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Patient access in fourteen high-income countries to new antibacterials approved by the FDA, EMA, PMDA, or Health Canada, 2010-2020

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Research in context

Evidence before this study

Lack of access to patented medicines in low- and middle-income countries is a well-known issue, including antibacterials. Prior to this study, it was known that antibacterials suffered a broken business model due to inability to recoup sunk research and development with limited sales of new drugs despite the need to have antibacterials ready for future preparedness. Prior studies measured time lag to availability using marketing approval dates, not commercial launch dates. In this study, we evaluated all antibacterials approved in fourteen high-income markets for the decade beginning January 1, 2010, to determine the delay in both approvals and commercial launches.

Added value of this study

Including commercial launch as well as marketing approval demonstrates that patients in high-income countries experience much longer waits for new antibacterials than previously understood. Commercial decisions driven by low reimbursement for antibacterials are more salient than regulatory approval lag. All but one antibacterial was placed on the WHO "Reserve" list, indicating stronger stewardship measures. Commercial launch lags affected "innovative" antibiotics as well, yielding sales in the context of antimicrobial stewardship which are too low to sustain research and development going forward. Commercial launch lags were not associated with other hypothesized factors such as national levels of drug resistance and national health spending. Sponsors of new antibacterials are suffering economically, with bankruptcies, low market capitalizations, and low sales revenues.

Implications of all the available evidence

Antibacterial reimbursement must be reformed in high-income countries, consistent with appropriate stewardship. Paying for antibiotics based on their preparedness value as infrastructure, delinked from sales volume, may be the best path to sustain innovation, stewardship, and global access.

Abstract (max 300 words)

Background: Inaccessibility of patented medicines in low- and middle-income countries (LMICs) is a frequent challenge. Yet it is typically assumed that high-income countries have complete access to the full arsenal of medicines. This study tests this assumption for patented antibacterials, a class widely acknowledged as having a broken business model. New antibiotics are saved as a last resort in order to prevent the development of resistance, resulting in insufficient revenues to offset costs.

Methods: We identified all antibacterials approved in Canada, Europe, Japan, and the USA for the decade beginning January 1, 2010 and evaluated differences in marketing authorizations and commercial launches in fourteen high-income countries. Delays in access were described as launch lags – the time in days between approvals and commercial launch. Associations between several factors including "innovativeness" were explored.

Findings: Eighteen new antibacterials were identified. The majority were accessible in the US (n=17, 94%), the United Kingdom (n=11, 61%), and Sweden (n=10, 56%), with the remaining eleven countries having access to less than half of them. European marketing authorization did not lead to widespread European access, as fourteen of the antibacterials were approved by EMA, but many fewer were commercially launched. Five antibacterials were deemed as "innovative", but there was no significant difference in access between "innovative" and "non-innovative" antibacterials. Surprisingly, antibacterials not listed on the EML had shorter launch lags. Japan had the longest median launch lags. Canada had the fewest drugs commercially available (n=2, 11%).

Interpretation: Patient access to new antibacterials is limited not just in LMICs, as previously reported, but also in high-income countries such as Canada, Japan, France, Germany, Italy, and Spain. The major driver of delayed access appears to be poor commercial prospects for reimbursement, leading to company decisions to delay or forego commercialization in many high-income countries due to expectations of insufficient profitability.

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Introduction

Innovative medicines are often unavailable in low- and middle-income countries (LMICs) for a decade or more after introduction in high-income countries.[1] Once available, the medicines may still be inaccessible given lack of effective healthcare insurance protections or access to affordable care.[2]

These concerns are also recognized within antibacterials,[3] where stewardship adds additional complexity. The more a given antibacterial is used, the greater the selection pressure to develop resistance.[4] This characteristic, combined with the paucity of novel antibacterial candidates in clinical development, gives a strong incentive to steward novel antibacterials to be used only as a last resort. Since revenues of novel drugs are driven by unit sales, antibacterial innovators struggle to achieve profitability, with large companies exiting the market and small companies going bankrupt. As these programs struggle to survive, they reduce their expenses by limiting introduction of new antibacterials to markets where sales are expected to exceed regulatory and other additional costs.

In 2010, the Infectious Diseases Society of America called for ten new antibiotics by 2020.[5] This goal was achieved in terms of the number of drug approvals, but actual patient access requires commercial launches in many countries, which itself requires sustainable commercial markets. Prior work has described limited access to new antibacterials in LMICs, in part due to the inability of many to afford these drugs.[3] This study examines patient access for new antibacterials in fourteen high-income countries, to better understand other barriers to patient access to effective antibacterial therapy.

Data and methods

We included all new molecular entity (NME) antibiotics (drugs with a J01 classification from the Anatomical Therapeutic Chemical (ATC) classification maintained by the World Health Organization) that were approved by either the United States Food & Drug Administration (FDA), the European Medicines Agency (EMA), Health Canada, or the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) for the decade from 1 January 2010 until 31 December 2019. We also included fidaxomicin, classified as an A07 antidiarrheal drug for the treatment of *Clostridioides difficile*-associated infection (CDI), and bezlotoxumab, classified as J06 for recurrent CDI, which is generally associated with prior antibiotic use. We excluded generics, topical drugs, drugs with other ATC classifications, and combination drugs without any NME component.

For each such drug (referred to hereinafter as an "antibacterial"), we recorded the date of FDA, EMA, Health Canada, or PMDA approval, International Nonproprietary Name (INN), brand name, current sponsor, route of administration, and various regulatory designations in the countries studied. This information was collected as of 31 December 2020 from government websites (see the Supplemental Materials) as well as filings with the United States Securities and Exchange Commission (SEC), and company press releases. Sponsors are categorized as "large" if they employ 250 or more full-time equivalent employees; otherwise, "small or medium enterprises" or "SMEs."

We collected commercial launch (first commercial sale) dates in the following fourteen high-income countries: Canada, Croatia, Denmark, France, Germany, Greece, Italy, Japan, Norway, Romania, Spain, Sweden, the United Kingdom, and the United States. Date of commercial launch in each country was obtained from the sponsor. If sponsor data was not available, the earliest reported commercial launch date from public or commercial databases was used instead.

We collected possible indicators of drug quality. From the World Health Organization, we determined whether each drug was on the Essential Medicines List (EML) and its placement on the "Access, Watch, and Reserve" (AWaRe) list of antibacterials.[6,7] We also used the assessments of innovation from the WHO Antibacterial Agents in Clinical Development reports.[8,9] From the Pew Charitable Trusts, we determined whether the antibacterial was considered by Pew to be innovative.[10] Both Sweden and National Health England are piloting post-approval incentives for antibacterials, so we tracked which drugs have been selected as of 31 December 2020.

Sales data in the United States for the trailing 12-month period ending June 2020 were obtained from Needham & Co. analyst Alan Carr.[11] Sponsors were noted if, subsequent to first regulatory approval, they filed for bankruptcy in their country of domicile or, if publicly traded, had market capitalization lower than $300M. For the full data set and additional methods, see the Supplementary Materials.

We analyzed the data using comparative descriptive and inferential statistics. We calculated median launch lags by country (including EMA as a country for this purpose) and drug. Launch lag is the time from first regulatory approval in the US, EU, Japan or Canada to the date of commercial launch in a given

country. For second and subsequent regulatory approvals, we calculated the time from approval in the first country (generally, the United States) to the date of approval and, separately, commercial launch in the studied country. For antibacterials not yet approved or commercially launched in any of the other studied countries, we reported the time from first regulatory approval to the study end date of December 31, 2020, as "lag to date".

To examine median launch lag between innovative and non-innovative drugs among the eleven antibacterials launched in two or more countries in our sample, we tested the difference in median launch lag for statistical significance using the Related-Samples Wilcoxon signed-rank test. Antibacterials were defined as "innovative" if designated as "innovative" or "possibly innovative" by WHO or as "novel" by the Pew Charitable Trusts. The same analysis was performed for drugs on the EML, as a proxy for global clinical need, and difference in median launch lag between listing and non-listing in the EML was assessed for significance. We also tested the difference in median launch lag by sponsor characteristics, proxied by SME status using the Wilcoxon test.

To assess how the burden of drug resistance, as a determinant of demand in countries, is associated with median launch lags, we performed a bivariate correlation using Spearman's rho (r_s), with p=0.01 (2-tailed) for all fourteen countries. The burden was proxied by the Drug Resistance Index (DRI).[12] For Japan with no data in the DRI, we used the values in the dataset from Sweden, given Japan's relative success against drug resistance.[13] We also assessed correlation between median launch lag outside the US and the 12-month trailing sales in the US for antibacterials with multiple launches by Spearman's rho.

Results

Eighteen antibacterials met the inclusion criteria (sixteen J01 antibiotics and two products for CDI, bezlotoxumab and fidaxomicin) as shown in Table 1.

In all but one of the countries studied, the majority of the drugs have not been commercially launched as of 31 December 2020 (Table 1): Canada (n=2, 11%); Japan, Denmark, and Croatia (n=5 launched, 28%); Romania and Greece (n=6, 33%); Spain, Norway, Italy, and Germany (n=7, 39%); and France (n=8, 44%). Only in Sweden (n=10, 56%), the United Kingdom (n=11, 61%), and the United States (n=17, 94%) have the sponsors launched a majority of these drugs. In Canada, only two of the five approved drugs are commercially launched. Only four antibacterials are commercially launched in all European countries studied. Only two antibacterials (fidaxomicin and ceftolozane/tazobactam) have been commercially launched in all fourteen high-income countries studied. They were first approved in 2011 and 2014 and are marketed by large companies. Median launch lags are presented in Figure 1.

Granting of marketing authorization did not necessarily lead to commercial launch, as can be seen clearly in Canada and the five largest drug markets in Europe, where much of the launch lag has occurred after regulatory approval for the drug. (Figure 2) The sponsor for lascufloxacin has not yet filed for regulatory approval with the FDA, Health Canada, or EMA. For two of the four antibacterials lacking EMA approval (plazomicin and omadacycline), pending EMA market authorization approvals were voluntarily rescinded by the sponsors due to poor economic prospects for sales in Europe. The sponsor of plazomicin (Cipla Europe NV, successor to Achaogen after the bankruptcy sale) cited the cost of the required approval and post-approval work making the product "financially and commercially unviable with the limited indication that was to be accepted."[14] For omadacycline, the sponsor (Paratek Ireland Limited) was similarly pragmatic: "The insistence for a second CAP [community acquired pneumonia] study to support approval for this indication in EU has significantly changed the value proposition" and

therefore “all partner discussions have now been discontinued.”[15] Paratek predicted that European patient access to omadacycline would be delayed by five years.

In total, five antibacterials were deemed “innovative”: (lefamulin and meropenem/vaborbactam by both WHO and Pew; ceftazidime/avibactam by Pew and predating the WHO reports; bezlotoxumab by WHO but not evaluated by Pew; and cefiderocol, described below).[10] Lefamulin was approved by Health Canada on 16 July 2020 and by EMA on 27 July 2020, but has not launched outside the United States. Meropenem/vaborbactam was approved and launched in the US in 2017, and despite being approved by the EMA in 2018, it is only available in three of the other studied countries. Ceftazidime/avibactam was approved and launched in the US in 2015, approved by the EMA in 2016, and is available in all but two of our select countries (Canada and Japan). Bezlotoxumab was approved and launched in the US in 2016, approved by the EMA in 2017, and is not available in five of the high-income countries studied (Canada, Croatia, Denmark, Greece, and Romania).

Cefiderocol, assessed as “possibly innovative” by WHO, is one of the few new antibiotics active against the metallo-β-lactamases (NDM, IMP, etc.) that make bacteria resistant to carbapenems. Cefiderocol was approved by EMA on 23 April 2020 but was not launched anywhere in Europe as of 31 December 2020 (note that cefiderocol was commercially launched in Sweden as part of their pilot program on January 1, 2021, the day after the end of this study period, so we coded it as launched in Sweden). Cefiderocol has not been approved in either Canada or Japan. Comparing the four “innovative” and “possibly innovative” antibacterials with multiple launches (excepting lefamulin, launched only in the US) with the others, we found that there was no significant difference in median launch lags, p=0.465, among all eleven antibacterials with launches in more than one country.

Eight of the drugs are on the 2020 WHO EML (ceftaroline, delafloxacin, ceftolozane/tazobactam, omadacycline, eravacycline, plazomicin, meropenem/vaborbactam, and ceftazidime/avibactam).[6] Eravacycline, omadacycline, and plazomicin are not launched in any of the countries studied other than the United States. Delafloxacin is launched in two of the countries studied (United Kingdom, and United States). Ceftaroline is launched in twelve of the countries studied (United States, plus all of the European countries studied, but not Canada or Japan).

Of the eleven antibacterials with launches in more than one country, we found a significant difference in median launch lag, p=0.043, between listing and non-listing on the EML. Unexpectedly, such multiple-launch antibacterials listed on the EML had longer median launch lags. The five multiple-launch EML drugs (ceftaroline, meropenem/ vaborbactam, ceftazidime/avibactam, ceftolozane/tazobactam, delafloxacin) had a median launch lag of 780 days, compared to 414 days for the six non-listed multiple-launch drugs (fidaxomicin, dalbavancin, tedizolid, imipenem/cilastatin/relabactam, cefiderocol and bezlotoxumab).

Seven of the eighteen drugs (39%) were sponsored by SMEs, accounting for six of the eleven drugs (55%) approved by the FDA since 1 January 2016. Drugs sponsored by SMEs are being launched more slowly in Europe, Canada, and Japan. Five of the seven SME drugs have not been launched outside the United States. The other two SME drugs (delafloxacin and meropenem/vaborbactam) have only been launched in the United Kingdom, the United States, France, and Sweden (meropenem/vaborbactam only for France and Sweden). The median launch lag for SME and large company drugs was 510 days (seventeen months) and 420 days (fourteen months), respectively. There was no significant difference in launch delay by SME status, p=0.180.

There was no statistically significant relationship between the burden of drug resistance and median launch lag. The results suggested a very weak negative but statistically not significant correlation between DRI and median launch lag (r_s = -0.033, n = 13, p = 0.915).

None of the above-mentioned antibacterials have been commercially successful by ordinary drug development standards (Figure 3). In the United States, commercial sales for all but three of these drugs (ceftazidime/avibactam, fidaxomicin, and ceftaroline) are below $100 million for the most recent 12-month trailing period, and none of the eighteen drugs exceeded $150 million in sales despite having been on the US market for up to ten years (ceftaroline). The last twelve months sales in the first approval market for all eighteen drugs is a median of $16.2 million and a cumulative sum of $714.3 million. Sponsors for four drugs filed for bankruptcy after first regulatory approval, and sponsors for three other drugs had market capitalizations less than $300 million. There was also no statistically significant correlation between US 12-month trailing sales and median launch lag outside the US (r_s = 0.297, n = 10, p = 0.405).

Additional results are described in the Supplemental Materials.

Discussion

While the innovation crisis in antibiotics is well-known,[16-18] we describe serious limitations on commercial launch and therefore patient access in high-income countries. Most new antibacterials approved by the FDA, EMA, PMDA, or Health Canada since 1 January 2010 are not commercially available to patients in many high-income countries due to a combination of delayed marketing authorization submission/approval and delayed commercial launch even after marketing approval. Given the long commercial launch lags in many European countries despite EMA authorization, and in Canada, after Health Canada authorization, regulatory approval is clearly not the only barrier. The major driver of delayed access appears to be poor commercial prospects for reimbursement, leading to company decisions to delay or forego commercialization in many high-income countries due to expectations of insufficient profitability.

Antibacterials are generally approved based upon non-inferiority clinical trial designs, meaning that the new drug is shown not to be inferior to a comparator, typically an older generic antibacterial.[19] In many European countries, this trial design automatically adjusts the reimbursement amount to the same amount as the comparator drug. Even if a new antibacterial demonstrates improved efficacy after commercialization, it is difficult to have the unit price increased. Knowing this, companies take these regulations into consideration when determining their commercialization strategies. Other constraints on revenues include payment for hospital antibiotics through diagnostic related groups (which do not account for higher priced antibacterials),[20] governments requiring significant price reductions,[21] and the impact of stewardship, which lowers sales volumes. For the two sponsors that withdrew marketing applications from EMA, costs from required approval and post-approval work outweighed the limited prospects for net revenues.

Commercial drug innovation is supported by sales during the patent term.[22] For antibacterials, sales in the United States are currently insufficient to sustain innovation.[16-18,23,24] Delayed or abandoned commercial launches in other high-income countries result in a large share of the patent term outside of the United States yielding little or no revenues. Even within the first launch market of choice (the United States for seventeen of eighteen drugs, 94%), the trailing 12-month sales for the entire sector were low: a cumulative sum of $714.3 million, which means that the entire antibacterial branded market – all antibacterials approved for the decade beginning 1 January 2010 – was valued at less than a single

blockbuster drug. Mean sales of $16.2 million are insufficient to cover ongoing commercialization costs, including manufacturing, regulatory, medical affairs, and post-approval commitments, with no opportunity to recover sunk R&D costs. This economic situation explains why sponsors for seven of the eighteen products suffered either bankruptcy or market capitalizations below the sunk cost of R&D, with the bulk of this economic damage coming since April 2019. Relative sales success in the United States did not predict commercial launch in the other high-income countries studied, suggesting that these markets are segmented by national characteristics driving commercial prospect for sales, but these national characteristics do not include the level of drug resistance, measured by the DRI, or national health expenditures (data in Supplemental Materials).

For all of these drugs, careful stewardship may be a cause of lower sales. For the antibacterials categorized on the WHO AWaRe list, all but one was placed on the most restrictive "Reserve" category, essentially saving the drug for future patients. While a laudable public health imperative, the economic impact on the companies is clearly apparent. In light of modern stewardship practices,[7,25,26] it is very difficult for companies selling newly launched Reserve antibacterials to earn sufficient revenues from volume of sales alone.

An alternative explanation for low sales and delayed launches could be inadequate antibacterial innovation in the past decade, with these drugs selling poorly because they simply are not clinically important drugs. But we find poor sales and delayed patient access even for the antibacterials labeled as novel by the Pew Charitable Trusts or innovative by the WHO, as well as those placed on the Essential Medicines List by the WHO.

Canada and Japan present interesting case studies in the data. Both are significant markets for consumer goods, but they trail all other high-income countries studied for commercial launches of antibacterials, at rates far exceeding prior studies of Canadian and Japanese drug lags. Japan was traditionally a strong launch market for antibiotics,[27,28] with significant leadership from Japanese companies. For example, data from 1999-2007 found that the Japanese lag for anti-infectives was only 13.6 months.[27] Canadian data from 2000-2011 reported much shorter lags than what we report here.[28] A number of smaller and less wealthy European countries have seen greater numbers of commercial antibacterial launches than Canada and Japan. Plausible explanations include the consolidated marketing approval process through the EMA, as compared to the need to separately apply to Health Canada and the Japanese PMDA, and the need for additional clinical studies in Japan.[27,28] With Brexit on 31 December 2020, there is an opportunity to study the future impact of the new process for marketing approvals in the United Kingdom.

Sweden has also launched a program to encourage companies to commercially launch antibacterials in Sweden,[29] this program has already led to three new commercial launches in Sweden (cefiderocol, imipenem-cilastatin/relabactam, and meropenem/vaborbactam). This single program has moved Sweden from seven to ten launched drugs, moving to sole possession of third place in the high-income countries studied, behind only the Unites States and the United Kingdom. Sweden's program is therefore a highly successful access initiative. Sweden's program is explicitly not an innovation incentive, i.e., it is not attempting to provide a return on investment for the R&D costs of new antibacterials. It guarantees annual revenues of approximately US$400,000 per drug to enhance patient access in Sweden. The program's design is elegant in its simplicity and could be scaled up to also provide an innovation incentive proportional to Sweden's economic stature, or indeed any other country so inclined. The UK pilot, subscribing for two innovative drugs (ceftazidime/avibactam and cefiderocol), is explicitly designed as an innovation incentive.[30]

Fundamentally, the core challenge is that the fruit of a decade of antibacterial innovation has little financial value today if value is driven only by the frequency of current use, and obviously clinical impact is absent for patients in countries where the product is not commercially available. To address this, reimbursement must begin to recognize the preparedness value of having antibacterials on hand before they are needed. Preparedness value can be thought of as analogous to the value of having a fire extinguisher or entire fire department:[31] benefits of novel antibacterials can then be seen based on the "STEDI" attributes of Spectrum of coverage, Transmission interruption, Enablement of medical care, Diversity of antibiotic choice, and Insurance against pandemic spread.[32,33]

As the preparedness value is most fundamentally a function of offering novel utility, we also must re-orient the R&D community towards the higher risk but higher preparedness value of truly novel antibacterials and hence more clinically important drugs. Intrinsically useful properties can be defined well in advance of registration[31] and delinked pull approaches such as the PASTEUR Act and the UK antibiotic pilot propose rewards scaled to demonstration of high-value attributes.[30,34] We anticipate the European Union will fulfil its commitment to create a delinked antibiotic pilot in 2021.[35]

While this study did not assess the commercialization of new antibacterials in LMICs, our findings do not bode well for these countries, given low profitability expectations.[3] Delinked pull incentives may be required to persuade sponsors to serve these markets, even on a non-profit basis.

In conclusion, patient access to new antibacterials is limited, not just in LMICs, as previously reported, but also in high-income countries such as Canada, Japan, and many European countries. Companies appear to eschew antibacterial markets not offering attractive commercial prospects, which are almost all markets currently. If truly innovative antibacterials, like those identified by WHO and Pew, cannot find profitable markets, antibacterial innovation is in serious jeopardy, which reinforces calls for new economic incentives, delinked from unit sales.

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Tables

Table 1. Approval and commercial launch in fourteen high-income countries of NME antibacterials first approved by FDA, EMA, PMDA, or Health Canada, 2010-2019.

		Lag from first approval (FDA, EMA, PMDA, HC) to commercial launch, in days															
INN	**1st Approval**	**US**	**EMA***	**UK**	**Sweden**	**France**	**Germany**	**Italy**	**Norway**	**Spain**	**Greece**	**Romania**	**Croatia**	**Denmark**	**Japan**	**Canada**	**Launches**
cefiderocol	**14-Nov-19**	**102**	**23-Apr-20 (161)**	**Yes (306)**	**Yes (413)**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**3**
lascufloxacin	**20-Sep-19**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**Yes (103)**	**No**	**1**
lefamulin	**19-Aug-19**	**21**	**27-Jul-20 (343)**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**1**
imipenem-cilastatin/ relabactam	**16-Jul-19**	**321**	**13-Feb-20 (212)**	**Yes (382)**	**Yes (382)**	**No**	**No**	**No**	**Yes (290)**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**4**
omadacycline	**2-Oct-18**	**122**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**1**
sarecycline	**1-Oct-18**	**92**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**1**
eravacycline	**27-Aug-18**	**35**	**20-Sep-18 (24)**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**1**
plazomicin	**25-Jun-18**	**6**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**1**
meropenem/ vaborbactam	**29-Aug-17**	**33**	**20-Nov-18 (448)**	**Yes (815)**	**Yes (1037)**	**Yes (1064)**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**4**
delafloxacin	**19-Jun-17**	**196**	**16-Dec-19 (910)**	**Yes (1121)**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**2**
bezlotoxumab	**21-Oct-16**	**115**	**18-Jan-17 (89)**	**Yes (174)**	**Yes (131)**	**Yes (1045)**	**Yes (527)**	**Yes (618)**	**Yes (206)**	**Yes (557)**	**No**	**No**	**No**	**No**	**Yes (413)**	**No**	**9**
ceftazidime/ avibactam	**25-Feb-15**	**35**	**23-Jun-16 (484)**	**Yes (748)**	**Yes (827)**	**Yes (1967)**	**Yes (720)**	**Yes (1049)**	**Yes (310)**	**Yes (999)**	**Yes (980)**	**Yes (933)**	**Yes (1184)**	**Yes (841)**	**No**	**No**	**12**
ceftolozane/ tazobactam	**14-Dec-14**	**49**	**18-Sep-15 (278)**	**Yes (352)**	**Yes (383)**	**Yes (598)**	**Yes (322)**	**Yes (657)**	**Yes (383)**	**Yes (443)**	**Yes (383)**	**Yes (808)**	**Yes (657)**	**Yes (352)**	**Yes (1630)**	**Yes (291)**	**14**
oritavancin	**6-Aug-14**	**56**	**18-Mar-15 (224)**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**1**
tedizolid	**20-Jun-14**	**10**	**23-Mar-15 (276)**	**Yes (315)**	**Yes (438)**	**Yes (577)**	**Yes (276)**	**Yes (1046)**	**Yes (390)**	**Yes (294)**	**Yes (681)**	**Yes (742)**	**No**	**Yes (276)**	**Yes (1432)**	**No**	**12**
dalbavancin	**23-May-14**	**39**	**19-Feb-15 (272)**	**Yes (914)**	**Yes (1279)**	**Yes (1097)**	**Yes (918)**	**Yes (740)**	**No**	**Yes (619)**	**Yes (954)**	**Yes (862)**	**Yes (923)**	**No**	**No**	**No**	**10**
fidaxomicin	**27-May-11**	**35**	**05-Dec-11 (192)**	**Yes (371)**	**Yes (371)**	**Yes (542)**	**Yes (585)**	**Yes (889)**	**Yes (385)**	**Yes (554)**	**Yes (432)**	**Yes (797)**	**Yes (1711)**	**Yes (371)**	**Yes (2651)**	**Yes (1648)**	**14**
ceftaroline	**29-Oct-10**	**64**	**22-Aug-12 (663)**	**Yes (726)**	**Yes (764)**	**Yes (844)**	**Yes (717)**	**Yes (1007)**	**Yes (755)**	**Yes (1162)**	**Yes (1315)**	**Yes (795)**	**Yes (2764)**	**Yes (734)**	**No**	**No**	**12**
N approved or launched	**18**	**17**	**14**	**11**	**10**	**8**	**7**	**7**	**7**	**7**	**6**	**6**	**5**	**5**	**5**	**2**	

*EMA approval only shown, not commercial launch

Figures

Figure 1: Median launch lags (MLL), in days, in fourteen high-income countries for NME antibacterials first approved by FDA, EMA, PMDA, or Health Canada, 2010-2019

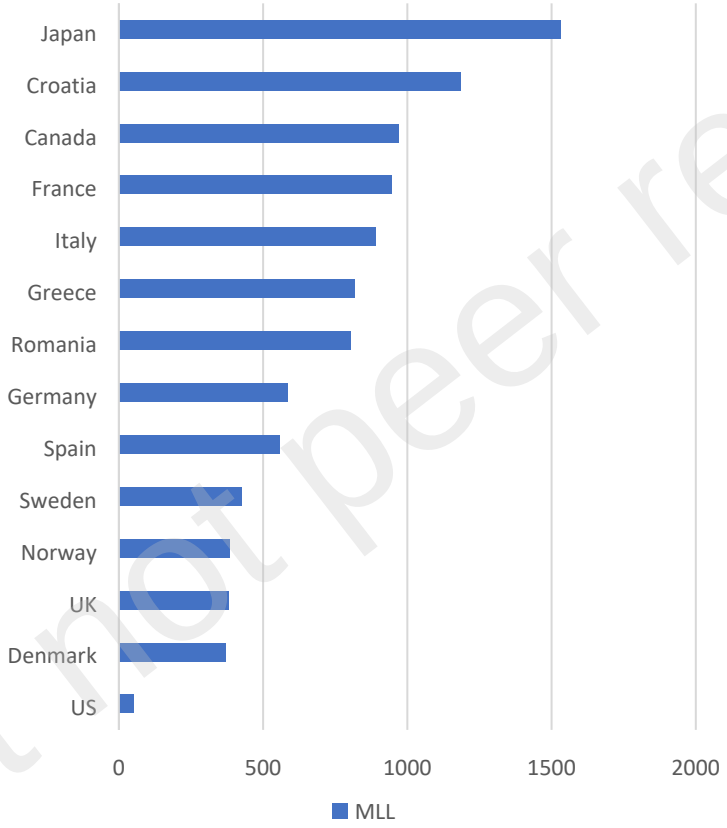

Figure 2. Delay in days before and after EMA approval for recently-approved antibiotics, in five high-income European countries

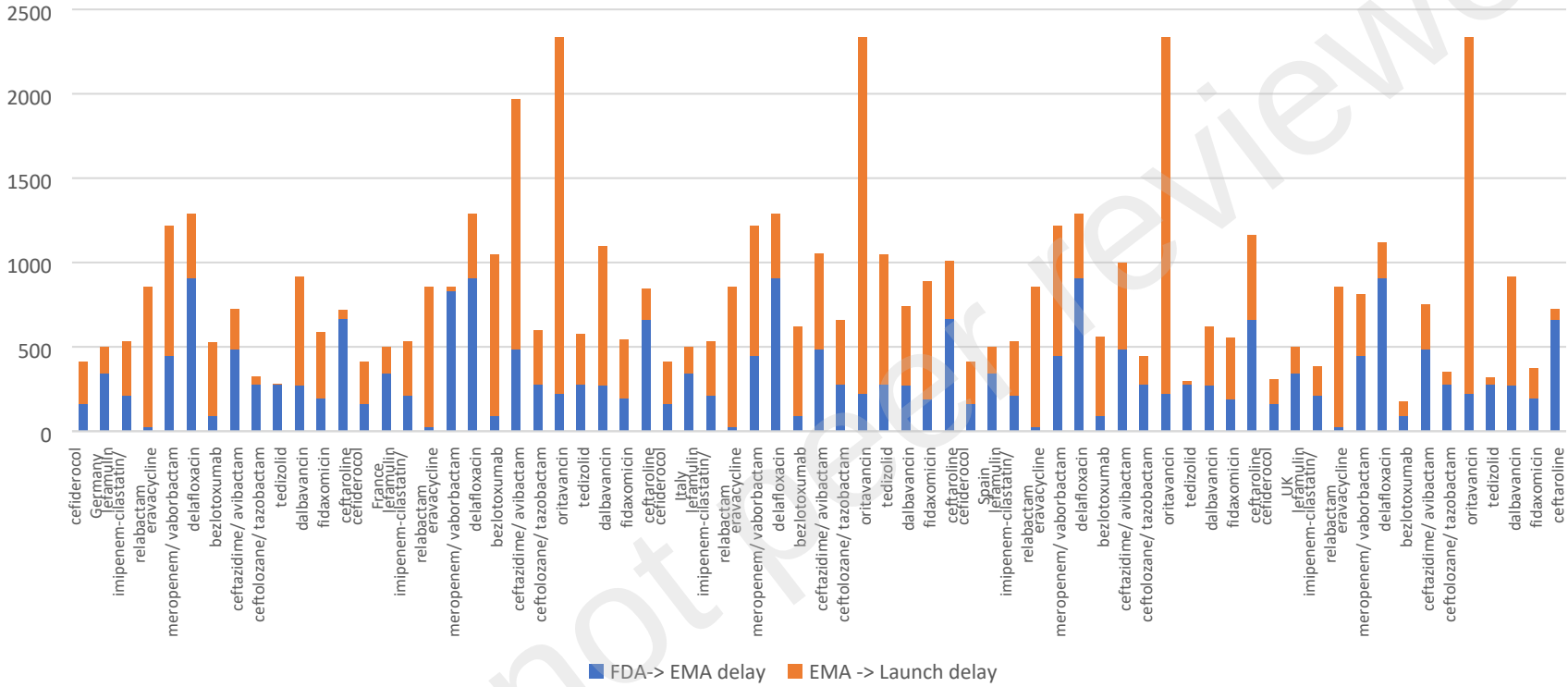

Figure 3: US trailing 12-month sales for antibacterials approved 2010-2019, by launch date, sponsor size, and number of high-income country commercial launches, with linear trend