



HAL
open science

Evaluating the Clinical Burden and Mortality Attributable to Antibiotic Resistance: The Disparity of Empirical Data and Simple Model Estimations

Cedric Abat, Jean-Marc Rolain, Gregory Dubourg, Pierre-Edouard Fournier,
Herve Chaudet, Didier Raoult

► **To cite this version:**

Cedric Abat, Jean-Marc Rolain, Gregory Dubourg, Pierre-Edouard Fournier, Herve Chaudet, et al.. Evaluating the Clinical Burden and Mortality Attributable to Antibiotic Resistance: The Disparity of Empirical Data and Simple Model Estimations. *Clinical Infectious Diseases*, 2017, 65 (1), pp.S58-S63. 10.1093/cid/cix346 . hal-01730961

HAL Id: hal-01730961

<https://hal.science/hal-01730961>

Submitted on 10 Dec 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Evaluating the Clinical Burden and Mortality Attributable to Antibiotic Resistance: The Disparity of Empirical Data and Simple Model Estimations

Cédric Abat, Jean-Marc Rolain, Grégory Dubourg, Pierre-Edouard Fournier, Hervé Chaudet, and Didier Raoult

URMITE, UMR 63, CNRS 7278, IRD 198, INSERM U1905, Institut Hospitalo-Universitaire Méditerranée Infection, Faculté de Médecine et de Pharmacie, Aix-Marseille Université, Marseille, France

Given the proliferation of cataclysmic predictions about antibiotic resistance, cases of which are estimated to amount to 12 500 per year in France, we herein decided to compare the empirical clinical microbiology data from our institution with estimates and predictions from 10 major international scientific articles and reports. The analysis of 7 years of antibiotic resistance data from 10 bacterial species and genera of clinical interest from our institution identified no deaths that were directly attributable to extremely drug-resistant bacteria. By comparing our observations to the 10 articles and reports studied herein, we concluded that their results lack empirical data. Interventions are urgently needed to significantly reduce both mortality and the healthcare costs associated with bacterial infections, including the implementation of local and national laboratory data-based surveillance systems for the routine surveillance of antibiotic resistance that would be helpful for a better understanding of how to manage antibiotic-resistant bacteria in the future.

Keywords. antibiotic resistance; extra deaths; multidrug resistant bacteria; old antimicrobial drugs.

In recent decades, major technological improvements have emerged around the world, particularly through the massive spread of the internet. It was recently estimated that of the 7.3 billion human beings worldwide as of June 2016, >3.6 billion (49.5% of the world's population) have access to and actively use the internet (<http://www.internetworldstats.com/stats.htm>). This impressive development accelerates the sharing of a diverse range of information, including health-related information. One of the main problems associated with this sharing is that individuals can distort or skew the information based on their perceptions and preconceived ideas about a given event, which can create panic among the population [1]. Therefore, the way information is communicated to the public is of critical importance.

In recent years, we have seen the proliferation of cataclysmic predictions about human health that, fortunately, have never fully materialized. These include, in particular, bioterrorism, Creutzfeldt-Jakob disease, severe acute respiratory syndrome (SARS), the H5N1 and H7N9 influenza viruses, Middle East respiratory syndrome (MERS), and Ebola. These infectious threats have killed hundreds or, in some cases, thousands of people, but

the death toll remains far from the million deaths per year due to tuberculosis (1.1 million in 2015) [2], and far from the 29 000 and 15 000 estimated annual deaths due to *Clostridium difficile* in the United States and Europe, respectively [3, 4]. This disproportional reaction is particularly observable in Table 1.

The new fear that is currently taking control around the world is antibiotic resistance, and its purportedly huge impact on humans. Over the last decade, resistance to antibiotics has become a new fear, both within the scientific community and in the media, leading to several alarmist reports of the potential inability to treat patients in the future [5–14] (Table 2), and as many as 10 million extra human deaths per year by 2050 [9]. This raises the question of whether we urgently need to develop new antibiotics to maintain the efficacy in the treatment of infectious diseases [15] and/or whether these alarmist reports represent the reality of clinical practice.

Given the importance of the issue, the Institut Hospitalo-Universitaire Méditerranée Infection (IHU) has implemented its own empirical bacterial antibiotic-resistance surveillance systems [16, 17] to provide a strong foundation for discussions on the subject, rather than being based on predictions deriving from mathematical models that have yet to succeed in predicting the evolution of any other infectious risks [18–20]. In this investigation, we compare the empirical data available from the IHU bacterial antibiotic-resistance surveillance network with the estimates and predictions from various articles and reports [5–14] (Table 2).

Correspondence: Didier Raoult, URMITE, UMR CNRS 7278, IRD 198, INSERM U1905, Faculté de Médecine, 27 Boulevard Jean Moulin, 13385 Marseille CEDEX 5, France (didier.raoult@gmail.com).

Clinical Infectious Diseases® 2017;65(S1):S58–63

© The Author 2017. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com. DOI: 10.1093/cid/cix346

Table 1. Number of Articles Published in PubMed, Number of Deaths, and Number of Deaths/Number of Publications Ratios for Bioterrorism, Bovine Spongiform Encephalopathy, Avian Flu H5N1 and H7N9, Severe Acute Respiratory Syndrome, Middle East Respiratory Syndrome, Ebola, Tuberculosis, and *Clostridium difficile*

Keywords for PubMed Research	No. of Articles Published in PubMed ^a	Peak of Publication (Year)	No. of Deaths	Deaths/Publications Ratio ^b	References
Bioterrorism	5808	889 (2002)	5 ^c	0.001	Jernigan et al, 2002; Gursky et al, 2003 [33, 34]
Bovine spongiform encephalopathy	3559	278 (2001)	224	0.1	http://www.who.int/mediacentre/factsheets/fs180/en/
H5N1	6858	754 (2009)	362	0.1	McConnell and Raoult, 2014 [35]
H7N9	7898	789 (2014)	44	0.01	McConnell and Raoult, 2014 [35]
SARS	7811	1157 (2003)	774	0.1	McConnell and Raoult, 2014 [35]
MERS	13 328	1496 (2003)	60	0.005	McConnell and Raoult, 2014 [35]
Ebola	5902	1904 (2015)	11 315	1.9	http://apps.who.int/ebola/current-situation/ebola-situation-report-6-january-2016
Tuberculosis	231 313 (6723 in 2016)	7599 (2015)	1.1 million per year	163.6	GBD 2015 Mortality and Causes of Death Collaborators, 2016
<i>Clostridium difficile</i>	11 720 (1070 in 2016)	1082 (2015)	At least 44 000 per year	41.1	Barbut et al, 2013; Lessa et al, 2015 [3, 4]

Abbreviations: GBD, Global Burden of Disease Study; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.

^aNumber of articles published in PubMed up to 18 November 2016.

^bRatios calculated by dividing the number of deaths due to each infectious disease of interest to the total number of publications available in PubMed. Only publications related to bioterrorism events involving infectious agents were included in the calculation. For tuberculosis and *C. difficile*, we used the number of publications of 2016 to estimate the deaths/publications ratio.

^cHuman deaths due to anthrax.

EMPIRICAL OBSERVATIONS

The Global Burden of Disease study group recently published a systematic analysis of the number of deaths due to 249 causes of death, in which they identified that the worldwide number of human deaths due to infectious diseases has dramatically decreased from 10.7 million deaths in 2005 to 8.6 million in 2015 [2]. This is in stark contrast to the global fear about the resurgence of infectious diseases. In particular, this study underlines that the number of global deaths due to lower respiratory infections, which were classified as the leading cause of human death in 1990, and which were the third leading cause of human death in 2015, has decreased from 2.8 million deaths in 2005 to 2.7 million in 2015—that is, a 3.6% decrease over the last 10 years [2]. The decrease is even more striking in children <5 years of age, for whom a 36.9% decrease was observed over the same period [2]. Such observations can be partly explained by improved management of the patients in hospital settings, particularly by the screening and isolation strategies that were developed to control specific pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) [21]. However, as previously discussed [21], other factors have to be considered, in particular the discovery and worldwide spread of antibiotic compounds [15], which continues to grow, with a 36% increase in the worldwide human consumption of antibiotics between 2000 and 2010 [12]. Thus, one of the best-known positive impacts of antibiotics on human health is the introduction in the 1940s of antituberculosis medicines, which contributed to the dramatic decrease in worldwide prevalence and mortality of tuberculosis [22]. This decrease is still observable today, with

a drop from 1.3 million deaths in 2005 to 1.1 million deaths in 2015—that is, an impressive 15.4% decrease over the last 10 years [2]—and an estimated 47% decrease between 1990 and 2015 (http://www.who.int/gho/tb/epidemic/cases_deaths/en/). Another example is the impact of penicillin on pneumonia, which was highlighted by a dramatic decrease from 20%–40% to 5% in the worldwide mortality rate for pneumococcal pneumonia over the last 8 decades [12].

OBSERVATIONS FROM MARSEILLE

The IHU surveillance system network includes 4 automated laboratory data–based surveillance systems: epidemiological surveillance and alert based on microbiological data (EPIMIC), established in 2002 [16], and the bacterial real-time laboratory-based surveillance system (BALYSES), the Marseille antibiotic resistance surveillance system (MARSS), and the Provence-Alpes-Côte d’Azur surveillance epidemiologic system (PACASurvE), established in 2013 [17, 23]. EPIMIC, BALYSES, and MARSS analyze data produced by the Timone hospital clinical microbiology laboratory on a weekly basis, and PACASurvE analyzes data produced by 214 microbiology laboratories from France’s Provence-Alpes-Côte d’Azur (PACA) region on a weekly basis. In combination, these surveillance systems make it possible to monitor the weekly number of patients where >650 bacterial species were isolated from clinical human samples collected and cultured in the 4 Assistance Publique–Hôpitaux de Marseille public hospitals.

Of these surveillance systems, EPIMIC and MARSS monitor weekly bacterial antibiotic resistance profiles (39 antibiotic

Table 2. Sources of Data Compared in Our Study

Source of Data	Description of the Analysis	Studied Pathogens/Antibiotic Profiles	Number of Extra Deaths (Region) ^a	References
Institut Hospitalo-Universitaire Méditerranée Infection	Retrospective analysis of 27 681 nonredundant bacterial infections using real clinical microbiology data	<i>Staphylococcus aureus</i> , <i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i> , <i>Enterobacter cloacae</i> , <i>Enterobacter aerogenes</i> , <i>Burkholderia cepacia</i> , <i>Stenotrophomonas maltophilia</i> , <i>Proteus</i> spp, <i>Serratia</i> spp, and <i>Morganella morganii</i>	0 (Marseille, France)	Unpublished data
World Health Organization report	Estimate based on the analysis of 221 studies	MRSA, 3GC, and fluoroquinolone-resistant <i>E. coli</i> , and 3GC and CR <i>K. pneumoniae</i>	NC	World Health Organization, 2014
European Centre for Disease Prevention and Control report	Estimates based on data from the European Antimicrobial Resistance Surveillance System	MRSA, VISA/VRSA, VRE, <i>Streptococcus pneumoniae</i> resistant to penicillin, 3GC and CR <i>E. coli</i> , 3GC and CR <i>K. pneumoniae</i> , and CR <i>P. aeruginosa</i>	25 000 (Europe)	ECDC/EMA Joint Technical Report, 2009
Centers for Disease Control and Prevention	Estimates based on 20 main sources of data	<i>Clostridium difficile</i> , CR Enterobacteriaceae, <i>Neisseria gonorrhoeae</i> , MDR <i>Acinetobacter baumannii</i> , <i>Campylobacter</i> spp, fluconazole-resistant <i>Candida</i> spp, ESBL-producing Enterobacteriaceae, VRE, MDR <i>P. aeruginosa</i> , <i>Salmonella</i> spp, <i>Shigella</i> spp, MRSA, <i>S. pneumoniae</i> , <i>Mycobacterium tuberculosis</i> , VRSA, erythromycin-resistant group A streptococci, and clindamycin-resistant group B streptococci	23 000 (United States)	Centers for Disease Control and Prevention, 2013
Burden study report	Estimates based on data from the European Antimicrobial Resistance Surveillance System	MRSA, glycopeptide-resistant <i>Enterococcus</i> spp, 3GC <i>E. coli</i> , 3GC <i>K. pneumoniae</i> , CR <i>P. aeruginosa</i> , CR <i>K. pneumoniae</i> , and CR <i>A. baumannii</i>	12 500 (France)	Colomb-Cotinat et al, 2015
Antimicrobial Resistance Review	Prediction of the number of deaths due to 6 public health issues using several sources of data	<i>E. coli</i> , <i>K. pneumoniae</i> , <i>S. aureus</i> , HIV, malaria, and tuberculosis	10 million in 2050 (worldwide)	O'Neill, 2014
Burden study group	Estimates based on data from the European Antimicrobial Resistance Surveillance System	Bloodstream infections due to MRSA and 3GC <i>E. coli</i>	8000 (Europe)	De Kraker et al, 2011
Laxminarayan et al, 2016	Analysis using estimates produced by Liu et al, 2015 [36] focusing on neonatal sepsis	Unspecified resistant pathogens responsible for neonatal sepsis	214 000 (worldwide)	Laxminarayan et al, 2016
European Society of Clinical Microbiology and Infectious Diseases	No methodology available	No methodology available	1 million in 2025 (Europe) 10 000 (United Kingdom)	ESCMID, 2015
Centers for Disease Control and Prevention	Estimates based on data from the EIP-ABCs population-based surveillance system	Invasive MRSA	>11 000 (United States)	Dantes et al, 2013
Laxminarayan et al, 2013	Estimates based on risk factor analysis produced by Kayange et al, 2010 [37] focusing on neonatal deaths	ESBL Gram-negative bacteria and MRSA	>58 000 (India)	Laxminarayan et al, 2013

Abbreviations: 3GC, third-generation cephalosporin resistant; CR, carbapenem resistant; ECDC, European Centre for Disease Prevention and Control; EIP-ABC, Emerging Infections Program—Active Bacterial Core; EMA, European Medicines Agency; ESBL, extended-spectrum β-lactamase; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; HIV, human immunodeficiency virus; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; NC, not calculated; VISA, vancomycin-intermediate *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*; VRSA, vancomycin-resistant *Staphylococcus aureus*.

^aNumber of extra deaths due to antibiotic and/or antimicrobial resistance.

resistance patterns for EPIMIC and 65 antibiotic-resistance profiles for 15 bacterial species of interest to MARSS) [16, 17]. Since 2010, they have monitored the results of >140 000 bacterial antibiotic resistance tests—that is, the results of >25 000 antibiotic resistance test per year. This 15-year experiment has tracked intriguing epidemiological events. For example, we identified that the level of MRSA strains routinely isolated in hospitals in Marseille dramatically decreased over the years, particularly invasive strains, for which the level of MRSA decreased from 27.4% in 2010 to 12.8% in 2015, for unexplained reasons [21]. A comparison of our level of MRSA to European data from the European Antimicrobial Resistance Surveillance Network and

available international literature shows that this phenomenon is, in fact, a worldwide unexplained epidemiological event [21], emphasizing that the bacterial epidemiology is evolving, particularly through the continuous appearance and disappearance of bacterial clones that are more competitive. This phenomenon has been observed several times in the past, and was recently observed with the appearance and worldwide spread of the *Escherichia coli* sequence type 131 clone [24]. Our monitoring system has also enabled us to see that the level of resistance to some critical antibiotics (including vancomycin and imipenem) of invasive strains belonging to 11 bacterial species of particular clinical interest (*Enterobacter cloacae*, *Escherichia coli*,

Enterococcus faecalis, *Enterococcus faecium*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus agalactiae*, and *Streptococcus pneumoniae*) did not globally change or even decrease from 2001 to 2015 [15]. All these examples from the surveillance of antibiotic resistance on the local scale clearly demonstrate that the prevalence of resistance of bacteria to any given antibiotic is difficult to predict, as it depends on a multiplicity of biological, genetic, and ecological factors, creating a complex frame with high stochasticity [25]; therefore, estimates of extra deaths based on such data are highly speculative.

EXTENSIVELY DRUG-RESISTANT BACTERIA AND HUMAN EXTRA DEATHS

Recently, we decided to collect and analyze the results of 7 years of bacterial antibiotic resistance test performed in our clinical microbiology laboratory, to determine the true impact of extensively drug-resistant (XDR) bacterial strains (ie, bacterial strains susceptible to <2 generic antibiotic compounds) on the mortality of patients hospitalized in our facility (representing 1% of patients hospitalized in France). We focused our analysis on 10 bacterial species and genera of particular interest. Overall, we identified that 27 681 nonredundant bacterial infections due to the bacterial species of interest occurred over the study period, with 37 bacterial strains that were truly XDR. We then checked whether the 37 patients infected by the 37 XDR strains died in the 30 days following the infection. From this, we identified only 4 patients who met the criteria of inclusion. Looking their medical history in detail, we observed that all were admitted in intensive care units with comorbidities (1 for a hemorrhagic cerebellar stroke, 1 for septic shock, 1 for severe aortic valve endocarditis due to MRSA, and 1 for febrile respiratory distress worsened by cystic fibrosis) and that their deaths were not necessarily attributable to XDR bacterial infections. Although this analysis did not include case-controlled studies, which is a major limitation of our analysis, it allows us to conclude that, in our clinical experience, only 1 death was observed due to an XDR bacterial strain, which occurred in 2002 with an XDR *Enterobacter aerogenes* that became successively resistant to imipenem then colimycin, but which was still susceptible to gentamicin [26, 27]. The patient eventually died after a 10-week stay in the intensive care unit. The real role of the bacteria in the death of this patient is uncertain, but we certainly reached a therapeutic impasse of sorts and the patient died. In the literature, studies describing human deaths due to therapeutic impasses are scarce. Moreover, even in these cases, it is not clear whether or not the clinicians tested second-line antibiotics to treat the bacterial infections, as several useful antibiotics are no longer available [28], although they are effective against multi-drug-resistant (MDR) bacteria [29]. One of the most striking examples of such efficacy is the successful use of antileprosy drugs in combination with other drugs to treat patients with

pulmonary tuberculosis due to an XDR *Mycobacterium tuberculosis* strain [30]. Taken together, these observations clearly demonstrate that the relationship between XDR bacterial infections and mortality is difficult to determine, and that further analysis is needed to clarify this relationship.

WHAT SHOULD WE MAKE OF THE ALARMING ESTIMATES AND PREDICTIONS ABOUT ANTIBIOTIC RESISTANCE?

Comparing our observations to the estimates and predictions from the articles and reports mentioned in Table 2 [5–14], it is clear that authors are not analyzing true clinical microbiology data. Thus, estimates of the number of extra deaths due to MDR bacterial infections are based solely on mathematical models and formulae. In any case, the real number of deaths attributable to MDR bacteria can be counted, as such data could easily be retrieved from hospital settings. Moreover, each of these reports uses a different definition of MDR bacteria, and the attributability of deaths to those bacteria were not analyzed. Thus, the alarmist messages presented in these reports usually concern 1 bacterial species for a given antibiotic (eg, resistance to carbapenems or colistin in gram-negative bacteria), rather than resistance to a panel of antibiotics from different classes [5–14].

CONCLUSIONS AND PERSPECTIVES

Although clinical microbiology data and the results obtained from our analysis can be biased for several reasons, including the way data are extracted and analyzed and the fact that the bacterial epidemiology may vary from one place to another place, the local antibiotic resistance surveillance systems we have implemented in our institution, combined with our strategy to test a large panel of antibiotics, including older antibiotics against MDR bacteria, and the count of deaths associated with XDR, have enabled us to demonstrate that the current fears and alarmist reports both in the scientific community and in the media might be far removed from reality. The difference between our data and the estimates and predictions from the studied articles and reports [5–14] (Table 2) clearly raises the question of the usefulness of these predictive mathematical models and the quality of data that have been used to build them, as compared to empirical counting and observation of the realities on the ground. Indeed, modeling extra deaths using deductive models without actually counting the real number of deaths attributable to MDR bacteria does not reflect reality, and cannot be used as a standard, because there are many confounding factors, such as emergence of new bacterial clones, comorbidities, local epidemiology, the availability of drugs, etc. Thus, it is impossible to predict the number of extra deaths based on exceedingly simple mathematical models when there are so many uncontrolled factors [31]. This is illustrated fairly well by Alice's living croquet theory [32], borrowed from Lewis

Carroll's game of "living croquet," where the mallets are live pink flamingoes and the balls are live hedgehogs who behave unpredictably, making it impossible to predict the outcome of the game. It is the same with predicting extra deaths attributable to bacterial infections due to MDR bacteria, because trends of resistance to antibiotics are unpredictable, and many additional factors are currently unknown or misunderstood.

This raises the question of what can be done. In the past, some antibiotics, such as imipenem, were considered to be a "magic bullet," explaining their overuse for decades. However, the recent emergence of carbapenemase-producing bacteria should prompt us to reconsider old drugs. Considering that it is still unclear how antibiotic-resistant bacterial infection impacts hospitalized patients, we believe that it is reasonable to recommend (1) the adaptation of empirical therapeutic treatments to local antibiotic-resistance epidemiology; (2) the implementation of antibiotic stewardship to guarantee best therapeutic usage; (3) the revival of our historical armamentarium of antibiotics, including those that are no longer distributed by drug companies; (4) the management of patients with bacterial infections in infectious diseases units in coordination with clinical microbiologists; and (5) the implementation of laboratory data-based surveillance systems for the routine surveillance of antibiotic resistance. Such approaches have already been implemented in our institute in its role as an experimental research hospital to fight bacterial infections, including infections due to MDR bacteria. The results from these ongoing approaches to patients with MDR bacterial infections will help us better understand how to manage such patients in the future.

Notes

Financial support. This work was supported by the Centre National de la Recherche Scientifique and the IHU Méditerranée Infection.

Supplement sponsorship. This article appears as part of the supplement "Emerging Concepts and Strategies in Clinical Microbiology and Infectious Diseases," sponsored by IHU Méditerranée Infection.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

- Lewis RE, Tyshenko MG. The impact of social amplification and attenuation of risk and the public reaction to mad cow disease in Canada. *Risk Anal* 2009; 29:714–28.
- GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388:1459–544.
- Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. *N Engl J Med* 2015; 372:825–34.
- Barbut F, Cornely O, Fitzpatrick F, et al. *Clostridium difficile* infection in Europe-A CDI Europe report. Available at: <http://www.multivu.com/assets/60637/documents/60637-CDI-HCP-Report-original.pdf>. Accessed 19 January 2017.
- European Center for Disease Prevention and Control (ECDC)/European Medicines Agency (EMA) Joint Technical Report. The bacterial challenge: time to react. Available at: <http://ecdc.europa.eu/en/publications/>

- [Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf](http://ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf). Accessed 19 January 2017.
- World Health Organization. Antimicrobial resistance. Global report on surveillance. Available at: http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf. Accessed 19 January 2017.
 - Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. Available at: <https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf>. Accessed 19 January 2017.
 - Colomb-Cotinat M, Lacoste J, Coignard B, et al. Morbidité et mortalité des infections à bactéries multi-résistantes aux antibiotiques en France en 2012. Available at: http://invs.santepubliquefrance.fr/content/download/116892/409658/version/1/file/Rapport_DMI_RATB_Burden_BAT.PDF. Accessed 19 January 2017.
 - O'Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. Available at: https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf. Accessed 19 January 2017.
 - de Kraker ME, Davey PG, Grundmann H; BURDEN Study Group. Mortality and hospital stay associated with resistant *Staphylococcus aureus* and *Escherichia coli* bacteremia: estimating the burden of antibiotic resistance in Europe. *PLoS Med* 2011; 8:e1001104.
 - Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance—the need for global solutions. *Lancet Infect Dis* 2013; 13:1057–98.
 - Laxminarayan R, Matsoso P, Pant S, et al. Access to effective antimicrobials: a worldwide challenge. *Lancet* 2016; 387:168–75.
 - European Society of Clinical Microbiology and Infectious Diseases. Antibiotic armageddon in UK and Europe by 2025. Available at: https://www.escmid.org/file-admin/src/media/PDFs/2News_Discussions/Press_activities/ECCMID_2015/ECCMID_one_million_deaths_UK_consumer.pdf. Accessed 19 January 2017.
 - Dantes R, Mu Y, Belflower R, et al. National burden of invasive methicillin-resistant *Staphylococcus aureus* infections, United States, 2011. *JAMA Intern Med* 2013; 173:1970–8.
 - Rolain JM, Abat C, Jimeno MT, Fournier PE, Raoult D. Do we need new antibiotics? *Clin Microbiol Infect* 2016; 22:408–15.
 - Colson P, Rolain JM, Abat C, Charrel R, Fournier PE, Raoult D. EPIMIC: a simple homemade computer program for real-time epidemiological surveillance and alert based on microbiological data. *PLoS One* 2015; 10:e0144178.
 - Abat C, Chaudet H, Colson P, Rolain JM, Raoult D. Real-time microbiology laboratory surveillance system to detect abnormal events and emerging infections, Marseille, France. *Emerg Infect Dis* 2015; 21:1302–10.
 - Raoult D. Molecular, epidemiological, and clinical complexities of predicting patterns of infectious diseases. *Front Microbiol* 2011; 2:1–2.
 - Cauchemez S, Valleron AJ, Boëlle PY, Flahault A, Ferguson NM. Estimating the impact of school closure on influenza transmission from sentinel data. *Nature* 2008; 452:750–4.
 - Abat C, Chaudet H, Rolain JM, et al. Traditional and syndromic surveillance of infectious diseases and pathogens. *Int J Infect Dis* 2016; 48.
 - Rolain JM, Abat C, Brouqui P, et al. Worldwide decrease in methicillin-resistant *Staphylococcus aureus*: do we understand something? *Clin Microbiol Infect* 2015; 21.
 - Ortblad KF, Salomon JA, Bärnighausen T, Atun R. Stopping tuberculosis: a biosocial model for sustainable development. *Lancet* 2015; 386:2354–62.
 - Abat C, Huart M, Garcia V, et al. *Enterococcus faecalis* urinary-tract infections: do they have a zoonotic origin? *J Infect* 2016; 73:1–9.
 - Dautzenberg MJ, Haverkate MR, Bonten MJ, Bootsma MC. Epidemic potential of *Escherichia coli* ST131 and *Klebsiella pneumoniae* ST258: a systematic review and meta-analysis. *BMJ Open* 2016; 6:e009971.
 - Baquero F, Tedim AP, Coque TM. Antibiotic resistance shaping multi-level population biology of bacteria. *Front Microbiol* 2013; 4:15.
 - Diene SM, Merhej V, Henry M, et al. The rhizome of the multidrug-resistant *Enterobacter aerogenes* genome reveals how new "killer bugs" are created because of a sympatric lifestyle. *Mol Biol Evol* 2013; 30:369–83.
 - Thiolas A, Bollet C, La Scola B, Raoult D, Pagès JM. Successive emergence of *Enterobacter aerogenes* strains resistant to imipenem and colistin in a patient. *Antimicrob Agents Chemother* 2005; 49:1354–8.
 - Pulcini C, Bush K, Craig WA, et al. ESCMID Study Group for Antibiotic Policies. Forgotten antibiotics: an inventory in Europe, the United States, Canada, and Australia. *Clin Infect Dis* 2012; 54:268–74.
 - Dubourg G, Okdah L, Le Page S, Rolain JM, Raoult D. In vitro activity of 'old antibiotics' against highly resistant gram-negative bacteria. *Int J Antimicrob Agents* 2015; 46:718–20.
 - Brouqui P, Aubry C, Million M, Drancourt M, Raoult D. Totally resistant tuberculosis: will antileprosy drugs be helpful? *Int J Antimicrob Agents* 2013; 42:584–5.
 - de Kraker MEA, Stewardson AJ, Harbarth S. Will 10 million people die a year due to antimicrobial resistance by 2050? *PLoS Med* 2016; 13:e1002184.
 - Raoult D. Alice's living croquet theory. *Int J Antimicrob Agents* 2016; 47:249.

33. Gursky E, Inglesby TV, O'Toole T. Anthrax 2001: observations on the medical and public health response. *Biosecur Bioterror* **2003**; 1:97–110.
34. Jernigan DB, Raghunathan PL, Bell BP, et al. Investigation of bioterrorism-related anthrax, United States, 2001: epidemiologic findings. *Emerg Infect Dis* **2002**; 8:1019–28.
35. McConnell J, Raoult D. Emerging respiratory viruses: is it 'much ado about nothing'? (Shakespeare). *Clin Microbiol Infect* **2014**; 20:187–8.
36. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* **2015**; 385:430–40.
37. Kayange N, Kamugisha E, Mwizamholya DL, Jeremiah S, Mshana SE. Predictors of positive blood culture and deaths among neonates with suspected neonatal sepsis in a tertiary hospital, Mwanza-Tanzania. *BMC Pediatr* **2010**; 10:39.