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Global antimicrobial resistance in Gram-negative pathogens and clinical need

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Resistance in Gram-negative bacteria has become a serious problem in many regions of the world as it may reduce the treatment options substantially. Carbapenem-resistance is a good marker for such situations and is most prevalent in *Acinetobacter*, *Pseudomonas* but also increasingly in *Enterobacteriaceae*, especially *Klebsiella*. This review gives a rough global picture highlighting the epicentres of resistance. The medical need for novel treatment options globally is undeniable even if many countries with good stewardship and infection control conditions are not highly affected. Antibiotic pipelines are encouraging, as new drugs in development reduce the resistance rate to individual pathogens. Despite some progress, efforts to discover and develop novel drugs that are not prone to cross-resistance to existing antibiotic classes should be intensified.

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Introduction

The percentage of resistant strains in many Gram-negative pathogens has been rising globally for the last 10 years. Antibiotics pipelines have not kept up with this trend. No novel antibiotic with a new chemical structure, an unexploited target or new mode of action has been developed and marketed for several decades. Substantial improvements in the ability of known antibiotic classes to respond to emerging resistance have not been seen since the first carbapenem became available in 1985.

As highlighted in the WHO Global Priority List of antibiotic-resistant bacteria developed to guide research, discovery and development of new antibiotics, carbapenem-resistant (CR) *Enterobacteriaceae*, *Pseudomonas aeruginosa* (PA) and *Acinetobacer baumannii* (AB) complex are critical priority targets for new antibiotics to fill the gap of urgently needed treatment options [1••]. This article focuses on hospital-associated CR *Enterobacteriaceae* with *Klebsiella pneumoniae* (KP) as the predominant CR species among *Enterobacteriaceae*, as well as CR PA and CR AB. All three pathogens frequently show an extensively drug resistance phenotype.

About one-third of acute-care hospital-acquired infections, and more than 40% in intensive care units, are caused by these three WHO priority pathogens [2,3]. These infections are difficult to treat and are associated with higher morbidity and mortality than infections due to susceptible strains [4]. A meta-analysis has described the increased mortality associated with CR Gram-negative pathogens; the pooled crude mortality in patients with CR *Enterobacteriaceae* (CRE) infections is about 40% [5]. Urinary tract infections cause lower mortality than bloodstream infections. Similarly, a meta-analysis showed that patients infected with CR PA had significantly higher pooled mortality than those infected with carbapenem-susceptible PA [6]. Increased mortality in CR AB-infected patients compared to those infected with susceptible bacteria confirm similar results to patients infected with PA [7•]. Though a higher likelihood of inappropriate therapy may be a major reason for the increased mortality, other factors such as more severe co-morbidity or increased virulence may contribute to this finding [8].

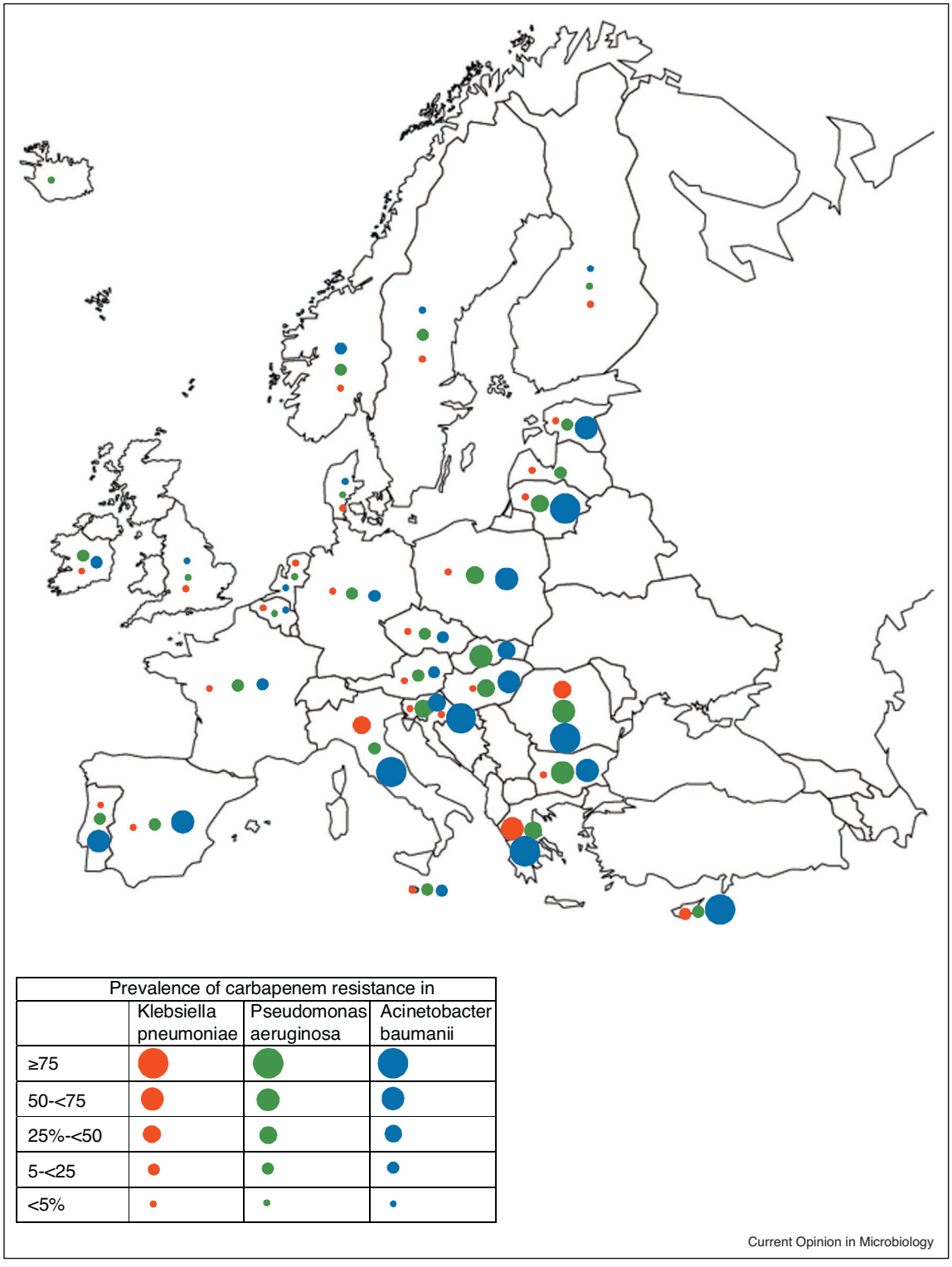
Resistance

Carbapenem resistance is usually a good surrogate for extensively drug resistance (XDR), especially in KP and AB, less so in PA.

Klebsiella pneumoniae

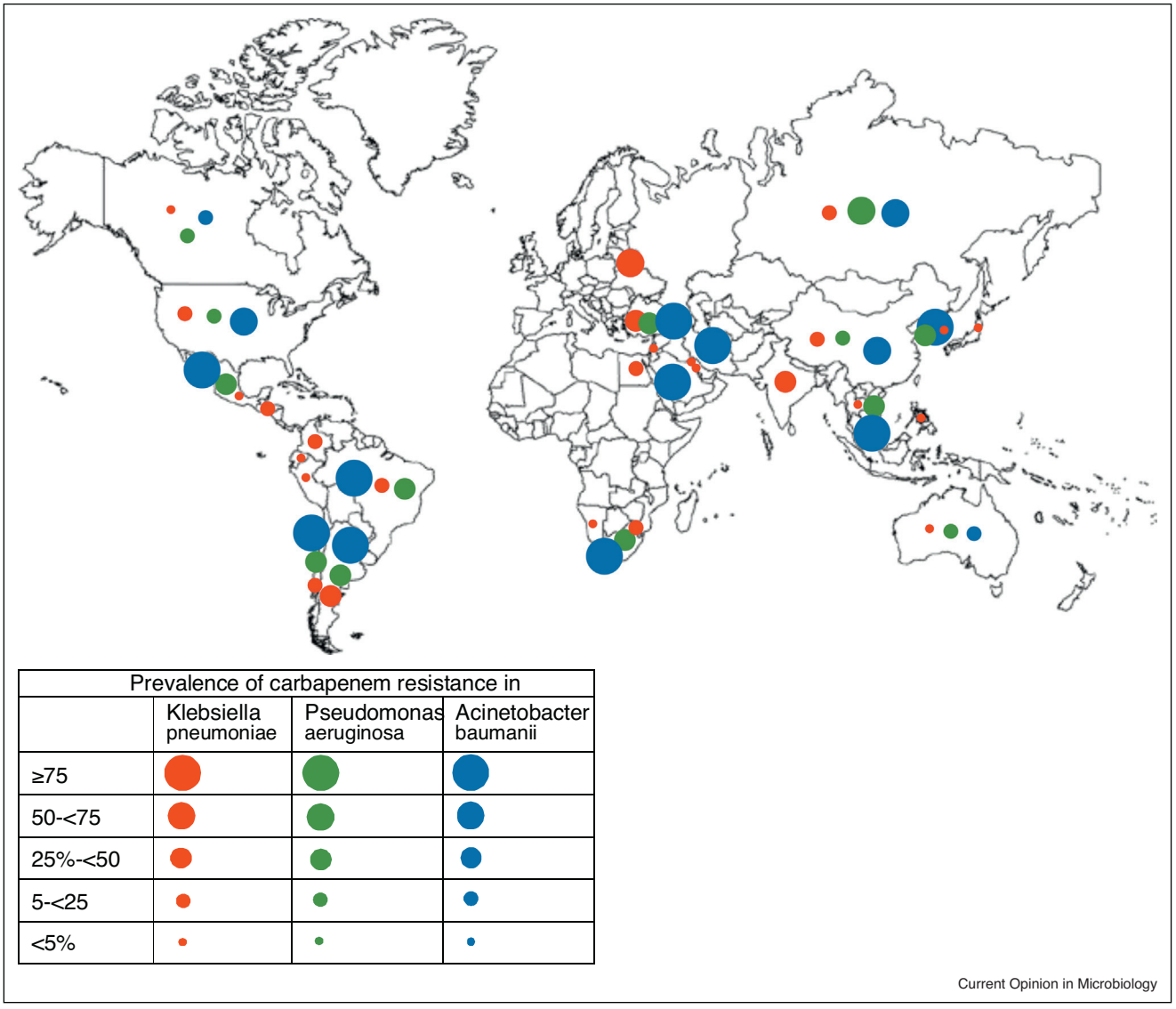
KP is a common Gram-negative pathogen in healthcare facilities. In Europe, the rate of resistance to third generation cephalosporins with co-resistance to fluoroquinolones and aminoglycosides, the most common multi-drug resistance (MDR) phenotype, ranges from 0 to 60% (EARS-net report 2015). A similar wide range is seen with the rate of resistance to carbapenems, which are important antibiotics for the treatment of such MDR strains (Figure 1). If CR is part of a combined resistance pattern, XDR may result where the therapeutic options are severely limited [9]. Similar to the variation seen across Europe, wide inter-country variations are also seen globally (Figure 1). India reports high CR in KP (about

Figure 1



Resistance rates of carbapenem-resistant Gram-negative pathogens in Europe.
Sources: Latest available data, mostly 2012–2016.
EARS-Net, WHO, CDC National Healthcare Safety Network, KARMS Korea, SENTRY, INFORM, CANWARD, AURA 2016, MARATHON Russia.

Figure 2



Resistance rates of carbapenem-resistant Gram-negative pathogens globally, see Figure 1.

60%) [10], whereas CR and XDR may be below 10% in China [11]. CR rates in Southeast Asia are still low but increasing [12] with high rates reported in Singapore. Similarly, some South American countries such as Argentina and Brazil show resistance rates above 15% [13,14] (Figure 2). Comprehensive surveillance systems are still lacking in many parts of the world and leave a spotty picture.

CR in KP is predominately caused by the production of carbapenemases that also affect most other beta-lactam antibiotics. KP is the predominant species among the group of CRE. In the US, 90% of CRE are KP and 92% of them produce a carbapenemase, mostly KPC-2 and KPC-3 [15]. Other classes of beta-lactamases (BL) are rare in the US, for example, NDM-1 and OXA-48 enzymes. Similar results are found in many European countries but the variation between countries is large [16••]. Italy has a high rate of CR in KP (36%), of which 97% carry the gene for KPC (mostly KPC-3), only 1.2% for VIM, a metallo-β-lactamase (MBL) gene [17]. The epidemiology in Europe seems to change with increasing occurrence and spread of carbapenemases in Europe since 2013 (ECDC, EuSCAPE). Non-carbapenemase-mediated mechanism of resistance in CR KP is rare but, in general, largely unknown [14]. The prevalence of specific carbapenemases differs in different parts of the world. While KPC-type enzymes prevail in Europe and North America,

MBL-type and OXA-type BLs are much more common than KPC in other parts of the world, for example, OXA-48, VIM, NDM, GES, IMP [14,18,19].

Pseudomonas aeruginosa

Besides the limited therapeutic options due to frequent resistance, PA is a difficult-to-treat pathogen and, compared with other Gram-negative bacteria, is associated with a higher mortality that cannot be attributed to resistance [9]. Rates of resistance to carbapenems in European countries ranged from 0% (Iceland) to 66% (Romania) in 2015, with a clear divide between West and East (EARS-Net) (Figure 1). Combined resistance in PA was common in European countries: About 14% of the isolates were resistant to at least three antimicrobial groups, and 5.5% were resistant to all five antimicrobial groups under regular EARS-Net surveillance (EARS-Net). CR rates in the US range from 10% to 25% and showed that isolates with plasmid-mediated carbapenemases were rare [20,21]. XDR phenotypes are observed in almost 10% of cases [22]. In South American countries CR rates are about 40% [13] and in Asia-Pacific countries <10–50% [23]. Nationwide average CR rates in China are 9–24% with 1–8% XDR [11] (Figure 2).

Unlike KP, in PA intrinsic/chromosomal-mediated resistance mechanisms, but not carbapenemases, play a major role in carbapenem resistance. Typical resistance mechanisms in CR PA are alterations or loss of outer membrane proteins, which are required for the uptake of carbapenems and can be combined with overexpression of the chromosomal cephalosporinase AmpC, upregulation of efflux systems that can confer resistance to unrelated antibiotic groups. Acquisition of resistance genes that confer plasmid-mediated BLs contribute only slightly to resistance. MBL enzymes have been identified rarely in Europe (VIM) but may be more prevalent in other regions of the world [24–26]. Due to a wide variety of chromosomal resistance mechanisms, including unspecific ones that affect unrelated antibiotic classes as well as multiple mobile or mobilizable genetic elements, CR PA are usually MDR or even XDR [9].

Acinetobacter baumannii group

Infections due to AB are more likely to occur in critically ill patients with severe comorbidities, immunosuppression or major trauma. Globally, CR AB is the most common CR organism associated with nosocomial infection, followed by CR PA. Despite generally extremely high CR rates, some European countries continue to have few problems with CR in Acinetobacter (Figure 1). It ranges from 0% (Belgium) to 95% (Greece) (EARS-Net). In most cases CR is combined with resistance to fluoroquinolones and aminoglycosides. Globally, CR rates are generally high but the available data are not comprehensive and often restricted to single or regional hospital data (Figure 2). In South American countries 80% or more CR is reported [13]. The China Surveillance of Antimicrobial Resistance Program noted a sharp increase of CR from 2004 to 2014. It increased from 13% in 2004 to 70% in 2014 and that of XDR *A. baumannii* increased from 11% in 2004 to 60% in 2014 [27]. Generally, CR AB strains have a high potential for being XDR or even pan-drug resistance (PDR) where no active antibiotic exists [9].

CR among AB is conferred by multiple coexisting mechanisms, with production of BLs being the most prevalent one. Additionally, decrease in permeability of the outer membrane, upregulated efflux pumps, and modification of penicillin-binding proteins (PBP) contribute to a variety of mechanisms. The BLs of the Class D, the intrinsic OXA-51 and OXA-23 enzyme groups are unique to AB. Additional common carbapenem-hydrolysing enzymes are OXA-24-like, OXA-40-like and OXA-58-like BLs [28,29]. Similar to KP, the occurrence of BLs differs among Europe, North America and Asia, Africa where higher rates of BLs are found. Almost 30% of AB strains may produce the MBLs NDM and VIM or both in addition to overproduction of OXA-23, as reported from India [30]. Through changing the expression level of the enzyme production even the chromosomally encoded and weak OXA-51-like enzymes can cause CR. As there seems to be a link between the BL genes and heightened expression of virulence determinants, these strains present a special clinical problem [31].

Clinical need for novel antibiotics

Reliable data regarding the treatability based on the prevalence of XDR or PDR Gram-negative bacteria do not exist. Hospital-based reports indicate that such pathogens with limited or no treatment options are increasingly diagnosed. Without doubt, new antibiotics with activity against these pathogens are urgently needed [32••]. Over at least two decades carbapenems provided last-resort coverage for the increasingly common MDR Gram-negative pathogens. Carbapenems became first-line treatment in many parts of the world. Now we are confronted with the spread of CR resistance in Gram-negatives, especially *Klebsiella*, *Pseudomonas* and *Acinetobacter*, with linked co-resistance to unrelated antibiotic classes, leading to XDR or even PDR with limited or no therapeutic options. In response to the clinical need for new antibiotics against the most resistant Gram-negative pathogens pharmaceutical companies have pursued different strategies. Drugs in advanced clinical development are based on two concepts: modification of known antibiotic classes and well-known combinations with beta-lactamase inhibitors (BLI). Two BLI combinations were recently registered — ceftazidime/avibactam and ceftolozane/tazobactam [33•]. Both drugs provide some susceptibility gains compared with existing drugs. The BLI combinations in late-stage clinical development consist of a carbapenem in combination with a new BLI (meropenem-vaborbactam, imipenem-relebactam). Such a combination works

against KPCs and other class A BLs and AmpC (class C) [34,35]. These combinations are useful for CR KP, for example in EU and North America where class A enzymes prevail, but they are less useful in many Asian and African as well as some European countries due to the lack of inhibition of MBLs and OXAs. The earlier clinical pipelines include more BLI combinations but also BLI-derived compounds that function as synergistic PBP2 inhibitors [36,37]. Cefiderocol is a new approach to the cephalosporin class as it is conjugated to a siderophore which facilitates uptake into the Gram-negative cell. This siderophore-cephalosporin is intrinsically stable to hydrolysis by most β-lactamases [38] and has good *in vitro* activity against the most resistant Gram-negative pathogens that have been studied so far [39]. Other BLI combinations with existing drugs have been revived to provide short-term solutions. Combining aztreonam and avibactam utilizes the stability of the monobactam against MBLs, and the inhibitory function of avibactam against most other BLs. This combination improves the activity of aztreonam when BLs are the major resistance mechanism, for example, in KP and AB. Other BLI combinations are being developed, for example, cefepime/tazobactam, but have little advantage over already registered drugs.

The aminoglycoside and tetracycline class has been revisited and new analogues developed that address main class-specific resistance mechanisms and improve the rate of susceptibility. The aminoglycoside plazomicin was designed for the treatment of MDR and aminoglycoside-resistant Enterobacteriaceae [40] though new resistance types that are often part of multiple co-resistances are spreading especially in Asian countries [41]. The synthetic tetracycline eravacycline may be an alternative therapeutic option for CR KP and AB, although its activity may be impaired in the presence of co-existing efflux mechanisms. Its *in vitro* activity is better than that of minocycline but only slightly improved compared to tigecycline [42].

The only novel compound without expected cross-resistance to existing antibiotic classes in mid-stage clinical trials is murepavadin, a *Pseudomonas*-specific AMP mimetic [43]. Future monoclonal antibodies, for example, MEDI-3902 and vaccines against *Pseudomonas*, may support pre-emptive approaches in critically ill patients [44]. To date, we see broad-spectrum antibiotics in the pipeline such as carbapenems and cephalosporins in combination with BLIs and Gram-negative focused drugs such as aminoglycoside and tetracycline derivatives. Unlike 20 years ago, also small-spectrum or pathogen-specific drugs seem to be accepted in the medical community, although the challenges of using these in daily practice are numerous and need to be assessed.

In contrast to the near-universal activity of ceftazidime, ciprofloxacin and carbapenems against Enterobacteriaceae when they were introduced 20–30 years ago, the anticipated future compounds of known antibiotic classes have gaps in susceptibility that are expected to grow fast once the drugs are widely used. Such widened gaps caused by incomplete cross-resistance, up-regulation of existing resistance mechanisms and the rapid global spread of transferable genetic elements will require new attitudes towards the use of antibiotics. The call for strengthened stewardship programmes, infection control, monitoring of antibiotic use and funding of such programmes applies strongly to any future antibiotic to keep its effectiveness as long as possible. If new antibiotics are intended to treat infections due to the most resistant Gram-negative pathogens, there is no way around the need for reliable and fast susceptibility tests to ensure effective treatment.

Conclusions

Resistance is a problem that may affect everyone in a globalised world. The extent of this problem has a wide range and is more severe in certain regions of the world, such as Asia, southeast Europe, South America and Africa. The resistance surveillance systems are mostly insufficient or non-existent and it is reports from single hospitals or groups of hospitals that shape our understanding of the global resistance problem. As recently stated by the WHO, carbapenem-resistant enterobacteria, *Pseudomonas* and *Acinetobacter* are critical priority targets for antibacterial drug R&D. New antibiotics in late clinical development will increase the susceptibility rates of these pathogens but they will have no universal or near-universal coverage because of some remaining cross-resistance to existing antibiotics. The call to intensify efforts to discover novel antibiotics that have no potential for cross-resistance remains.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. •• World Health Organization: *Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics*. 2017. http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf.
WHO published a priority pathogens list to guide and promote antibacterial drug R&D. It based on a multi-criteria decision analysis that incorporates both evidence-based data and expert opinion.

2. Weiner LM, Webb AK, Limbago B, Dudeck MA, Patel J, Kallen AJ, Edwards JR, Sievert DM: **Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014**. *Infect Control Hosp Epidemiol* 2016, **37**:1288-1301.

3. Vincent J, Rello J, Marshall J *et al.*: **International study of the prevalence and outcomes of infection in intensive care units**. *JAMA* 2009, **302**:2323-2329.

4. Kaye KS, Pogue JM: **Infections caused by resistant Gram-negative bacteria: epidemiology and management**. *Pharmacotherapy* 2015, **35**:949-962.

5. Xu L, Sun X, Ma X: **Systematic review and meta-analysis of mortality of patients infected with carbapenem-resistant *Klebsiella pneumoniae***. *Ann Clin Microbiol Antimicrob* 2017, **16**:18.

6. Liu Q, Li X, Li W, Du X, He J-Q, Tao C, Feng Y: **Influence of carbapenem resistance on mortality of patients with *Pseudomonas aeruginosa* infection: a meta-analysis**. *Sci Rep* 2015, **5**:11715.

7. • Lemos EV, de la Hoz FP, Einarson TR, McGhan WF, Quevedo E, Castañeda C, Kawai K: **Carbapenem resistance and mortality in patients with *Acinetobacter baumannii* infection: systematic review and meta-analysis**. *Clin Microbiol Inf* 2013, **20**:416-423.

Performing a systematic review and meta-analysis, the authors show an influence of carbapenem-resistance on mortality compared to carbapenem-susceptibility though heterogeneity and confounding factors require a cautious interpretation of the results.

8. Beceiro A, Tomás M, Bou G: **Antimicrobial resistance and virulence: a successful or deleterious association in the bacterial world?** *Clin Microbiol Rev* 2013, **26**:185-230.

9. Thaden JT, Park LP, Maskarinec SA, Ruffin F, Fowler VG, van Duin D: **Increased mortality associated with bloodstream infections caused by *Pseudomonas aeruginosa* as compared to other bacteria: results of a 13-year prospective cohort study**. *Antimicrob Agents Chemother* 2017.

10. Gandra S, Mojica N, Klein EY, Ashok A, Nerurkar V, Kumari M, Ramesh U, Dey S, Vadwai V, Das BR *et al.*: **Trends in antibiotic resistance among major bacterial pathogens isolated from blood cultures tested at a large private laboratory network in India, 2008–2014**. *Int J Infect Dis* 2016, **50**:75-82.

11. Xu A, Zheng B, Xu YC, Huang ZG, Zhong NS, Zhuo C, Xu A, Zheng B, Xu YC, Huang ZG, Zhong NS, Zhuo C: **National epidemiology of carbapenem-resistant and extensively drug-resistant Gram-negative bacteria isolated from blood samples in China in 2013**. *Clin Microbiol Inf* 2016, **22**:S1-S8.

12. Suwantarat N, Carroll KC: **Epidemiology and molecular characterization of multidrug-resistant Gram-negative bacteria in Southeast Asia**. *Antimicrob Resist Infect Control* 2016, **5**:15.

13. Sader HS, Castanheira M, Farrell DJ, Flamm RK, Mendes RE, Jones RN, Sader HS, Castanheira M, Farrell DJ, Flamm RK, Mendes RE, Jones RN: **Tigecycline antimicrobial activity tested against clinical bacteria from Latin American medical centres: results from SENTRY Antimicrobial Surveillance Program (2011–2014)**. *Int J Antimicrob Agents* 2016, **48**:144-150.

14. Marimuthu K, Venkatachalam I, Khong WX, Koh TH, Cherng BPZ, Van La M, De PP, Krishnan PU, Tan TY, Choon RFK *et al.*: **Clinical and molecular epidemiology of carbapenem-resistant enterobacteriaceae among adult inpatients in Singapore**. *Clin Infect Dis* 2017, **64**:S68-S75.

15. Satlin MJ, Chen L, Patel G, Gomez-Simmonds A, Weston G, Kim AC, Seo SK, Rosenthal ME, Sperber SJ, Jenkins SG *et al.*: **Bacteremia due to carbapenem-resistant Enterobacteriaceae (CRE): a multicenter clinical and molecular epidemiologic analysis in the nation's epicenter for CRE**. *Antimicrob Agents Chemother* 2017 http://dx.doi.org/10.1128/AAC.02349-16.

16. •• Grundmann H, Glasner C, Albiger B, Aanensen DM, Tomlinson CT, Andrasević AT, Cantón R, Carmeli Y, Friedrich AW, Giske CG *et al.*: **Occurrence of carbapenemase-producing *Klebsiella pneumoniae* and *Escherichia coli* in the European survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study**. *Lancet Infect Dis* 2017, **17**:153-163.

The EuSCAPE project provides information for monitoring incidence and spread of carbapenemases and carbapenemase-producing Enterobacteriaceae in Europe. The authors describe the change in carbapenemase epidemiology in Europe.

17. Conte V, Monaco M, Giani T, D'Ancona F, Moro ML, Arena F, D'Andrea MM, Rossolini GM, Pantosti A, AR-ISS Study Group on Carbapenemase-Producing K. pneumoniae: **Molecular epidemiology of KPC-producing *Klebsiella pneumoniae* from invasive infections in Italy: increasing diversity with predominance of the ST512 clade II sublineage**. *J Antimicrob Chemother* 2016, **71**:3386-3391.

18. Perovic O, Chetty V: **Antimicrobial Resistance Surveillance from sentinel public hospitals, South Africa, 2015**. *Commun Dis Surveill Bull* 2016, **14**:56-67.

19. Khalifa HO, Soliman AM, Ahmed AM, Shimamoto T, Hara T, Ikeda M, Kuroo Y, Kayama S, Sugai M, Shimamoto T: **High carbapenem resistance in clinical Gram-negative pathogens isolated in Egypt**. *Microbial Drug Resist* 2017 http://dx.doi.org/10.1089/mdr.2015.0339.

20. Lob SH, Hackel MA, Kazmierczak KM, Young K, Motyl MR, Karlowsky JA, Sahm DF: **In vitro activity of imipenem-relebactam against Gram-negative ESKAPE pathogens isolated by clinical laboratories in the United States in 2015 – results from the SMART Global Surveillance Program**. *Antimicrob Agents Chemother* 2017 http://dx.doi.org/10.1128/AAC.02209-16.

21. Walters MS, Bulens S, Hancock EB, Phipps EC, Muleta D, Mounsey J, Kainer M, Concannon C, Dumyati G, Bower C *et al.*: **Surveillance for carbapenem-resistant *Pseudomonas aeruginosa* at five United States sites—2015**. *Open Forum Infect Dis* 2016, **3**:350.

22. Sader HS, Huband MD, Castanheira M, Flamm RK: ***Pseudomonas aeruginosa* antimicrobial susceptibility results from four years (2012 to 2015) of the international network for optimal resistance monitoring program in the United States**. *Antimicrob Agents Chemother* 2017, **61** http://dx.doi.org/10.1128/AAC.02252-16.

23. Mendes RE, Jones RN, Mendoza M, Castanheira M, Bell JM, Turnidge JD: **Emerging markets resistance surveillance programme report for 12 Asia-Pacific nations**. *9th Annual International Symposium on Antimicrobial Agents and Resistance (ISAAR)*. 2013. Poster #179.

24. Rojo-Bezares B, Cavalié L, Dubois D, Oswald E, Torres C, Sáenz Y: **Characterization of carbapenem resistance mechanisms and integrons in *Pseudomonas aeruginosa* strains from blood samples in a French hospital**. *J Med Microbiol* 2016, **65**:311-319.

25. Li J, Zou M, Dou Q, Hu Y, Wang H, Yan Q, Liu We: **Characterization of clinical extensively drug-resistant *Pseudomonas aeruginosa* in the Hunan province of China**. *Ann Clin Microbiol Antimicrob* 2016, **15**:35.

26. Pragasam AK, Vijayakumar S, Bakthavatchalam YD, Kapil A, Das BK, Ray P, Gautam V, Sistla S, Parija SC, Walia K *et al.*: **Molecular characterisation of antimicrobial resistance in *Pseudomonas aeruginosa* and *Acinetobacter baumannii* during 2014 and 2015 collected across India**. *Indian J Med Microbiol* 2016, **34**:433-441.

27. Gao L, Lyu Y, Li Y: **Trends in drug resistance of *Acinetobacter baumannii* over a 10-year period: nationwide data from the China Surveillance of Antimicrobial Resistance Program**. *Chinese Med J* 2017, **130**:659-664.

28. Ning N-z, Liu X, Bao C-m, Chen S-m, Cui E-b, Zhang J-l, Huang J, Chen F-h, Li T, Qu F *et al.*: **Molecular epidemiology of bla_{OXA-23}-producing carbapenem-resistant *Acinetobacter baumannii* in a single institution over a 65-month period in north China**. *BMC Infect Dis* 2017, **17**:14.

29. Ahmed SS, Dinc G, Rossella B, Alp E, Ulu-Kilic A, Melchers WJG, Hopman J, Voss A: **Molecular characterization of carbapenem resistant *Acinetobacter baumannii* and investigation of genetic diversity between local and international clones**. *J Pure Applied Microbiol* 2016, **10**:1675-1682.

30. Vijayakumar S, Gopi R, Gunasekaran P, Bharathy M, Walia K, Anandan S, Veeraraghavan B: **Molecular characterization of invasive carbapenem-resistant *Acinetobacter baumannii* from a tertiary care hospital in South India**. *Inf Dis Therapy* 2016, **5**:379-387.

31. Dahdouh E, Gomez-Gil R, Pacho S, Mingorance J, Daoud Z, Suarez M: **Clonality, virulence determinants, and profiles of resistance of clinical *Acinetobacter baumannii* isolates obtained from a Spanish hospital**. *PLOS ONE* 2017, **12**: e0176824.

32. •• Perez F, El Chakhtoura NG, Papp-Wallace KM, Wilson BM, Bonomo RA: **Treatment options for infections caused by carbapenem-resistant Enterobacteriaceae: can we apply "precision medicine" to antimicrobial chemotherapy?** *Expert Opin Pharmacother* 2016, **17**:761-781.
This informative overview of carbapenem-resistant Enterobacteriaceae describes resistance mechanisms, epidemiology, clinical impact, treatment options as well as some new beta-lactamase inhibitor combinations.

33. • Bush K: **A resurgence of beta-lactamase inhibitor combinations effective against multidrug-resistant Gram-negative pathogens**. *Int J Antimicrob Agents* 2015, **46**:483-493.
Overview of recently approved and future beta-lactamase inhibitor combinations. The review explains the different chemical classes of beta-lactamase inhibitors and compares their activities.

34. Lapuebla A, Abdallah M, Olafisoye O, Cortes C, Urban C, Landman D, Quale J: **Activity of imipenem with relebactam against Gram-negative pathogens from New York City**. *Antimicrob Agents Chemother* 2015, **59**:5029-5031.

35. Castanheira M, Rhomberg PR, Flamm RK, Jones RN: **Effect of the beta-Lactamase inhibitor vaborbactam combined with meropenem against serine carbapenemase-producing Enterobacteriaceae**. *Antimicrob Agents Chemother* 2016, **60**:5454-5458.

36. Sader HS, Castanheira M, Huband M, Jones RN, Flamm RK: **WCK 5222 (Cefepime-Zidebactam) antimicrobial activity against clinical isolates of Gram-negative bacteria collected worldwide in 2015**. *Antimicrob Agents Chemother* 2017, **61** http://dx.doi.org/10.1128/AAC.00072-17.

37. Livermore DM, Mushtaq S, Warner M, Vickers A, Woodford N: **In vitro activity of cefepime/zidebactam (WCK 5222) against Gram-negative bacteria**. *J Antimicrob Chemother* 2017, **72**:1373-1385.

38. Ito-Horiyama T, Ishii Y, Ito A, Sato T, Nakamura R, Fukuhara N, Tsuji M, Yamano Y, Yamaguchi K, Tateda K: **Stability of novel siderophore cephalosporin S-649266 against clinically relevant carbapenemases**. *Antimicrob Agents Chemother* 2016, **60**:4384-4386.

39. Falagas ME, Skalidis T, Vardakas KZ, Legakis NJ, Hellenic Cefiderocol Study G: **Activity of cefiderocol (S-649266) against carbapenem-resistant Gram-negative bacteria collected from inpatients in Greek hospitals**. *J Antimicrob Chemother* 2017 http://dx.doi.org/10.1128/AAC.00072-17.

40. Almaghrabi R, Clancy CJ, Doi Y, Hao B, Chen L, Shields RK, Press EG, Iovine NM, Townsend BM, Wagener MM *et al.*: **Carbapenem-resistant *Klebsiella pneumoniae* strains exhibit diversity in aminoglycoside-modifying enzymes, which exert differing effects on plazomicin and other agents**. *Antimicrob Agents Chemother* 2014, **58**:4443-4451.

41. Wangkheimayum J, Paul D, Dhar D, Nepram R, Chetri S, Bhowmik D, Chakravarty A, Bhattacharjee A: **Occurrence of acquired 16s methyltransferase mediated aminoglycoside resistance in clinical isolates of Enterobacteriaceae within a tertiary referral hospital of northeast India**. *Antimicrob Agents Chemother* 2017 http://dx.doi.org/10.1128/AAC.01037-16.

42. Livermore DM, Mushtaq S, Warner M, Woodford N: **In vitro activity of eravacycline against carbapenem-resistant *Enterobacteriaceae* and *Acinetobacter baumannii***. *Antimicrob Agents Chemother* 2016, **60**:3840-3844.

43. Scorciapino MA, Rinaldi AC: **Antimicrobial peptidomimetics: reinterpreting nature to deliver innovative therapeutics**. *Front Immunol* 2012, **3**:171.

44. DiGiandomenico A, Keller AE, Gao C, Rainey GJ, Warrener P, Camara MM, Bonnell J, Fleming R, Bezabeh B, Dimasi N *et al.*: **A multifunctional bispecific antibody protects against *Pseudomonas aeruginosa***. *Sci Transl Med* 2014, **6**:262ra155.