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Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia

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In view of the alarming spread of antimicrobial resistance in the absence of new antibiotics, this study aimed at assessing the availability of potentially useful older antibiotics. A survey was performed in 38 countries among experts including hospital pharmacists, microbiologists, and infectious disease specialists in Europe, the United States, Canada, and Australia. An international expert panel selected systemic antibacterial drugs for their potential to treat infections caused by resistant bacteria or their unique value for specific criteria. Twenty-two of the 33 selected antibiotics were available in fewer than 20 of 38 countries. Economic motives were the major cause for discontinuation of marketing of these antibiotics. Fourteen of 33 antibiotics are potentially active against either resistant Gram-positive or Gram-negative bacteria. Urgent measures are then needed to ensure better availability of these antibiotics on a global scale.

In the European Union, at least 25 000 persons are estimated to die each year from an infection caused by multidrug-resistant bacteria [1]. In the United States, just one organism, methicillin-resistant *Staphylococcus aureus* (MRSA), kills more Americans every year (approximately 19 000) than emphysema, human immunodeficiency virus/AIDS, Parkinson's disease, and homicide combined [2]. There is a gap between the current worldwide spread of multiresistant bacteria and the development of new antimicrobial drugs [1, 3–5]. Few new antibiotics are in the drug development pipeline; in particular, recent analyses have shown that few antibiotics in development have documented in vitro activity against antibiotic-resistant Gram-negative bacteria [1, 3]. Furthermore, the arsenal of available antimicrobial drugs is becoming smaller because older drugs are disappearing from the market or are temporarily unavailable. The ESCMID (European Society of Clinical Microbiology and Infectious Diseases) Study Group for Antibiotic Policies (ESGAP) performed a review in 2006 which showed that shortages of narrow-spectrum antibacterial drugs forced clinicians to use broad-spectrum drugs, adversely influencing the policies of prudent use [6, 7]. The reasons for shortages and market withdrawals of older antibiotics are incompletely understood. However, the lack of profit for drugs in limited market areas (small countries) and increasing regulatory requirements and bureaucracy appear to play a role. Several older, potentially useful, sometimes "forgotten" antibiotics are not

Received 25 July 2011; accepted 13 October 2011.

Presented in part: poster presentation at the European Congress of Clinical Microbiology and Infectious Diseases and oral presentations at the Journées Nationales d'Infectiologie (French Infectious Diseases Society meeting) and Interscience Conference on Antimicrobial Agents and Chemotherapy in 2011.

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Clinical Infectious Diseases 2012;54(2):268–74

DOI: 10.1093/cid/cir838

available in many countries, either never having been introduced or having now been withdrawn [8–10]. In view of the alarming development of resistance in the absence of new antibiotics, it seemed opportune to collect reliable information on the availability of currently useful older antibiotics. This study had 3 objectives: (1) to select systemic antibiotics (Anatomical Therapeutic Chemical [ATC] code J01) with (potential) activity on resistant microorganisms and/or having a unique value for specific criteria and that had at any time been marketed in Europe, the United States, Canada, and Australia; (2) to assess the evidence base of efficacy of these antibiotics in infections caused by current antibiotic-resistant bacteria, or their unique value; and (3) to make an inventory of these selected antibiotics' availability in Europe, the United States, Canada, and Australia.

MATERIALS AND METHODS

Selection of Potentially Useful Antibiotics

We reviewed the list of all systemic antibacterials (ATC code J01, http://www.whocc.no/atc_ddd_publications/guidelines/) [11] that have been approved for human use by the US Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA) and/or in the following countries: Europe (35 countries, Supplementary Table 1), Canada, and Australia. Exclusion criteria included (1) antibiotics currently marketed in all countries of interest; (2) antituberculous, antifungal, antiparasitic, and antiviral drugs; and (3) topical- or inhaled-only antibacterials. Newly approved drugs, such as telavancin, ceftaroline, and fidaxomicin, were beyond the scope of our review.

Six experts (2 from Europe, 2 from the United States, and 2 from Australia) with clinical/microbiological expertise in the field were chosen as assessors. Five of them were authors of a leading reference textbook on antimicrobial drugs [12]. All authors selected the antibiotics for their potential value against current resistant bacteria and/or for their unique value for specific criteria, based on the textbook (Kucers') [12] and their own experience.

Assessment of the Potential of These Antibiotics Against Currently Resistant Bacteria and of Their Unique Value

PubMed was searched for literature relevant to the selected antibiotics, published until October 2010 inclusive. Based on this literature review and the expert panel advice, the potential activity of the selected antibiotics was assessed against a selection of resistant bacteria.

For assessment of the value of the antibiotics, the method described in the "European Centre for Disease Prevention and Control/European Medicines Agency joint technical report 2009–the bacterial challenge: time to react" was applied [1, 3]. The following antibiotic-resistant bacteria were selected because they frequently cause bloodstream infections and because the associated antibiotic resistance trait is, in most cases, a marker for multiple resistance to antibiotics: MRSA; vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus*; vancomycin-resistant enterococci (VRE; eg, *Enterococcus faecium*); penicillin-resistant *Streptococcus pneumoniae*; third-generation cephalosporin–resistant Enterobacteriaceae (eg, *Escherichia coli*, *Klebsiella pneumoniae*); carbapenem-resistant Enterobacteriaceae (eg, *K. pneumoniae*); and carbapenem-resistant nonfermentative Gram-negative bacteria (eg, *Pseudomonas aeruginosa*).

The selected agents were assessed for their antibacterial activity against the selected bacteria based on actual data available in the reference textbook [12] and/or the literature. In the absence of available in vitro data, the expert panel also took into account reasonable assumptions of the activity of some agents based on the properties of similar agents (ie, of the same class or with a common mechanism of action) to construct a "best-case scenario."

In vitro activity of each agent against the selected bacteria was assigned based on the following approaches:

- Actual data on in vitro activity were reviewed whenever available. If actual data on in vitro activity were not reported for an agent against any of the selected pathogens, assumptions were made regarding likely activity based on the properties of the antibiotic class or of the mechanism of action involved.
- The assessment of in vitro activity disregarded any known potential for cross-resistance and coresistance.
- Although in vitro activity alone cannot predict in vivo efficacy, it was decided not to take into account any available pharmacokinetic data or pharmacokinetics/pharmacodynamics (PK/PD) analyses when scoring the antibacterial activity of agents because the amount of data available was very variable. However, if there was already information available on nonclinical or clinical efficacy, these data were factored into the assessment.
- The assignment of in vitro activity, which took into account available data together with assumptions based on class properties or mechanisms of action as well as the route of administration, took the most optimistic view of what the agent might be able to achieve and represents a best-case scenario.

The unique value of each of these antibiotics, according to specific criteria (eg, oxacillin allows a narrow-spectrum treatment of methicillin-susceptible *S. aureus* [MSSA]), was also determined, based on the comments of the expert panel. Criteria included (1) microbiological criteria: spectrum, mechanism of action; (2) pharmacokinetic criteria; and (3) clinical criteria: "niche" antibiotic (unique value for specific pathogens or indications), last available molecule of its class, and absence of alternative.

Each antibiotic was randomly assigned to 2 experts for assessment, except for those antibiotics where 1 of the experts was

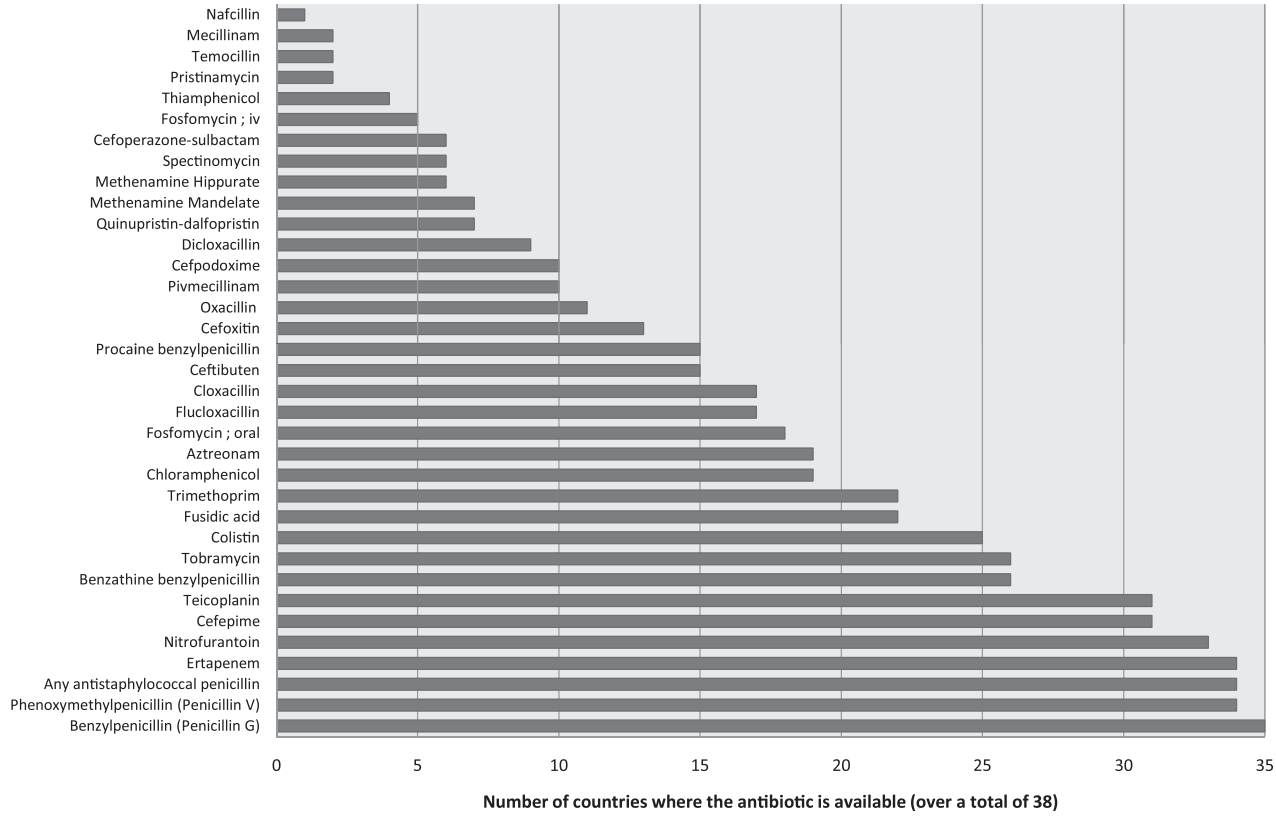

Figure 1. Availability of the selected 33 antibiotics in 38 countries (Europe, United States, Canada, and Australia), displayed by antibiotic.

the author of the Kucers' chapter, in which case the antibiotic was assigned to the author. If the 2 assessments were concordant, the evaluation was final. In case of nonagreement between the 2 experts, the antibiotic was evaluated by all 6 experts to reach a consensus.

Survey on the Availability of Selected Antibiotics in Europe, the United States, Canada, and Australia

Contacts (belonging to personal networks of the authors and/or being members of ESGAP and/or ESCMID PK/PD of Anti-infectives Study Group) in the selected countries were approached by e-mail in the northern hemisphere in Autumn 2010–Winter 2011 to report on the availability of the selected antibiotics in their country. The data collected were entered in a Microsoft Excel spreadsheet. These data were compared by the lead author (C. P.) with information on the national drug agencies' Web sites (Supplementary Table 2) and the Martindale pharmacopoeia [13]. Whenever possible, a distinction was made between antibiotics easily available through usual marketing processes and antibiotics available via a special regulatory scheme. The availability of inhalational formulations and reasons for withdrawal or abbreviated (<1 year) marketing of the antibiotic were also explored.

RESULTS

Thirty-three valuable antibiotics were selected (Figure 1). Many had multiple features considered to be of value.

Assessment of the Potential of Selected Antibiotics Against Resistant Bacteria and of Their Unique Value

Thirty-one of 33 antibiotics were found to be either active against resistant bacteria or having unique value after the literature review; cefpodoxime and ceftibuten were included in the survey but, upon inspection of their current susceptibility profiles, did not meet any of the criteria established for future utility. A summary of the results is presented in Tables 1 and 2 (a more detailed assessment by antibiotic is available as Supplementary Appendix 1). Fourteen of 33 antibiotics were active against resistant Gram-positive bacteria (MRSA, VISA, penicillin-resistant pneumococci, or VRE). Fourteen of 33 antibiotics were active against resistant Gram-negative bacteria (third-generation cephalosporin–resistant Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, or non-fermentative bacteria). Twenty-two antibiotics were considered to have a unique value, including 9 antibiotics having a unique value for treating specific pathogens or for specific indications

Table 1. Selected Systemic Antibacterial Agents and In Vitro/In Vivo Activity Against Selected Resistant Bacteria Based on Actual Data

	Gram-positive bacteria				Gram-negative bacteria		
Agent	MRSA	VISA/VRSA	PRSP	VRE	3rd gen. cep. R ENB	Carb. R ENB	Carb. R NF GNB
Antistaphylococcal penicillins: nafcillin and isoxazolyl penicillins: oxacillin, cloxacillin, dicloxacillin, and flucloxacillin							
Aztreonam						□[a]	□[a]
Cefepime			■		□[b]		
Cefoperazone-sulbactam			■		■		
Cefoxitin					□[c]		
Cefpodoxime and ceftibuten							
Chloramphenicol and thiamphenicol	■	■	□	■	□		□
Colistin					■	■	■
Ertapenem			□		□		
Fosfomycin	■		■	■	■	■	□
Fusidic acid	■	■		■			
Mecillinam and pivmecillinam					□		
Methenamine[d]	■	■		■	■	■	■
Nitrofurantoin	■			■	■		
Penicillin V and penicillin G							
Pristinamycin	■		■	□			
Quinupristin-dalfopristin	■	■	■	■[e]			
Spectinomycin	□						
Teicoplanin	■		■	■[f]			
Temocillin					■	■	
Tobramycin	□	□		□	■	■	■
Trimethoprim	■		■		■		
Summary of the potential activity of the antibacterial agents against selected resistant bacteria							
■	9	4	7	7	8	5	3
□	2	1	2	2	5	1	3
Total	11	5	9	9	13	6	6

Activity: ■ indicates usually active and □ indicates sometimes active. The activity of each drug is variable, according to the clinical situation (eg, bacterial species for Gram-negative bacteria, mechanism of resistance, site of infection, pharmacokinetics/pharmacodynamics indices). Data presented in the table represent the best-case scenario, are mainly level 3 quality of evidence, and are not treatment guidelines. A more in-depth analysis is available in Supplementary Appendix 1.

Abbreviations: Carb. R ENB, carbapenem-resistant Enterobacteriaceae; Carb. R NF GNB, carbapenem-resistant nonfermentative Gram-negative bacteria; ESBL, extended-spectrum β-lactamase; 3rd gen. cep. R ENB, third-generation cephalosporin–resistant Enterobacteriaceae; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; PRSP, penicillin-resistant *Streptococcus pneumoniae* (MIC >2 mg/L); VISA, vancomycin-intermediate *S. aureus*; VRSA, vancomycin-resistant *S. aureus*; VRE, vancomycin-resistant enterococci.

[a] Active only if a metallo-β-lactamase is produced in the absence of overexpressed AmpC or in the absence of an ESBL.

[b] Active on AmpC chromosomally mediated β-lactamases; active on ESBLs only if MIC <4 mg/L.

[c] Inactive on some Enterobacteriaceae such as *Enterobacter* species, *Citrobacter* species, *Serratia* species, and *Providencia* species.

[d] Potentially active against resistant bacteria because it is converted to formaldehyde in acidic urine and therefore has broad-spectrum ''disinfectant'' properties (except on urease-producing strains), but lacks evidence.

[e] Active on *Enterococcus faecium*.

[f] Active except on VanA type.

(5 antistaphylococcal penicillins for MSSA infections, penicillin G for syphilis, spectinomycin for gonorrhea, penicillin V, and temocillin).

Availability of These Antibiotics in Europe, the United States, Canada, and Australia

The availability data obtained for the United States, Canada, Australia, and 35 European countries are shown in Figure 1 and Supplementary Figure 1. Detailed information is available in Supplementary Appendix 2. We had no data for 1 European country, and data regarding 2 other European countries were collected using national Web sites, in the absence of national contacts. Surprisingly, the number and the mode of availability (marketed or via a special system) differed considerably from one country to another. Twenty-two of the 33 selected antibiotics were marketed in fewer than 20 countries.

Table 2. Unique Value of the Selected Antibacterial Agents, Using Microbiological, Pharmacokinetic, and Clinical Criteria

Criteria	The 22 Antibiotics Having Unique Value for 1 or Several Criteria
Microbiological criteria: spectrum, 14 antibiotics	- Antistaphylococcal penicillins (nafcillin and isoxazolyl penicillins: oxacillin, cloxacillin, dicloxacillin, and flucloxacillin): narrow-spectrum drug to treat MSSA infections
	- Cefoxitin: infections due to *Mycobacterium abscessus, Mycobacterium fortuitum*, and *Mycobacterium chelonae*
	- Chloramphenicol and thiamphenicol: gonococci, broad-spectrum drug (eg, *Rickettsia*, *Stenotrophomonas maltophilia*)
	- Penicillin G: *Treponema pallidum*
	- Quinupristin-dalfopristin: *Enterococcus faecium*
	- Spectinomycin*: Neisseria gonorrhoeae*
	- Teicoplanin: *E. faecium* with vanB/C resistance and amoxicillin-resistant *Enterococcus gallinarum/casseliflavus*
	- Temocillin: *Burkholderia cepacia*
	- Tobramycin: *Pseudomonas aeruginosa*
Microbiological criteria: mechanism of action, 6 antibiotics	- Chloramphenicol and thiamphenicol
	- Colistin
	- Fosfomycin
	- Fusidic acid
	- Nitrofurantoin
PK criteria, 5 antibiotics	- Chloramphenicol and thiamphenicol: excellent diffusion into central nervous system and eye
	- Ertapenem: once-daily parenteral (IV/IM) administration; convenient as OPAT
	- Fosfomycin oral formulations: 1 dose only for uncomplicated cystitis
	- IV fosfomycin: excellent diffusion into central nervous system and eye
	- Teicoplanin: OPAT possible
Clinical criteria: ''niche'' agent (unique value for specific pathogens or indications), 9 antibiotics	- Antistaphylococcal penicillins (nafcillin and isoxazolyl penicillins: oxacillin, cloxacillin, dicloxacillin, and flucloxacillin): ''niche'' agent for MSSA infections
	- Penicillin V: rheumatic fever and postsplenectomy prophylaxis regimens
	- Penicillin G: *T. pallidum*
	- Long-acting forms of penicillin G: syphilis and chemoprophylaxis of rheumatic fever
	- Spectinomycin: ''niche'' agent for gonorrhoea
	- Temocillin: ''niche'' agent for *B. cepacia* infections (EMA/FDA: orphan status in cystic fibrosis)
Clinical criteria: last (only) available antibiotic of its class, 8 antibiotics	- Aztreonam (only monobactam): useful in case of β-lactam allergy because cross-reactivity with penicillins and cephalosporins is rare
	- Chloramphenicol and thiamphenicol
	- Colistin (only available polymyxin E)
	- Fosfomycin
	- Fusidic acid
	- Methenamine
	- Spectinomycin
Clinical criteria: absence of alternative, 2 antibiotics	- Colistin: absence of alternative for some multiresistant Gram-negative strains
	- Quinupristin-dalfopristin: amoxicillin-, daptomycin-, and vancomycin-resistant *E. faecium*

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration; IV, intravenous; IM, intramuscular; MSSA, methicillin-susceptible *Staphylococcus aureus*; OPAT, Outpatient Parenteral Antibiotic Therapy; PK, pharmacokinetics.

Economic motives are the major cause for discontinuation of marketing of these antibiotics, for example, penicillin G and cloxacillin in Croatia (not profitable to the local industry) or penicillin V and oxacillin in Latvia (for more information, see Supplementary Appendix 2). In Switzerland, cefoxitin and aztreonam were withdrawn due to small volume sales. In Turkey,

colistin was recently approved, produced, and marketed by a local company, in response to the urgent need following the countrywide rise in multidrug-resistant Gram-negative infections.

DISCUSSION

The major finding of this inventory was that many potentially useful antibiotics, usually low cost and marketed as generics, and with a long history of tolerability and safety data, are not available in many countries. This is a worrisome situation, given the current worldwide bacterial resistance crisis. Urgent measures are needed to ensure a better availability of these antibiotics on a global scale. It is also worrisome that obtaining a reliable overview on the availability of these antibiotics in the selected Western countries was quite difficult. We also noted discrepancies between the data sent by the national contacts, many of whom were senior specialists in the field, and the data available on the national drug agencies' Web sites and/or in the Martindale drug reference, which illustrates the lack of transparency and information on drug availability. Moreover, in many different countries, some antibiotics are available through special and sometimes complicated regulatory systems, usually delaying the delivery of the drug, at the price of time-consuming paperwork.

Temocillin and mecillinam could be useful for extended-spectrum β-lactamase–producing organisms (but only if there is a low minimal inhibitory concentration for mecillinam and low inoculum); fosfomycin and colistin may also be used to treat infections caused by carbapenem-resistant Gram-negative bacilli (Table 1). These are agents that, in the opinion of the authors, hold the greatest promise of utility worldwide for managing infections that result from many currently resistant Gram-negative organisms. However, they were available in only 2, 2, 5, and 25 countries, respectively.

In half of the cases, neither PK/PD data nor clinical data were available for drugs known to be active in vitro (Supplementary Appendix 1) [14]. Studies on PK/PD could justify greater availability of those products with advantageous PK/PD characteristics. In particular, more data on animal models and clinical studies are needed; in vitro surveillance data on these drugs are lacking in the available networks such as the European Antimicrobial Resistance Surveillance Network and SENTRY; clinical registers are nonexistent. We hope that our inventory can contribute to the renewed interest of the producers to market their products in the respective countries.

In view of our results, we would recommend that treating physicians consider the forgotten antibiotics on our list for treatment of resistant pathogens. However, use of these drugs should be based on susceptibility testing provided that standardized susceptibility testing and interpretive criteria are available (from the Clinical and Laboratory Standards Institute or the European Committee on Antimicrobial Susceptibility Testing); not all resistant species may respond to each of the drugs as predicted in the tables. Our assessment was based on a best-case scenario and therefore does not represent treatment guidelines.

Companies should give full transparency on the marketing, distribution, and dispensing of medicines in all countries, and these data must be easily available. Many of the older antibiotics are now only produced by pharmaceutical industries in developing nations, which may further impede the access to these drugs, because there may be a lack of influence of regulatory bodies in Europe and elsewhere. In such cases, the EMA and similar regulators in other regions should establish formal contact to enhance the availability of these antibiotics. In case of withdrawal of a drug in an individual country because of economic reasons, all possible efforts should be made to guarantee the availability in case of urgent medical need. In addition, the drug agencies should inform the medical community before withdrawal of the drug in order for the latter to possibly respond and perhaps prevent the withdrawal. There is a role for drug agencies (such as the EMA and FDA) in adapting regulations accordingly. In our opinion, policy makers are well advised to guarantee the availability of older and generic antibiotics and other drugs that are essential for medical care, beyond market-driven agendas. Reduction of the market registration fees for such needed antibiotics might be one method to relieve the costs for the pharmaceutical companies.

An equally challenging problem for manufacturers and potential prescribers is obtaining registration of older antibiotics that have never been registered before in that country or region. In many cases, the data available do not reach modern regulatory requirements and standards. For example, the introduction of fusidic acid into the US market has required a small US-based pharmaceutical company to undertake extensive in vitro, animal, and clinical studies to comply with the FDA requirements for new agents [15]. This process is ongoing, costly, and will take years, and it is occurring in the face of extensive clinical experience with the agent in several countries over the course of nearly 40 years. To expedite the process of newly registering older antibiotics, it is a matter of urgency that regulatory agencies worldwide develop new, perhaps less burdensome procedures so that these agents can be used globally in a timely manner. Better international harmonization is certainly needed for the regulatory agencies to attain all of these objectives.

Our study is strengthened by the use of an already published method, thus allowing us to compare data on older antibiotics with data on new antibiotics that are still in development [3]. Due to the chosen method, our inventory was limited to selected countries/regions. However, it would be interesting to extend the inventory to other regions such as Asia, South America, and Africa, depending on the complexity and diversity of their regulatory environments.

In conclusion, we have identified 31 particularly useful antibiotics that are available in a limited number of countries surveyed. These antibiotics will be forgotten by new generations of clinicians, unless they are reminded of their potential utility, thus limiting the best medical practice in that country. Urgent measures are now needed to ensure a better availability of these antibiotics on a global scale and to conduct additional research regarding the benefit of these antibiotics in current clinical infections.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Authors' contributions. I. C. G., N. F. M., and W. A. C. conceived the idea of the article. C. P. collected the data and wrote the article with contributions from all authors. All authors contributed to the data analysis and read and approved the final version.

Acknowledgments. The following persons provided the data on the availability of the selected antibiotics in their countries: Albania (Ahmet Hysa and Pellumb Pipero), Australia (John Turnidge), Austria (Ursula Theuretzbacher), Belgium (Inge Gyssens), Bulgaria (Todor Kantardjiev), Canada (Donna Lowe), Croatia (Vera Vlahovic-Palcevski), Denmark (Niels Frimodt-Møller), Estonia (Ott Laius and Irja Lutsar), Finland (Miika Bergman), France (Céline Pulcini), Germany (Sibylle Matz and Antina Ziegelmann), Greece (Helen Giamarellou), Hungary (Ria Benkö and Elisabeth Nagy), Iceland (Mímir Arnórsson), Republic of Ireland (Colm Bergin and Muireann O'Connor), Italy (Evelina Tacconelli), Kosovo (Lul Raka), Latvia (Uga Dumpis), Lithuania (Asta Jurkevičienė), Luxembourg (Marcel Bruch and Elisabeth Heisbourg), Republic of Macedonia (Golubinka Bosevska), Malta (Peter Zarb), the Netherlands (Inge Gyssens), Norway (Gunnar Skov Simonsen), Poland (Waleria Hryniewicz), Portugal (Liliana Cristina Ramos Dias), Romania (Mihaela Lupse), Serbia (Biljana Carevic), Slovenia (Bojana Beović), Spain (José Ramón Paño Pardo), Sweden (Hakan Hanberger), Switzerland (Stephan Harbarth), Turkey (Murat Akova), United Kingdom (Heather Kennedy and Charis Marwick), United States (William Craig). We also thank Pieter-Jan Cortoos (Belgium) for validating the data.

Potential conflicts of interest. K. B. receives retirement income from Bristol-Myers Squibb, Pfizer (Wyeth/Lederle), and Johnson & Johnson and has served as a consultant for Anacor, Basilea, Cempra, Cubist, Merck, and Shionogi. W. A. C. has served on scientific advisory boards as a consultant and received research grants for animal studies from numerous pharmaceutical companies. M. L. G. is Editor-in-Chief of *Kucers' The Use of Antibiotics*. I. G. has served as a consultant for Bayer Healthcare and Pfizer and has received a research grant from Bayer Healthcare. S. H. is a member of the speakers' bureau for bioMérieux and Brahms, participates on the scientific advisory boards of bioMérieux, Destiny Pharma, LASCCO, and DaVolterra, and has received research funding for investigator-initiated research by Pfizer. J. W. M. has served as a consultant for Astellas, AstraZeneca, Basilea, Merck and Novartis and has received research grants from Astellas, Cubist, Jansen and Merck. C. P. has received funding for travel/accommodations/meeting expenses from MSD and Pfizer. J. T. has served on advisory boards for Pfizer Australia, Novartis Australia, Janssen-Cilag Australia, and AstraZeneca Australia. N. F.-M. reports no potential conflicts of interest.

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.

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