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Emerging antibiotic resistance: Why we need new antibiotics!

Andreas F. Widmer

University of Basel

Introduction

Antibiotics have revolutionised medicine: Today, deadly infections such as meningitis and pneumonia can be treated by appropriate antibiotics with a treatment success rate of up to 90%. Diseases such as tuberculosis, plague and many others are almost "forgotten" in the western hemisphere as diseases that heavily influenced not only the individual, but society at large. Thanks to the development of antibiotics, "it is time to close the book on infectious diseases, and declare the war against pestilence won", a statement reportedly made by the US Surgeon General. Depending on the source, the quote is dated 1969 [1]. However, Alexander Fleming already feared the emergence of penicillin resistance, which was observed less than 10 years after he received the Nobel Prize for his discovery. In the last century, the development of new classes of antibiotics allowed success in the fight against the emergence of antimicrobial resistance, as antibiotics were developed more quickly than resistance emerged. However, this rapid growth in the development of antibiotics came to an end in the last decade of the last century.

Emergence of antimicrobial resistance is an inherent risk of any antimicrobial therapy: it can lead to the selection of a resistant subpopulation or increase the risk of acquiring genetic elements such as plasmids from other bacteria to escape the antimicrobial exposure. Stuart Levy called the immediate beneficial impact on health at the expenses of severe, perhaps irreversible effects on bacterial populations by selection of resistant (sub)populations "the Antibiotic Paradox", which finally results in novel threats for global health [2]. In 2015, governments adopted a global action plan at the World Health Assembly, which was followed by a political declaration from the United Nations G eneral Assembly. Today, antimicrobial resistance is on the agendas of the G 7 and G 20 groups [3]. The World Health Organization (WHO) even declared antimicrobial resistance to be one of the top 10 global public health threats [4].

This paper focuses on bacterial resistance only, but the problem extends to fungi [5], viruses [6] and parasites [7], as well as to disinfectants [8]; For example, resistance to zidovudine rapidly emerged during the very first attempts to treat human immunodeficiency virus (HIV) infection. However, defining antimicrobial resistance in fungi or viruses is much more complex than for bacteria [9, 10] and beyond the scope of this paper.

Correspondence:
Prof. Dr. med. Andreas F. Widmer
University of Basel
Klingelbergstrasse 61
CH-4056 Basel
Andreas.Widmer[at]unibas.ch

Global burden of bacterial antimicrobial resistance

In 2019, an estimated 4.95 million global deaths were associated with antimicrobial resistance, with 1.27 million directly attributed to multidrug resistant organisms in 2019 [11]. Jim O'Neill reported in a review on antimicrobial resistance that it is estimated that by 2050 10 million deaths per year will be attributable to antimicrobial resistance and a cumulative 100 trillion USD of economic output are at risk due to the rise of drug-resistant infections [12]. However, this statement has been challenged as an exaggeration [13].

The WHO has published a list of multiresistant pathogens where the need of development of new effective antibiotics is stratified by the microorganism (table 1) [14].

The highest burden of antimicrobial resistance is observed in low-income countries [11]. But multidrug resistant organisms – in particular plasmid-borne carbapenemase-producing Enterobacterales – are also found in India, in wastewater samples as well as drinking water supplies [15]. Even colistin resistance was detected in this country, one of the last effective drugs against multidrug resistant organisms [16].

Basically, antimicrobial resistance can be inherent to the bacterial species, due to selection of resistant subpopula-

Table 1:
WHO priority pathogens list for research and development of new antibiotics [14].

Priority 1: critical	*Acinetobacter baumannii*, carbapenem-resistant
	Pseudomonas aeruginosa, carbapenem-resistant
	Enterobacteriaceae, carbapenem-resistant, ESBL-producing
Priority 2: high	*Enterococcus faecium*, vancomycin-resistant
	Staphylococcus aureus, methicillin-resistant, vancomycin-intermediate and resistant
	Helicobacter pylori, clarithromycin-resistant
	Campylobacter spp., fluoroquinolone-resistant
	Salmonellae, fluoroquinolone-resistant
	Neisseria gonorrhoeae, cephalosporin-resistant, fluoroquinolone-resistant
Priority 3: medium	*Streptococcus pneumoniae*, penicillin-non-susceptible
	Haemophilus influenzae, ampicillin-resistant
	Shigella spp., fluoroquinolone-resistant
ESBL: extended spectrum beta-lactamase	

tions during antibiotic therapy, acquired by horizontal gene transfer or plasmids, or multidrug resistant organisms may be transmitted from patient to patient by direct or indirect contact, in particular in healthcare institutions.

However, farming, wastewater and others factors also contribute to the exposure of the community and the environment to antibiotics. Antimicrobial use as growth promotor, pre-emptive treatment of calves from different barns, hog feeding and, in particular, chicken farms where the whole flock is treated if some of the chickens are sick. This selective pressure increased the risk of development of multidrug resistant organisms: for example, Swiss broiler chickens are frequently colonised with *Campylobacter pylori* and *Escherichia coli*, up to 50% being resistant to ciprofloxacin and other classes of antibiotics. In Switzerland, the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in pigs increased from 18% in 2012 to 54% in 2021 [17].

Not surprisingly, clonal complex ST398 spread from pigs to pig farmers and vice versa [18, 19]. Even the soil of the pig barns can transport MRSA by the airborne route to neighbouring fields. [20]. In addition, sewage water can harbour multidrug resistant organisms, be used for irrigation, and finally end up in the food chain, and even be spread to hospitals by moth flies [21, 22].

Therefore, the concept of "one health" is required to tackle antimicrobial resistance on a large scale. Like global warming, emergence of resistance is not an immediate threat, but it is slowly growing to become a major threat to global health, as well as an economic crisis, until a point of no-return might be reached. Such long-term effects are difficult to communicate and it is even more difficult to find funding for investigating new antibiotic classes that may not be immediately needed for today's infectious disease challenges. The emergence of multidrug resistant organisms continues and is likely inevitable, but we can lower the speed of progression to gain time for drug development.

In the past, the pharmaceutical industry continuously developed new antibiotics or derivatives of existing antibiotic classes with an extended spectrum that was ahead of emerging resistant bacteria. Until the last century, emergence of resistance was on the radar of infectious diseases societies but was neglected by non-specialists. But today, the 2021 report by the WHO describes the antibacterial pipeline "as stagnant and far from meeting global needs". Since 2017, only two new antibiotic classes have been approved. It is believed that this race – between emergence of antibiotic resistance and development new effective antibiotics – has currently been lost.

Antimicrobial resistance emerges over decades, but it likely will need decades to develop new antibiotics to fight new, non-treatable multidrug resistant organisms and bring them to the market.

Why came antibiotic development almost to an end?

In the past, pharmaceutical companies recovered research and development costs by optimising sales and thus the consumption of their drugs. This strategy goes against the public health mandate to "steward" the use of antibiotics in order to preserve their effectiveness [23]. Physicians are trained to preserve antibiotics, use them "wisely" and limit the time of treatment. Society expects antibiotics to be almost always effective within 7 to 14 days, at very low cost and associated with few side effects. The need for antibiotics is high: around 30% of all patients in Swiss hospitals are exposed, at a minimum in short-term prophylaxis, to antimicrobial prophylaxis or therapy [24, 25]. Similarly, more than 30% of Swiss outpatients receive antibiotics from their general practitioner [26]. In western countries, almost nobody escapes antimicrobial therapy during their lifetime. Therefore, the demand for access to effective, reasonably priced antibiotics is extremely high.

During the 1980s, the number of antibiotics brought by pharmaceutical companies into clinical development increased to 39 in 1987 but had declined to 13 by 2001 [27]. In addition, time to market approval was around six years between 1980 and 1990 but doubled to over nine years for drugs filed at the US Food and Drug Administration (FDA) between 2000 and 2009 [27]. Therefore, the time of market protection after filing a patent significantly decreased, hence lowering the chance of selling the drug for long enough to compensate for research and development costs. Infectious diseases specialists in particular save new drugs for well-defined diseases, to minimise selective pressure and to ensure effectiveness for a long period of time before resistance becomes widespread. Subsequently, use of new antibiotics becomes widespread when the patent has expired. The median costs to bring a new drug to FDA approval exceed USD 1 billion [28], but expected initial sales are considerably less than USD 100 million/year for new antibacterial agents [29], making research and development of new antibiotics a very risky business. Even worse, the company that produced an important new antibiotic, meropenem/vaborbactam, which inhibits class A-serin-carbapenemases such as *Klebsiella pneumoniae* carbapenemase (KPC), declared bankruptcy [30]. Similarly, the company Achaogen brought plazomicin – a novel intravenous aminoglycoside antibiotic with activity against carbapenem-resistant Enterobacterales – successfully to registration in the US, but finally declared bankruptcy after minimal revenue and sales [31]. The competitor colistin – a very old, antibiotic with many side effects – was favoured by users owing to its very low cost. Ceftobiprole, a fifth-generation cephalosporin, was developed by the Swiss company Basilea and launched in 2007, but ceftarolin made it onto the US market despite having a smaller spectrum of activity [32].

Few pharmaceutical companies in the antibiotic field

Current antibiotics are mainly off patent and the cost of generics is very low, with the daily cost in the range of large cappuccino in a good restaurant. Not surprisingly, most production facilities have been outsourced: the majority of antibiotics or their basic components are produced in India and China [33]. The only integrated production chain for antibiotics in the Western world is in Kundl, Austria. Sandoz and the Austrian government will invest about €150 million over the next five years to improve antibiotic manufacturing at a (still) Novartis plant in Kundl. The company claims that "60 percent of the global production

of acid-stable penicillin" is produced in Kundl [34]. The current crisis in the Ukraine has shown how fast the "just in time" policy has broken down, and antibiotics are in the top list of drug shortages in Switzerland. Surveys from Australia and France also confirm that antimicrobials are predominant among medicine shortages [35].

Therefore, support for the development of new antibiotics must also include activities to provide access to currently available antibiotics. New antibiotic classes and reserve antibiotics should be sparingly used. Nevertheless, they may be required to be misused when "old" antibiotics with the optimal spectrum are out of stock. However, ensuring the supply chain for older antibiotics is not sufficient: the COVID-19 pandemic has clearly shown that outsourcing not only includes the risk of lack of access, but also loss of the know-how for emergency insourcing. It is reasonable to keep certain manufacturing plants on a local level to enable rapid adaption of production in the event of a severe crisis.

Proposals to support development of new antibiotics

The Infectious Diseases Society of America (IDSA) published an action plan in 2002, ultimately leading to its "10×20" call for 10 new antibacterial antibiotics by 2020 [36]. However, its success was very limited. Many agencies in the US, Europe, Canada, Australia and elsewhere also initiated programmes to support development of new antibiotics. The "STEDI" principles have been proposed as a guide for developing antibiotics [27]. The acronym refers to **S**pectrum (narrow to spare the microbiome and minimise resistance selective pressure), **T**ransmission (agents that reduce the spread of infectious disease), **E**nablement (new antibiotics that support medical procedures beyond curing infection, such as surgery), **D**iversity (investing in a variety of anti-infective strategies), and **I**nsurance (anticipate the future need for new agents and invest in them now). STEDI summarises an informative lens to view antibiotic development. These guidelines succeeded in accelerating research and development of antibiotics, but there is still a large gap in the drugs for infections where no compound is commercially available. A recent example from Switzerland is the isolation of *Mycobacterium chimaera* from bloodstream infections, where even a cocktail of five different antibiotics had only limited clinical success after several months of treatment [37].

Proposal for innovative financial incentives for development of antibiotics

Despite the urgent need in all fields of medicine, hardly any innovative antibiotics have come onto the market for decades [38]. This is because pharmaceutical companies, when taking investment decisions, perceive the expected market size and earning prospects for antibiotic development candidates to be bleak. These criteria serve as proxies for the unmet medical need and the incremental value the treatment generates for an individual patient compared to standard of care. Both inform the pricing negotiations with payers.

However, traditional pricing methods have long lost their capability to provide a financially viable incentive for antibiotics. The reasons are found both on the quantity and on the price side of the revenue equation:

1. Treatment duration to cure a bacterial infection is – with few exceptions — short.
2. Antibiotic stewardship measures to curb resistance-building result in low drug sales.
3. The prevailing rates of resistance in comparator medicines are not taken into account in pricing.
4. Current pricing methods do not consider the positive external effects antibiotics may have on the safety and effectiveness of any healthcare system.

When both the quantities of products used and achievable prices tend to be low, the ubiquitous and most efficient allocation mechanism of revenue = quantity x price loses its incentivising characteristics and antimicrobial development portfolios dwindle away. Experts refer to the "broken market" for antibiotic innovation [39].

This observation initiated the global search for alternative remuneration models. They require public policy involvement beyond the setting of a reimbursed price, which reflects the state responsibility for the adequate safety and effectiveness of their healthcare systems.

Pull incentives to reignite development of novel antibiotics

In search for alternative systems to incentivise antibiotic development several so-called pull models have been designed and are widely discussed in the international community. They aim to provide a market signal to potential investors that newly authorised antibiotics meeting public health priorities will be rewarded appropriately in a sustainable way, independent of drug volumes sold.

Pull models implemented on a national level may bring immediate benefits to the local healthcare system, for example in shape of sustainable access to the antibiotics procured under the selected model. However, in order to accumulate the power it takes to effectively incentivise the development of antibiotics, national efforts need to be bundled on an international level, in ways still to be defined (table 2).

Outlook for Switzerland

Two main pillars for treatment of multidrug resistant organisms are

– to delay further emergence of resistance by state-of-the art infection control and antibiotic stewardship, and
– to support development of new antibiotics.

Table 2:
Pull incentives to re-ignite development of novel antibiotics.

Market Entry Rewards (MER) foresee fixed payments to companies subject to the achievement of certain milestones such as marketing authorization [40] .
Value-based revenue guarantees, including versions such as the US Pasteur Act and the English value-based subscription model provided by the UK National Institute for Health and Clinical Excellence (NICE). The amount of annual fixed payments to the manufacturer are determined by the antibiotic's value to public health.
Transferable Exclusivity Extensions (TEE) generate revenue to the antibiotics manufacturer from extended market exclusivity granted to any other pharmaceutical product, not necessarily an antibiotic [41].

In Switzerland, very effective strategies have been initiated by the Office of Public Health (OFSP): the Swiss National Strategy on Antibiotic Resistance ("StAR"). StAR aims to maintain the effectiveness of antibiotics for humans and animals, and combat resistance. Launched in 2015, it in-cludes components of antimicrobial stewardship, guide-lines for therapy, improved surveillance of antibiotic use, and incidence of *Clostridioides difficile*. It is set-up in collaboration with professional societies as Swissnoso (www.swissnoso.ch), the national centre for infection prevention, the society for infectious diseases and microbiology as well as ANRESIS, the Swiss Centre for Antibiotic Resistance. STAR has been quite successful: the use of antibiotics in veterinary medicine has been halved, and in human medicine, MRSA and many other multidrug resistant organisms appear under control. In addition, uniform prescribing guidelines are now in force throughout Switzerland.

To promote the use of pull models, more countries should embark on the selection and piloting of a pull incentive, and Switzerland with its first-class research, significant pharmaceutical development capacity and respected international diplomacy should contribute. Such an engagement would benefit Switzerland and the global antimicrobial resistance-struck community alike.

The Round Table Antibiotics (https://roundtableantibiotics.ch), a multidisciplinary non-profit association, with its members coming from academia, politics and industry, supports the fight against antimicrobial resistance. It has the interdisciplinary technical expertise and project management skills to facilitate the development and testing of a pull incentive system in Switzerland. It provides scientific support for political stakeholders to facilitate activities for development of new antibiotics.

In summary, antibiotics have a huge impact on public health as well as the economy of societies: Today, community acquired infections can be rapidly treated, most surgeries require effective antimicrobial prophylaxis to reduce the risk of surgical site infections, stem-cell transplantation is very risky without effective antibiotics to combat neutropenic fever and decrease morbidity and mortality in particular for healthcare-associated infections. The loss of effective antibiotics would not only reduce public health and the health of individual patients but also increase the economic burden for the society by, for example, prolonged hospitalisation and absence from the workplace.

References

1. Fauci AS. Infectious diseases: considerations for the 21st century. Clin Infect Dis. 2001 Mar;32(5):675–85. http://dx.doi.org/10.1086/319235. PubMed. 1058-4838
2. Levy SB, Marshall B. Antibacterial resistance worldwide: causes, challenges and responses. Nat Med. 2004 Dec;10(12 Suppl):S122–9. http://dx.doi.org/10.1038/nm145. http://dx.doi.org/10.1038/nm1145. PubMed. 1078-8956
3. Årdal C, Baraldi E, Ciabuschi F, Outterson K, Rex JH, Piddock LJ, et al.; DRIVE-AB Steering Committee. To the G20: incentivising antibacterial research and development. Lancet Infect Dis. 2017 Aug;17(8):799–801. http://dx.doi.org/10.1016/S473-3099(17)30404-8. PubMed. 1474-4457
4. World Health Organization. Global Leaders Group on Antimicrobial Re-sistance. https://www.who.int/groups/one-health-global-leaders-group-on-antimicrobial-resistance
5. Vuichard-Gysin D, Sommerstein R, Martischang R, Harbarth S, Kuster SP, Senn L, et al. Candida auris - recommendations on infection prevention and control measures in Switzerland. Swiss Med Wkly. 2020;150:w20297.(doi): http://dx.doi.org/10.4414/smw.2020.20297. . eCollection 2020 Sep 21.
6. Gibas KM, Kelly SG, Arribas JR, Cahn P, Orkin C, Daar ES, et al. Two-drug regimens for HIV treatment. Lancet HIV. 2022 Oct;S2352-3018(22)00249-1. PubMed. 2352-3018
7. Plowe CV. Malaria chemoprevention and drug resistance: a review of the literature and policy implications. Malar J. 2022 Mar;21(1):104. http://dx.doi.org/10.1186/s12936-022-04115-8. PubMed. 1475-2875
8. Tschudin-Sutter S, Frei R, Kampf G, Tamm M, Pflimlin E, Battegay M, et al. Emergence of glutaraldehyde-resistant *Pseudomonas aeruginosa* . Infect Control Hosp Epidemiol. 2011 Dec;32(12):1173–8. http://dx.doi.org/10.1086/662624. PubMed. 1559-6834
9. Kahlmeter G, Turnidge J. How to: ECOFFs-the why, the how, and the don'ts of EUCAST epidemiological cutoff values. Clin Microbiol Infect. 2022 Jul;28(7):952–4. http://dx.doi.org/10.1016/j.cmi.2022.02.024. PubMed. 1469-0691
10. Gow NA, Johnson C, Berman J, Coste AT, Cuomo CA, Perlin DS, et al. The importance of antimicrobial resistance in medical mycology. Nat Commun. 2022 Sep;13(1):5352. http://dx.doi.org/10.1038/s41467-022-32249-5. PubMed. 2041-1723
11. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;18(21):02724–0.0140-6736
12. O'Neill J. Jim O'Neill. Nat Rev Drug Discov. 2016 Jul;15(8):526. http://dx.doi.org/10.1038/nrd.2016.160. PubMed. 1474-1784
13. de Kraker ME, Stewardson AJ, Harbarth S. Will 10 Million People Die a Year due to Antimicrobial Resistance by 2050? PLoS Med. 2016;13(11):e1002184. doi: http://dx.doi.org/10.1371/journal.pmed. .. eCollection 2016 Nov.
14. World Health Organisation. WHO publishes list of bacteria for which new antibiotics are urgently needed. https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed
15. Walsh TR, Weeks J, Livermore DM, Toleman MA. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. Lancet Infect Dis. 2011 May;11(5):355–62. http://dx.doi.org/10.1016/S1473-3099(11)70059-7. PubMed. 1474-4457
16. Davies M, Walsh TR. A colistin crisis in India. Lancet Infect Dis. 2018 Mar;18(3):256–7. http://dx.doi.org/10.1016/S473-3099(18)30072-0. PubMed. 1474-4457
17. Eidgenössisches Departement des Innern EDI, Bundesamt für Lebensmittelsicherheit und Veterinärwesen. . Bericht über den Vertrieb von Antibiotika und die Antibiotikaresistenzen in der Veterinärmedizin in der Schweiz. Gesamtbericht 2021. Available from: https://www.blv.admin.ch/dam/blv/de/dokumente/tiere/tierkrankheiten-und-arzneimittel/praevention/arch-vet-bericht-antibiotika-vertrieb-2021.pdf.download.pdf/Archvet_vertrieb_antibiotika_2021.pdf
18. Pirolo M, Visaggio D, Gioffrè A, Artuso I, Gherardi M, Pavia G, et al. Unidirectional animal-to-human transmission of methicillin-resistant *Staphylococcus aureus* ST398 in pig farming; evidence from a surveillance study in southern Italy. Antimicrob Resist Infect Control. 2019;8:187.(doi): http://dx.doi.org/10.1186/s13756-019-0650-z. . eCollection 2019.
19. Smith TC, Davis MF, Heaney CD. Pig Movement and Antimicrobial Use Drive Transmission of Livestock-Associated *Staphylococcus aureus* CC398. MBio. 2018 Dec;9(6):e02459–18. http://dx.doi.org/10.1128/mBio.-18. PubMed. 2150-7511
20. Bos ME, Verstappen KM, van Cleef BA, Dohmen W, Dorado-García A, Graveland H, et al. Transmission through air as a possible route of exposure for MRSA. J Expo Sci Environ Epidemiol. 2016;26(3):263-9. doi: http://dx.doi.org/10.1038/jes.2014.85. . Epub Dec 17.
21. Marathe NP, Regina VR, Walujkar SA, Charan SS, Moore ER, Lars-son DG, et al. A treatment plant receiving waste water from multiple bulk drug manufacturers is a reservoir for highly multi-drug resistant integron-bearing bacteria. PLoS One. 2013;8(10):e77310. doi: http://dx.doi.org/10.1371/journal.pone.0077310. . eCollection 2013.
22. Rupprecht T, Moter A, Wiessener A, Reutershan J, Lang-Schwarz K, Vieth M, et al. Spread of Multidrug-Resistant Bacteria by Moth Flies from Hospital Waste Water System. Emerg Infect Dis. 2020 Aug;26(8):1893–8. http://dx.doi.org/10.3201/eid2608.190750. PubMed. 1080-6059
23. Harbarth S, Theuretzbacher U, Hackett J, Adriaenssens N, Anderson J, Antonisse A, et al.; DRIVE-AB consortium. Antibiotic research and development: business as usual? J Antimicrob Chemother.

2015;70(6):1604–7. http://dx.doi.org/10.093/jac/dkv020. PubMed. 1460-2091

24. Metsini A, Vazquez M, Sommerstein R, Marschall J, Voide C, Troil-let N, et al. Point prevalence of healthcare-associated infections and antibiotic use in three large Swiss acute-care hospitals. Swiss Med Wkly. 2018;148:w14617. http://dx.doi.org/10.4414/smw.2018.14617.
25. Zingg W, Metsini A, Balmelli C, Neofytos D, Behnke M, Gardiol C, et al.; Swissnoso Network. National point prevalence survey on healthcare-associated infections in acute care hospitals, Switzerland, 2017. Euro Surveill. 2019 Aug;24(32):1800603. http://dx.doi.org/10.2807/1560-7917.ES.2019.24.32. PubMed. 1560-7917
26. Glinz D, Leon Reyes S, Saccilotto R, Widmer AF, Zeller A, Bucher HC, et al. Quality of antibiotic prescribing of Swiss primary care physicians with high prescription rates: a nationwide survey. J Antimicrob Chemother. 2017 Nov;72(11):3205–12. http://dx.doi.org/10.1093/jac/dkx278. PubMed. 1460-2091
27. Dheman N, Mahoney N, Cox EM, Farley JJ, Amini T, Lanthier ML. An Analysis of Antibacterial Drug Development Trends in the United States, 1980-2019. Clin Infect Dis. 2021 Dec;73(11):e4444–50. http://dx.doi.org/10.1093/cid/ciaa859. PubMed. 1537-6591
28. Wouters OJ, McKee M, Luyten J. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. JAMA. 2020 Mar;323(9):844–53. http://dx.doi.org/10.1001/jama.2020.1166. PubMed. 1538-3598
29. Rex JH, Outterson K, Antibacterial R. Antibacterial R&D at a Crossroads: We've Pushed as Hard as We Can … Now We Need to Start Pulling! Clin Infect Dis. 2021 Dec;73(11):e4451–3. http://dx.doi.org/10.1093/cid/ciaa852. PubMed. 1537-6591
30. Clancy CJ, Nguyen MH. Estimating the size of the United States market for new antibiotics with activity against carbapenem-resistant Enterobacteriaceae. Antimicrob Agents Chemother. 2019 Oct;63(12):e01733–19. http://dx.doi.org/10.1128/AAC.-19. PubMed. 1098-6596
31. Mullard A. Achaogen bankruptcy highlights antibacterial development woes. Nat Rev Drug Discov. 2019 Jun;18(6):411. http://dx.doi.org/10.1038/d41573-019-00085-w. PubMed. 1474-1784
32. Widmer AF. Ceftobiprole: a new option for treatment of skin and soft-tissue infections due to methicillin-resistant *Staphylococcus aureus* . Clin Infect Dis. 2008 Mar;46(5):656–8. http://dx.doi.org/10.1086/526528. PubMed. 1537-6591
33. Bjerke L. Antibiotic geographies and access to medicines: Tracing the role of India's pharmaceutical industry in global trade. Soc Sci Med. 2022;312:115386.(doi): http://dx.doi.org/10.1016/j.socscimed.2022.115386. .
34. Wagemut und Unternehmergeist. So startete die Penicillin-Produktion. Available from: https://www.sandoz.at/stories/75-jahre/penicillin-fuer-oesterreich
35. Beraud G. Shortages Without Frontiers: Antimicrobial Drug and Vaccine Shortages Impact Far Beyond the Individual! Front Med (Lausanne). 2021;8:.(doi): http://dx.doi.org/10.3389/fmed.2021.593712. .
36. Infectious Diseases Society of America. The 10 x '20 Initiative: pursuing a global commitment to develop 10 new antibacterial drugs by 2020. Clin Infect Dis. 2010 Apr;50(8):1081–3. http://dx.doi.org/10.1086/652237. PubMed. 1537-6591
37. Sommerstein R, Hasse B, Widmer AF. Invasive Mycobacterium chimaera Infections and Heater-Cooler Devices in Cardiac Surgery. Emerg Infect Dis. 2020 Mar;26(3):632–3. http://dx.doi.org/10.3201/eid2603.191818. PubMed. 1080-6059
38. Butler MS, Gigante V, Sati H, Paulin S, Al-Sulaiman L, Rex JH, et al. Analysis of the Clinical Pipeline of Treatments for Drug-Resistant Bacterial Infections: Despite Progress, More Action Is Needed. Antimicrob Agents Chemother. 2022 Mar;66(3):e0199121. http://dx.doi.org/10.1128/AAC.01991-21.PubMed. 1098-6596
39. Outterson K, Powers JH, Daniel GW, McClellan MB. Repairing the broken market for antibiotic innovation. Health Aff (Millwood). 2015 Feb;34(2):277–85. http://dx.doi.org/10.1377/hlthaff.2014.1003. PubMed. 1544-5208
40. Okhravi C, Callegari S, McKeever S, Kronlid C, Baraldi E, Lindahl O, et al. Simulating Market Entry Rewards for Antibiotics Development. J Law Med Ethics. 2018 Jun;46(1_suppl suppl):32–42. http://dx.doi.org/10.1177/1073110518782913. PubMed. 1748-720X
41. Rome BN, Kesselheim AS. Transferrable Market Exclusivity Extensions to Promote Antibiotic Development: An Economic Analysis. Clin Infect Dis. 2020 Oct;71(7):1671–5. http://dx.doi.org/10.093/cid/ciz039. 1537-6591