REVIEW

Do we need new antibiotics?

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Abstract

For several years, alarmist articles both in mass media and in the scientific community have reported an increase in antibiotic resistance, even citing an inability to treat patients infected with multidrug-resistant bacteria (MDR) responsible for high mortality worldwide. In this review we summarize and discuss the key points associated with the reality of (i) the existence of pandrug-resistant bacteria, (ii) the increase of resistance worldwide, (iii) the link between resistance and death, and (iv) the need to develop new antibiotics. Data on antibiotic resistance in Europe for the main bacteria associated with invasive infections apparently demonstrate that apart from *Klebsiella pneumoniae*, which is resistant to carbapenems in three countries (Romania, Italy and Greece), the level of resistance to three or more classes of antibiotics (defined as MDR phenotype) has remained low and stable over the last 5 years and that therapeutic options exist both for reference antibiotics and for old antibiotics. The clinical outcome of patients infected by MDR bacteria remains controversial and death rates attributable to MDR bacteria versus non-MDR bacteria are still debated. The arsenal of antibiotics currently available (including 'old antibiotics') suffices for facing the waves of emergence of new bacterial resistance and should be considered as a World Heritage. This heritage should be managed in a non-profit model with international regulatory approval.

Keywords: Antimicrobial resistance, old antibiotics
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Introduction

Over the last decade a new fear has appeared in the scientific and medical community with the emergence and rapid spread of antibiotic resistance [1–4]. For several years, alarmist articles in both mass media and the scientific community have reported an increase in antibiotic resistance, even citing an inability to treat patients infected with multidrug-resistant bacteria (MDR) responsible for high mortality in Europe and the USA [1]. This has led to speculations about the end of the modern world because of both a global increase in bacterial resistance and the absence of discovery of new compounds to treat patients infected by MDR bacteria. Moreover, several models to evaluate the economic and human cost of antibiotic resistance have been proposed in Europe and in the USA [1], which have led some to propose research priorities to control antibiotic resistance. One main limiting factor for development of new antibiotics and/or repositioning of old drugs is that private pharmaceutical companies do not want to invest in this topic because of the lack of benefits [3] and/or because drug companies prefer to develop drugs for chronic diseases.

In this review we summarize and discuss the key points associated with the reality of (i) the existence of pandrug-resistant bacteria, (ii) the increase of resistance worldwide, (iii) the link between resistance and death, and, (iv) the need to develop new antibiotics.

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Source of Antibiotics

The Golden Age of antibiotics began in 1928 when Sir Alexander Fleming discovered penicillin. Antibiotics were first introduced into clinical practice in the 1930s. The majority of the modern classes of antibiotics were discovered between 1940 and 1980 by screening the antimicrobial activity of microorganisms cultured from soil only. Most antimicrobials are secondary metabolites produced by bacteria (*Actinobacteria*, *Firmicutes* and *Proteobacteria*) and fungi (*Penicillium*, *Cephalosporium* and *Aspergillus*). These are inexhaustible sources of natural products for the future (bacteriocins, non-ribosomal peptide synthetase and polyketide synthase secondary metabolites). These enzyme complexes (polyketide synthases and non-ribosomal peptide synthetases) are thiotemplate modular systems that are genetically organized in modules with large genes (>10 kb) [5]. Each module contains specific enzyme activity for adding particular amino acids that represents a natural way of synthesizing secondary metabolites [5]. These secondary metabolites have biological activities and unique pharmacological properties including antimicrobial activities. Significant genetic diversity exists among these genes. By identifying the repertoire involved in the biosynthesis of secondary metabolites, we will be able to model complex assembly steps and changes in metabolites during their biocatalysis. Analysis of bacterial genomes has shown a wide distribution of genes encoding non-ribosomal peptide synthetase and polyketide synthase in many phyla, most of them being encoded by silent bacterial operons [5,6]. Consequently, the number of thiotemplate modular system clusters without an associated known natural metabolite far outweighs the number of possible chemical structures [5]. The top–down approach of whole genome sequencing has provided plenty of gene sequences related to thiotemplate modular systems but relatively modest chemical and antimicrobial activity information. Over the last 50 years, only one new class of antibiotic that is used in clinical practice has been discovered: the narrow-spectrum daptomycin, used in clinical practice [7]. Discovering new classes of antibiotics from soil stopped in the 1970s, because most of the bacterial species from these external environments were impossible to culture. Approximately 99% of all species in external environments and in the human gut do not grow under standard laboratory conditions and are a promising source of new natural products [7,8]. Although the majority of antimicrobials have been discovered so far from environmental isolates, natural antimicrobial agents synthesized by microorganisms from the microbiome of mammals have not been explored exhaustively. Growing bacteria that have not previously been cultured is obviously an alternative way of discovering new compounds [9].

Source of Antibiotic Resistance

Antibiotic resistance was identified for nearly all antibiotics quickly after they were introduced into clinical practice but throughout the 1980s, many new antibiotics were introduced in the market. This solved the resistance problem until interest in development of new drugs by pharmaceutical companies decreased. The main source of antibiotic resistance determinants are the microorganisms themselves, fighting and surviving within competitive environments [10]. Microorganisms living in human digestive tracts are in extremely harsh competition with 300 to 500 different species of bacteria, archaea and fungi, with microbial concentrations ranging from 10^4 to 10^{12} from the duodenum to the colon. Moreover, long before the colonization of humans, these bacteria or their ancestors had to live in a world of competition that naturally led them to develop many antimicrobial compounds to survive [11]. Notably, the antibiotics currently used in human medicine are weapons used in this microbial battle. The first antibiotic resistance mechanisms were discovered following the emergence of resistant bacteria pathogenic to man. It took us a long time to believe that the appearance of these resistance phenomena was a direct consequence of the massive (and sometimes inappropriate) use of antibiotics in therapy. However, recent studies have shown that antibiotic resistance is an old phenomenon, from well before the use of antibiotics. In 2011, a research team from McMaster University (Canada) discovered different antibiotic resistance genes in permafrost sediments in the Yukon Territory (Canada) dating back over 30 000 years. Researchers have found an ancestral operon encoding for vancomycin resistance [11]. In 2012, the same team published similar results from 4 million-year-old samples taken from a cave in New Mexico (USA), particularly with the discovery of bacteria possessing genes that confer resistance to daptomycin or tigecycline, two very recent antibiotics used in human medicine [12]. Many antibiotic resistance genes (to antibiotics such as ampicillin, tetracycline, trimethoprim/sulfamethoxazole, streptomycin and chloramphenicol) were also found in asymptomatic human carriers in remote areas of the Amazon, where exposure to antibiotics is extremely low [10]. Metagenomic studies of soil, water [5–7] and also in the digestive microbiota of healthy men [8], gulls and broilers [9], have identified resistance genes that had never been described, and some of which are genetically distant from known genes. Therefore in the environment, in animals and in humans,

naturally resistant bacteria that constitute a reservoir of resistance genes exist.

The emergence of resistant pathogenic bacteria observed for 30 years in fact is the result of a recent mobilization of resistance genes from these pre-existing reservoirs. Under antibiotic selective pressure, resistant bacteria present within a community will be able to transfer the determinants conferring a selective advantage to other bacteria. We now believe that the emergence of worrying 'super bugs' is a consequence of the extreme plasticity of bacterial genomes. The number of antibiotic resistance genes identified in bacteria is only a small part of the existing directory in nature. We believe now that there are over 20 000 antibiotic resistance genes [12]. Consequently, the emergence and rapid spread of antibiotic resistance in the world can be explained not only by the increase in modern use of antibiotics in humans, but by a complex interaction in a microbial ecosystem comprising antibiotics and antibiotic resistance genes. This leads to a new paradigm: antibiotic resistance must henceforth be regarded as the existence of genes and/or gene sequences found in nature that can be mobilized at any time to spread in the bacterial community and transmitted to bacterial pathogens. However, the success of selection of such genes under selection pressure is unpredictable because our understanding of the origins and diffusion of antibiotic resistance in the microbial community remains low.

Therefore, the emergence of new types of antibiotic resistance and their distribution cannot be predicted because our understanding of how they are created, develop and are disseminated remains limited to date. For example, the NDM-1 gene was found to be a chimeric gene resulting from the fusion of a progenitor type metallo-β-lactamase gene with a partial sequence of a gene conferring resistance to aminoglycosides, probably created *de novo* in *Acinetobacter baumannii* [13]. It is therefore necessary to study the various reservoirs of resistance genes to discover new emerging resistance genes that could spread in the bacterial community in the future.

Is Antibiotic-Resistant Phenotype Stable?

There is a complex ecological interaction between the acquisition of antibiotic resistance and bacteria virulence and fitness that led to non-cumulative resistance in bacteria [14]. In fact, as many antibiotics target critical bacterial functions (e.g. cell wall synthesis, transcription, translation), it is assumed that resistant bacteria suffer from decreased fitness, i.e. slower bacterial growth and virulence [14]. However, compensatory mutations may contribute to enhanced fitness for resistant-bacteria [14]. Hence it is known that depending on the fitness cost of resistance, reversion of resistance could be achieved if selective pressure were absent with replacement of the resistant population by susceptible population [14]. Finally, resistant bacteria may also have reduced virulence as exemplified by a 'pandrug' colistin-resistant *A. baumannii* clinical isolate in a patient who received colistin therapy without clinical signs of infection [15]. This isolate had impaired virulence and fitness demonstrated in a rat model of pneumonia [16]. Clinical studies in hospitals to test the reversal of resistance in individuals in the absence of antibiotics have shown that decreasing antibiotic use may cause rapid changes in resistance frequency [14]. However, the rate of reversion by susceptible bacteria after removal of antibiotic pressure could be low and complex and depends on several factors including the individual, the bacterial species and the mechanism of resistance itself. Moreover, for some antibiotics such as chloramphenicol, for which use has declined in many countries in the world, resistance to this antibiotic remains stable over time [17]. At the community level, studies on national interventions to reduce antibiotic use have provided conflicting results regarding the change in the incidence of antibiotic resistance. In one interesting study in Iceland, it was shown that decreased use of antibiotics in children was followed within a few years by a decrease in penicillin-resistant *Streptococcus pneumoniae* [18]. However, it has been demonstrated that decreased antibiotic resistance was due to replacement of the resistant bacterial population by susceptible clones that were unrelated to the reduction of antibiotic use [19]. These results indicate that factors other than antibiotic resistance acquisition may favour the selection of particular successful clones and that these factors are the main drivers to determine the success or failure of such clones after resistance is acquired. Hence, because emergence of a successful susceptible clone in the community is unpredictable, the modelled trajectories of probable overall increase in resistance to antibiotics are highly speculative.

Do We Really Observe Increased Antibiotic Resistance?

Most of the data on antibiotic resistance are provided by surveillance networks, such as EARS-NET in Europe (http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/index.aspx). The data collected in this network represent an overview and a compilation of data from laboratories and hospitals in 30 European countries and are based on antibiotic resistance data only from invasive isolates. Although there is a trend to increased resistance to third-generation cephalosporins in *Enterobacteriaceae*, mainly in *K. pneumoniae*, resistance to methicillin in *Staphylococcus aureus* has dramatically decreased over the last

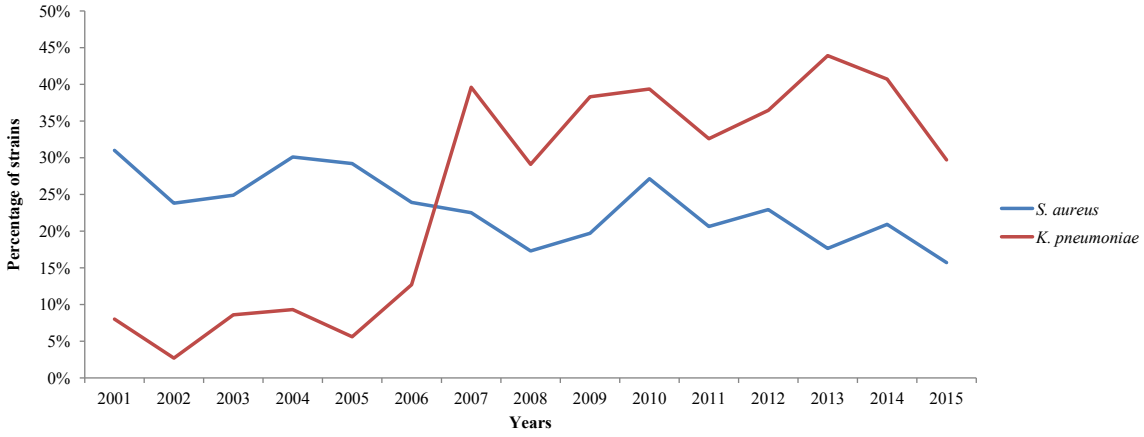

FIG. 1. Annual evolution of the percentage of invasive (blood cultures and cerebrospinal fluids) *Klebsiella pneumoniae* and *Staphylococcus aureus* strains resistant to ceftriaxone and methicillin, respectively, at Assistance Publique- Hôpitaux de Marseille, January 2001 to October 2015.

10 years worldwide without any definitive explanation [20,21] (Fig. 1). We also observe a very low level of resistance in enterococci in Marseille, France [22]. These results re-emphasize the fact that trajectories of antibiotic-resistant bacteria are unpredictable, probably because of the cyclic success of some bugs that tend to replace others, including MDR clones. As a consequence of the non-cumulative effect of antibiotic resistance and fitness cost for bacteria, the resistance rates to the main reference antibiotic in our hospitals in Marseille, France, have fallen or slightly increased for the more common pathogenic bacteria over the past 15 years (Table 1). Moreover, the rate of resistance to carbapenems in *Escherichia coli* remains low and is not worrying in our community (Table 1) or in Europe overall [23]. The percentage of *E. coli* invasive isolates with combined resistance to four classes of antibiotics (fluoroquinolones + aminopenicillins + third-generation cephalosporins + aminoglycosides) in Europe is only 4.6% in 2013 and has been stable since 2010 (4.3%) [23]. The real burden of MDR bacteria is seen for *A. baumannii* and *K. pneumoniae* in the hospital settings responsible for nosocomial infections or for imported carbapenemase-producing bacteria. However, in Europe, the mean percentage of *K. pneumoniae* invasive isolates resistant to carbapenems in 2013 was 8.3%. It was also <6% for 27 countries and very high and endemic in only three countries: Romania (20.5%), Italy (34.3%) and Greece (59.4%) [23]. Again for *K. pneumoniae*, the percentage of invasive isolates with combined resistance to four classes of antibiotics (fluoroquinolones + third-generation cephalosporins + carbapenems + aminoglycosides) in Europe in 2013 was 6.1%

TABLE 1. Evolution of the percentage of resistance of bacterial strains isolated from invasive samples (blood cultures and cerebrospinal fluids) and belonging to critical bacterial species, Assistance Publique - Hôpitaux de Marseille, January 2001 to October 2015

		Percentage of resistance (%)				Number of resistant bacterial strains			Total number of bacterial strains isolated and tested to determine their antibiotic resistance profile		
Bacterial species	Antibiotics	2001	2010	2015	Global evolution of the resistance	2001	2010	2015	2001	2010	2015
Enterobacter cloacae	Imipenem	0	0	0	→	0	0	0	NA	69	119
Escherichia coli	Ceftriaxone	0	10	17.7	↗	0	43	92	339	431	519
	Imipenem	0	0.2	0.2	→	0	1	1	339	437	519
Enterococcus faecalis	Vancomycin	0	0	0	→	0	0	0	NA	98	150
Enterococcus faecium	Vancomycin	0	0	0	→	0	0	0	NA	32	56
Klebsiella pneumoniae	Ceftriaxone	8	38.7	29.7	↗	5	74	69	59	191	232
	Imipenem	0	0	0.4	→	0	0	1	59	191	231
Proteus mirabilis	Imipenem	0	0	0	→	0	0	0	NA	28	32
Pseudomonas aeruginosa	Imipenem	29.8	17	30.9	↗	15	18	39	51	106	126
Staphylococcus aureus	Cefoxitin/Methicillin/Oxacillin	33.4	27	15.7	↘	106	111	58	319	411	369
Staphylococcus epidermidis	Cefoxitin/Methicillin/Oxacillin	NA	75.1	75.6	→	NA	582	680	NA	775	900
Streptococcus agalactiae	Oxacillin/Amoxicillin	0	0	0	→	0	0	0	NA	31	23
Streptococcus pneumoniae	Amoxicillin	0	0	8.6	↗	0	0	5	57	NA	58

[23]. Finally, combined resistance to three or more classes of reference antibiotics against *Pseudomonas aeruginosa* has slightly decreased in Europe (13.0% in 2013 versus 13.8% in 2010) [23]. In conclusion, data on antibiotic resistance in Europe for the main bacteria associated with invasive infections probably demonstrate that apart from *K. pneumoniae*, which is resistant to carbapenems in three countries (Romania, Italy and Greece), the level of resistance to three or more classes of antibiotics (defined as MDR phenotype) has remained low and stable over the last 5 years and that therapeutic options exist for reference antibiotics that are not analysed in the EARS-Net annual report 2013. Similarly, the percentage of combined resistance for *E. coli* and *K. pneumoniae* to three or more classes of antibiotics in our hospitals is very low (Tables 2 and 3).

Is There a Link Between MDR Bacteria and Death?

Whether death rates attributable to MDR bacteria are higher than non-MDR bacteria remains debatable, a recent meta-analysis on deaths attributable to carbapenem-resistant *Enterobacteriaceae* infections based on analysis of nine studies probably suggests that the number of deaths was significantly higher in patients with carbapenem-resistant infections in seven studies [24]. However, in this meta-analysis it was shown that patients infected with carbapenem-resistant bacteria were more likely to receive inappropriate empirical therapy and that attributability of death rates to antibiotic resistance does not take into account other confounding factors such as individual susceptibility, concurrent co-morbidities, or virulence characteristics of the isolates. In fact, along with septic shock and severe infections, underlying diseases and severity scores are the most common predictors of mortality in most studies [25], not antibiotic resistance [26]. To address this question at a local level we have retrospectively analysed mortality in southeast France in 2011 and in 2014 for susceptible and resistant bacterial species and found that the number of deaths due to resistant bacteria for a given species was lower than the number of deaths due to susceptible bacteria (Table 4).

Do We Really Need New Antibiotics? The Revival of Old Antibiotics and Patrimonial Management of Existing Compounds

In parallel, since 2001 in Marseille, France, no case of therapeutic impasse has been registered, that is to say no case of infection where the microorganism in question was pan-resistant. The only MDR bacteria that has emerged recently in that same Provence-Alpes-Côte d'Azur region is *K. pneumoniae*, especially strains of this species that produce carbapenemases that make them resistant to the β-lactam family. These bacteria, which are also resistant to other families of antibiotics, have been responsible for an epidemic in several facilities in the area since 2014. However, by testing the susceptibility of 41 strains producing carbapenemases to a panel of antibiotics, we have shown that none of these bacteria was pan-resistant [27]. This study was especially based on the use of old

TABLE 2. Total number of tested deduplicated invasive *Escherichia coli* isolates (n = 186[a]) resistant to one, two, three, four or five classes of antibiotics, Assistance Publique-Hôpitaux de Marseille, January to October 2015

Profile of resistance to antibiotics	No. of resistant strains	Percentage of resistance
Fully susceptible	63	33.9
One class of antibiotic		
Resistant to aminopenicillins	62	33.3
Resistant to fluoroquinolones	0	0.0
Resistant to third-generation cephalosporins	0	0.0
Resistant to aminoglycosides	3	1.6
Resistant to carbapenems	0	0.0
Total	**65**	**34.9**
two classes of antibiotics		
Resistant to aminopenicillins and to fluoroquinolones	17	9.1
Resistant to aminopenicillins and to third-generation cephalosporins	9	4.8
Resistant to aminopenicillins and to aminoglycosides	3	1.6
Resistant to aminopenicillins and to carbapenems	0	0.0
Resistant to fluoroquinolones and to aminoglycosides	0	0.0
Resistant to aminoglycosides and to carbapenems	0	0.0
Total	**29**	**15.6**
Three classes of antibiotics		
Resistant to aminopenicillins, to third-generation cephalosporins and to fluoroquinolones	24	12.9
Resistant to aminopenicillins, to fluoroquinolones and to aminoglycosides	1	0.5
Resistant to aminopenicillins, to third-generation cephalosporins and to aminoglycosides	0	0.0
Resistant to aminopenicillins, to fluoroquinolones and to carbapenems	0	0.0
Resistant to aminopenicillins, to third-generation cephalosporins and to carbapenems	0	0.0
Resistant to aminopenicillins, to aminoglycosides and to carbapenems	0	0.0
Total	**25**	**13.4**
Four classes of antibiotics		
Resistant to aminopenicillins, to third-generation cephalosporins, to fluoroquinolones and to aminoglycosides	3	1.6
Resistant to aminopenicillins, to third-generation cephalosporins, to fluoroquinolones and to carbapenems	1	0.5
Resistant to aminopenicillins, to third-generation cephalosporins, to aminoglycosides and to carbapenems	0	0.0
Resistant to aminopenicillins, to fluoroquinolones, to aminoglycosides and to carbapenems	0	0.0
Total	**4**	**2.2**
Five classes of antibiotics		
Resistant to aminopenicillins, to third-generation cephalosporins, to fluoroquinolones, to aminoglycosides and to carbapenems	0	0.0

[a]Total number of invasive *Escherichia coli* strains fully tested for the five classes of antibiotics of interest.

TABLE 3. Total number of tested deduplicated invasive *Klebsiella pneumoniae* isolates (n = 84[a]) resistant to one, two, three or four classes of antibiotics, Assistance Publique-Hôpitaux de Marseille, January to October 2015

Profile of resistance to antibiotics	No. of resistant strains	Percentage of resistance
Fully susceptible	54	64.3
One class of antibiotic		
Resistant to fluoroquinolones	5	6.0
Resistant to third-generation cephalosporins	3	3.6
Resistant to aminoglycosides	0	0.0
Resistant to carbapenems	0	0.0
Total	8	9.5
Two classes of antibiotics		
Resistant to third-generation cephalosporins and to fluoroquinolones	18	21.4
Resistant to third-generation cephalosporins and to aminoglycosides	0	0.0
Resistant to third-generation cephalosporins and to carbapenems	1	1.2
Resistant to fluoroquinolones and to aminoglycosides	1	1.2
Resistant to fluoroquinolones and to carbapenems	0	0.0
Total	20	23.8
Three classes of antibiotics		
Resistant to third-generation cephalosporins, to fluoroquinolones and to aminoglycosides	2	2.4
Resistant to third-generation cephalosporins, to fluoroquinolones and to carbapenems	0	0.0
Resistant to third-generation cephalosporins, to aminoglycosides and to carbapenems	0	0.0
Resistant to fluoroquinolones, to aminoglycosides and to carbapenems	0	0.0
Total	2	2.4
Four classes of antibiotics		
Resistant to third-generation cephalosporins, to fluoroquinolones, to aminoglycosides and to carbapenems	0	0.0

[a]Total number of invasive *Klebsiella pneumoniae* strains fully tested for the five classes of antibiotics of interest.

TABLE 4. Comparison between the mortality due to bacterial strains resistant and fully susceptible to antibiotics, Assistance Publique- Hôpitaux de Marseille, 2011–2014

	Years								
	2011				2014				
Pathology	Total number of infected patients	Total number of deaths due to the infection	Number of deaths due to the infection by a susceptible strain	Number of deaths due to the infection by a resistant strain	Total number of infected patients	Total number of deaths due to the infection	Number of deaths due to the infection by a susceptible strain	Number of deaths due to the infection by a resistant strain	p value[a]
Escherichia coli	1426	64	54	10	2,082	98	72	26	0.1
Staphylococcus aureus	492	65	53	12	988	60	42	18	0.2
Pseudomonas aeruginosa	415	54	34	20	700	79	52	27	0.9
Staphylococcus non aureus	511	44	37	7	668	52	35	17	0.06
Klebsiella pneumoniae	350	26	18	8	540	39	21	18	0.3
Streptococcus pneumoniae	164	14	12	2	183	18	18	0	0.2
Proteus spp.	137	6	4	2	263	11	7	4	1
Group D streptococcus	168	12	10	2	235	20	18	2	0.6
Haemophilus influenzae	66	7	7	0	108	8	7	1	1
Group B streptococcus	218	0	0	0	461	11	11	0	1
Total	3947	292	229	63	6,228	396	283	113	

[a]Analyses performed on R (Auckland, New-Zealand) using two-sided Pearson chi-square or Fisher exact tests as appropriate, p <0.05. Each p-value was obtained comparing the number of deaths due to the infection by a susceptible strain and the number of deaths due to the infection by a resistant strain in 2011 to that of 2014.

antibiotic molecules that current studies and analyses tend to neglect. These 'old' antibiotics, whose clinical efficacy is not in question, can treat infections for which the latest antibiotics, which are over-consumed, are not active enough [28]. These 'old' antibiotics, including chloramphenicol, clindamycin, clofazimine, colistin, cotrimoxazole, fosfomycin and minocycline, have proven very effective in the treatment of 'multi-resistant' bacterial infections [28]. However, it should be noted that those old antibiotics such as colistin are usually less effective when used in monotherapy and should be given in combination therapy to obtain a synergistic effect [29,30]. Similarly, Brouqui et al. were able, through the use of a combination of leprosy antibiotics (sulfadiazine, minocycline and clofazimine), to successfully treat a patient infected with a strain of *Mycobacterium tuberculosis* known as 'multidrug-resistant' [31]. This suggests that such old drugs may be useful in these cases and should be further investigated. The only problem with these 'old' antibiotics is their availability, since an international study in 2012 found that among a panel of 33 'essential' antibiotics, including older antibiotics, only one-third was available in half

industrialized countries [32]. Hence many potentially useful and safe antibiotics are no longer available in many countries because they are usually low cost and marketed as generics. Antibiotic development is no longer considered to be a wise economic investment for pharmaceutical companies [3]. Finally, we believe that susceptibility testing on these old antibiotics should be harmonized and integrated in routine practice when necessary, and that resistance rates should be added to surveillance programmes as already implemented in our institution [33].

Conclusion and Perspectives

Incomplete information circulates about antibiotic resistance and the end of the modern world in the media and the scientific community, including true rates of resistance and links with deaths. The arsenal of antibiotics currently available is enough to face the waves of emergence of new resistance in bacteria and should be considered as a World Heritage. This heritage should be managed in a non-profit model with international regulatory approval from bodies such as the European Medical Agency and Food and Drug Administration. Finally we believe that non-inferiority clinical trials are unethical and require large sample populations that do not really exist in the case of countries with a low incidence of MDR bacterial infections. However, clinical trials comparing old and new antibiotics in countries with high prevalence of MDR bacterial infections are warranted.

Transparency Declaration

No conflict of interest to declare.

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