	S		
Colistine			2 S		3 I

Overall public health burden and future societal impact?



Affected people / deaths worldwide

Table 1 Human behavior and ecosystems linked to the emergence of new infectious diseases

Disease	Human behavior/ecosystem	Year of first appearance	Affected people/deaths
vCJD	Feeding of cows with 'rendered' carcasses of cows and scrapie-infected sheep	1996	143/141
HCV	Unscreened blood products before 1992, medical practices involving unsterilized tools, including syringe reuse	1987 HCV discovered	170 million
SARS	Live animals food markets, air travel	2003	8,098/774 in 2002–2003
Legionella pneumophila	Air-conditioning cooling towers	1976	221/34 in 1976 outbreak
Ebola	Bush-meat hunting	1976, 1994	313/264 during last 2 years
HIV	Bush-meat hunting, sex, travel	1981	40 million/3 million per year
West Nile virus	Air travel, climatic change	1999 USA	9,858/262
Avian influenza	Open markets with aquatic birds, chickens, intensive cultivation of chickens and pigs	1997	43/31 in 2004
Antibiotic resistance	Widespread use of available antibiotics and spread in the environment	Few years after the introduction of each class of antibiotics	Not available

R. Rappuoli. Nat Med 2004.
From Pasteur to genomics: progress and challenges in infectious diseases

Apocalypse des antibiotiques en France d'ici à 2025 avec la propagation de bactéries résistantes provenant de Grèce et d'Afrique du Nord

L'ESCMID met en garde l'Europe du risque d'un million de morts causé par l'utilisation d'antibiotiques inefficaces d'ici à 2025

Antibiotic Armageddon in UK and Europe by 2025

ESCMID warns that Europe may surpass one-million deaths due to ineffective antibiotics by 2025

21st April, 2015, ESCMID: A group of leading scientists has warned that Britain and Europe collectively could face more than a million deaths in an impending "Antibiotic Armageddon" unless more is spent on developing new cures, rapid diagnostics and preventative measures to combat the spread of drug resistant diseases.

Recent modelling studies

- Until 2050 -- AMR may potentially …:
  - …cause the death of 300 million people
  - …decrease the world gross domestic product by 2-3.5% compared to what it should be
- Crude predictions based on large uncertainty and possible overestimates of the future health-economic impact of AMR

UK Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations. 2014.

Recent modelling studies (II)

UK Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations. 2014.

Methodological challenges and potential confounders

- Problem 1: Separate the effects of antibiotic-susceptible infection vs -resistant infection
- Problem 2: Adequacy of antibiotic therapy
- Problem 3: Severity of illness and underlying disease

Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study

Marie-Laurence Lambert, Carl Suetens, Anne Savey, Mercedes Palomar, Michael Hiesmayr, Ingrid Morales, Antonella Agodi, Uwe Frank, Karl Mertens, Martin Schumacher, Martin Wolkewitz

- Cohort study, 2005-2008
- 10 countries, 537 ICUs, 119699 pts
- Sophisticated statistical analyses adjusted for the timing of events (multistate modelling)

Lambert et al. Lancet Infect Dis 2011

Main findings

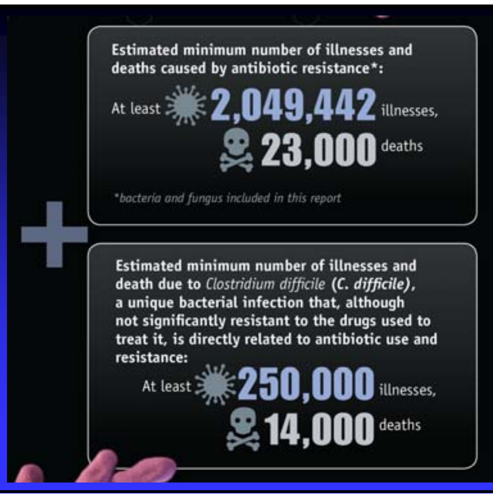
- High excess mortality associated with bacteremia and pneumonia
- *Pseudomonas aeruginosa:* greatest burden (not MRSA)
- AMR: only a relatively small contribution to the overall burden of health-care associated infections

Lambert et al. Lancet Infect Dis 2011

Bacteremia impact

	Hazard ratio for ICU deaths (95% CI)		Excess length
	Time-adjusted	Fully adjusted	Time-adjusted
Exposure			
Acinetobacter baumannii (ceftazidime sensitive)	7·7 (3·3–17·8)	4·4 (1·9–10·4)	−0·12
Acinetobacter baumannii (ceftazidime resistant)	5·3 (3·0–9·3)	3·3 (1·8–6·0)	1·34
Acinetobacter baumannii (unknown)	9·2 (6·6–12·8)	4·0 (1·9–10·4)	··
Escherichia coli (C3G sensitive)	5·8 (4·6–7·3)	2·7 (2·1–3·4)	0·13
Escherichia coli (C3G resistant)	7·1 (4·5–11·2)	3·6 (2·3–5·6)	3·17
Pseudomonas aeruginosa (ceftazidime sensitive)	7·1 (5·8–8·8)	3·2 (2·6–4·0)	3·71
Pseudomonas aeruginosa (ceftazidime resistant)	5·4 (3·7–7·8)	4·0 (2·7–5·8)	3·35
MSSA	3·6 (2·8–4·6)	2·1 (1·6–2·6)	0·91
MRSA	5·8 (4·5–7·5)	3·3 (2·5–5·2)	2·42
All four sensitive microorganisms	5·4 (4·7–6·1)	3·1 (2·7–3·6)	1·1
All four resistant microorganisms	5·5 (4·6–6·7)	3·6 (3·0–4·4)	2·5

Lambert et al. Lancet Infect Dis 2011



Threat level: URGENT

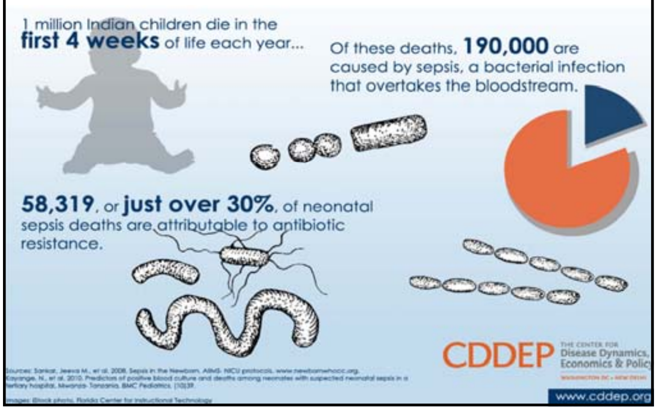
Threat level: SERIOUS

Table 1 | Annual cost of illness for selected conditions in US

Health problem	Societal cost ($bn, 2004)
Cardiovascular disease[w1]	380
Musculoskeletal conditions[w2]	300
Motor vehicle accidents[w3]	270
Occupational injury and illness[w4]	266
Mental disorders[w5]	260
Substance abuse[w6]	195
Cancer (all)[w7]	185
Diabetes[w8]	145
Alzheimer's disease[w9]	70
Antimicrobial resistance[w10]	55
Skin disease[w11]	48
Urinary incontinence[w12]	23
Asthma[w13]	16

BMJ 2013;346:f1493

Projected impact of antimicrobial-resistant neonatal sepsis in India



INFECTIOUS DISEASE

sciencemag.org SCIENCE

A return to the pre-antimicrobial era?

The effects of antimicrobial resistance will be felt most acutely in lower-income countries

By Stephen Baker[1,2,3]

6 MARCH 2015 • VOL 347 ISSUE 6226

Conclusions

- Consistency of data regarding the impact of antimicrobial resistance on clinical outcome in most MDRO infections
- Increasing evidence of:
  - **Increased likelihood of treatment failure**
  - **Increased morbidity and mortality**
  - **Added disease burden and treatment costs**
- Paucity of data regarding the global impact of antimicrobial resistance on public health (in particular in LMIC)