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VIEWPOINTS

Coronavirus Disease 2019, Superinfections, and Antimicrobial Development: What Can We Expect?

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Coronavirus disease 2019 (COVID-19) arose at a time of great concern about antimicrobial resistance (AMR). No studies have specifically assessed COVID-19–associated superinfections or AMR. Based on limited data from case series, it is reasonable to anticipate that an appreciable minority of patients with severe COVID-19 will develop superinfections, most commonly pneumonia due to nosocomial bacteria and *Aspergillus*. Microbiology and AMR patterns are likely to reflect institutional ecology. Broad-spectrum antimicrobial use is likely to be widespread among hospitalized patients, both as directed and empiric therapy. Stewardship will have a crucial role in limiting unnecessary antimicrobial use and AMR. Congressional COVID-19 relief bills are considering antimicrobial reimbursement reforms and antimicrobial subscription models, but it is unclear if these will be included in final legislation. Prospective studies on COVID-19 superinfections are needed, data from which can inform rational antimicrobial treatment and stewardship strategies, and models for market reform and sustainable drug development.

Keywords. coronavirus disease 2019; COVID-19; superinfections; antimicrobial resistance; antimicrobial development.

Repeated warnings have been sounded about public health threats posed by pandemic viral and antimicrobial-resistant infections [1, 2]. The world is currently experiencing widespread dissemination of coronavirus disease 2019 (COVID-19), which is imposing the worst infectious disease crisis since the 1918 influenza pandemic. During the 1918 and subsequent influenza pandemics, *Streptococcus pneumoniae* and other bacterial superinfections were common causes of mortality and morbidity [3]. Recent retrospective studies have suggested that aspergillosis and other fungal infections are underrecognized complications of severe influenza [4, 5]. The extent to which COVID-19 is complicated by bacterial or fungal superinfections is unclear.

Prior to emergence of COVID-19, an estimated 3 million Americans were infected each year with a high-priority antimicrobial-resistant pathogen [6, 7]. Antimicrobial-resistant infections are conservatively estimated to cause 700 000 deaths annually worldwide, a number that is projected to increase to 10 million per year by 2050 [8]. Despite the burden of antimicrobial resistance (AMR), antimicrobial development is in crisis. Five companies (Allergan, The Medicines Company, Achaogen, Melinta, and Tetraphase) that brought new agents to market in the past 3 years have declared bankruptcy or abandoned the field [9]. Several factors constrain the antimicrobial marketplace. Antimicrobials are generally administered for short treatment courses. Older agents remain active against a vast majority of infections. Responsible stewardship practices restrict use of newer agents to antimicrobial-resistant infections in which older drugs are inactive. Overly restrictive stewardship may limit uptake of new antimicrobials in favor of cheaper, less effective alternatives [10, 11]. Many aspects of modern medicine depend upon the ability to prevent and treat infections, but payment models based on per-prescription reimbursement do not capture the societal value of antimicrobials [12]. Without reforms to reimbursement and drug development models, sustainability of the antimicrobial pipeline is uncertain. In confronting COVID-19, it is imperative that medical, public health, policy, and political communities do not lose sight of looming AMR and antimicrobial development crises [2].

In this article, we review the limited published data on bacterial and fungal infections among COVID-19 patients, and offer perspectives on what to expect with superinfections, AMR, and antimicrobial development during the pandemic.

SUPERINFECTIONS AND ANTIMICROBIAL USAGE IN COVID-19: WHAT DO WE KNOW?

As of this writing, no studies have specifically investigated COVID-19 superinfections. Superinfections and antimicrobial (antibacterial, antifungal) usage are presented in a few sentences or within tables of articles, without mention of diagnostic criteria or case definitions. Information from retrospective reports published through 21 April 2020 is summarized in Table 1.

Secondary infections were reported in 5%–27% of adults infected with severe acute respiratory syndrome coronavirus 2

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Table 1. Clinical Reports Mentioning Superinfections and/or Antibiotic Use in Patients With Coronavirus Disease 2019

First Author [Reference]	Site(s)	Patients, No.	Type of Patients	Invasive MV	Antibiotic/ Antifungal Use	Steroid Use	Superinfections	Types of Infection/ Organisms
Huang [13]	Wuhan, 1 hospital	41	Hospitalized 32% in ICU	5%	Abx, 100%	22%	10% (31% in ICU)	NS NS
Chen N [15]	Wuhan, 1 hospital	99	Hospitalized	4%	Abx, 71%AF, 15%	19%	5%	NS MDR *Acinetobacter baumannii, Klebsiella pneumoniae, Aspergillus flavus, Candida albicans, Candida glabrata*
Yang[16]	Wuhan, 1 hospital	52	ICU	42%	Abx, 94%	58%	13.5%	Pneumonia, 9%; pneumonia + BSI, 2%; urinary, 2% KPC–*K. pneumoniae*, ESBL *K. pneumoniae*, ESBL *Pseudomonas aeruginosa, Serratia marcescens, A. fumigatus, Aspergillus flavus, C. albicans*
Guan[a][17]	China, 552 hospitals, 30 provinces	1099	Hospitalized 5% in ICU	2.3%	Abx, 58% (80% of severely ill) AF, 7.5%	19%	NS	NS NS
Zhou[18]	Wuhan, 2 hospitals	191	Hospitalized 26% in ICU	17%	Abx, 95%	30%	15%	NS NS
Wang [19]	Wuhan, 1 hospital	69	Hospitalized	NS	Abx, 98.5% AF, 12%	15%	17% (10% excluding *Candida*)[a]	Positive sputum cultures, no clinical details *Enterobacter cloacae, A. baumannii, C. albicans*
Dong [20]	Wuhan, 3 hospitals	11	Hospitalized	NS	Abx, 27%	27%	9%	Secondary pneumonia Gram-positive cocci and gram-negative rods, not further characterized
Chen T[b][14]	Wuhan, 1 hospital	274[c]	Hospitalized	43%	Abx, 91%	79%	NS	NS NS
Cao[21]	Wuhan, 1 hospital	102	Hospitalized 18% in ICU	14%	Abx, 99%	50%	17%	NS NS
Lian[22]	Zhejiang province, "all hospitals"	788	Hospitalized	1%	NS	13%	None[d]	NS NS
Du Y[23]	Wuhan, 2 hospitals	85	Hospitalized 100% died	21%	Abx, 91% AF, 15%	76.5%	33% (3/9) fungi[e] 0% (0/12) bacteria	NS NS
Chen X[24]	Wuhan, 1 hospital	48	Hospitalized 44% moderate, 56% severe or critically ill	NS	NS	NS	27% fungi[f] 2% bacteria	NS NS
Goyal[25]	NYC, 2 hospitals	393	Hospitalized	33%	NS	12% (25% if MV)	6% (12% if MV)	BSI[g] NS
Lescure[26]	France, 3 hospitals	5	Hospitalized 60% (n = 3), ICU 40% (n = 2), mild	20% (n = 1)	Abx, 20% (n = 1)	None	20% (n = 1)	Secondary pneumonia *A. baumannii, A. flavus*
Arentz[27]	Kirkland, WA, 1 hospital	21	ICU	71%	NS	NS	5% (n = 1)	BSI *P. aeruginosa*
Bhatraju[28]	Seattle, 9 hospital	24	ICU	75%	NS	None	None	NS NS

Studies were identified by a PubMed search conducted through 21 April 2020, using the terms "COVID-19," "novel coronavirus," and "SARS-CoV-2." Studies were included if they were published in English in a peer-reviewed publication, and if they provided data on superinfections or secondary infections, or data on antimicrobial use in hospitalized patients with coronavirus disease 2019.

Abbreviations: Abx, antibiotics; AF, antifungals; BSI, bloodstream infection; ESBL, extended-spectrum β-lactamase; ICU, intensive care unit; KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multidrug-resistant; MV, mechanical ventilation; NS, not stated; NYC, New York City; WA, Washington.

[a]Cultures positive for *Candida* may have represented colonization rather than disease.
[b]Studies did not include information on superinfections. They are included in the table because they are large studies that provide data on antimicrobial use.
[c]Compared 113 deaths with 161 survivors, from a cohort of 799 patients.
[d]Unclear from wording of article if no superinfections were diagnosed in patients receiving corticosteroids, or in the entire cohort.
[e]Sputum culture results. Other patients were not tested. It is unclear if positive cultures represented colonization or disease.
[f]Bacterial and fungal infections were reported in 44% and 4% of severely or critically ill patients, respectively.
[g]Data only provided for BSIs. Other types of superinfection were not mentioned.

(SARS-CoV-2) in several hospitals in Wuhan, China, through mid-February 2020, including 50%–100% of those who died [13, 15, 18, 20, 21, 24]. Secondary infections were identified in 13.5%–44% of intensive care unit (ICU) patients with COVID-19 [16, 20, 24]. The most common type of infection among ICU patients was bacterial or fungal pneumonia; bloodstream and urinary tract infections were also noted. Organisms cultured from patients included pandrug-resistant *Acinetobacter baumannii*, *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae*, extended-spectrum β-lactamase (ESBL)–producing *K. pneumoniae*, ESBL-producing *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Serratia marcescens*, *Aspergillus fumigatus*, *Aspergillus flavus*, *Candida albicans*, and *Candida glabrata* [15, 16, 19]. Median times to ICU admission and onset of secondary infection among patients at 2 hospitals were 10–12 days and 17 days after the first COVID-19 symptoms, respectively [13, 18]. Median time to death was 19 days, suggesting that superinfections were often terminal events. In March 2020 at 2 New York City hospitals, bacteremia was found in 6% and 12% of all COVID-19 patients and mechanically ventilated patients, respectively [25]. In the first European series, 1 of 3 patients with severe COVID-19 in France was diagnosed with secondary *A. baumannii* and *A. flavus* coinfection [26].

In a report from 552 hospitals in 30 Chinese provinces, 58% of patients with COVID-19 were treated with antibiotics [18]. Antibiotics and antifungals were administered to 80%–100% and 7.5%–15%, respectively, of critically ill COVID-19 patients in Chinese ICUs [13, 17, 19–21, 23]. At several Wuhan hospitals, fluoroquinolones, cephalosporins, carbapenems, azithromycin, vancomycin, and linezolid were the most common empiric agents, but details on dosing and treatment courses were lacking [14, 19, 21, 23, 29]. Empiric antimicrobial usage was likely widespread because 25%–70% of severely ill COVID-19 patients manifested evidence of sepsis, and it was very difficult to exclude bacterial or fungal superinfections based on signs and symptoms, physical findings, radiographic abnormalities, and laboratory results [13, 15, 18]. The French patient with severe COVID-19 and aspergillosis was treated with various combinations of meropenem, tigecycline, levofloxacin, aerosolized colistimethate, voriconazole, and/or isavuconazole before dying [26].

In contrast to the data above, studies of COVID-19 in 788 hospitalized patients in Zhejiang Province, China and in 24 patients in Seattle ICUs in January–February 2020 reported that there were no superinfections [22, 28]. In an article on 21 critically ill COVID-19 patients at a Kirkland, Washington hospital, 1 *P. aeruginosa* bloodstream infection was noted [27]. Other COVID-19 cases series did not report information on superinfections [29, 30]. It is unclear if superinfections were not encountered; if data were incomplete, unavailable, or not analyzed; or if information was simply not presented.

Reasons for discrepant findings between studies are unclear. Incidence of superinfections may have been impacted by differing criteria for hospital or ICU admission, overstated by failure to distinguish colonization from disease, or understated by high mortality rates among ICU patients (ranging from 16% to 78%) and insufficient patient follow-up among survivors [13, 16, 18, 27, 29, 30]. Fifty-eight percent of survivors in the Seattle cohort were still mechanically ventilated or in hospital at time of writing and 70% of survivors in the Kirkland hospital remained critically ill, which meant they remained at risk for superinfection. Finally, results may reflect differences in clinical and infection prevention practices. For example, corticosteroids were administered to 25%–80% of seriously ill patients in the Chinese and New York reports [16–19, 22, 25]. In contrast, no patients received corticosteroids in Seattle ICUs. Enhanced infection prevention measures for COVID-19 would be expected to reduce risks of nosocomial infections. In the chaotic first waves of COVID-19 to hit hospitals in disease epicenters, however, it is possible that preventive measures were employed less rigorously than they were later in the pandemic.

There are several plausible explanations for the paucity of data on superinfections. The most immediate priorities for hospitals and healthcare providers have been providing acute medical care, keeping critically ill patients alive, and protecting staff and non–COVID-19 patients, rather than collecting, analyzing, and publishing clinical data. Early publications understandably have focused on describing basic epidemiology, clinical manifestations, and outcomes of COVID-19. Since studies have been retrospective, there were no systematic protocols for collecting sputum, blood, or other samples for microbiologic cultures. Furthermore, diagnostic testing for superinfections was almost certainly constrained by restrictions on procedures such as bronchoscopies or induced sputum collection due to potential for SARS-CoV-2 aerosolization [31]. In general, laboratory and microbiology testing has been minimized in hospitalized patients due to extreme workloads and to protect from exposure to the virus. In addition, culture results may have been blunted by empiric antimicrobial use.

It is plausible that COVID-19 predisposes to superinfections through 2, non–mutually exclusive mechanisms. First, hospitalized patients, especially those who are undergoing mechanical ventilation or otherwise critically ill, are at increased risk for infections, independent of SARS-CoV-2 infection. To date, mechanical ventilation was reported in 21%–88% of ICU patients in COVID-19 series from China, Italy, New York City, and Washington [16, 23, 25, 27, 29, 30]. Second, severe COVID-19 is associated with immune dysregulation, which may create a milieu for bacterial or fungal proliferation [13, 32, 33]. Patients with severe COVID-19 have higher proinflammatory (eg, interleukin [IL] 2, soluble IL-2 receptor, IL-6, tumor necrosis factor–α) and anti-inflammatory (eg, IL-4, IL-10) cytokine levels, fewer CD4 and CD8 cells, and less interferon-γ expression by CD4 cells than those with more moderate disease, which likely contributes to lung pathology [32, 33]. Cytokine release

syndrome, immune exhaustion, and/or lung damage may predispose to superinfection.

SUPERINFECTIONS AND ANTIMICROBIAL USE IN COVID-19: WHAT CAN WE EXPECT?

Present uncertainties about COVID-19 superinfections will be resolved as the pandemic unfolds and greater time and resources are available to publish detailed data based on rigorous case definitions. Bacterial or fungal coinfections are unlikely to be common in patients with mild COVID-19 or in those with more serious disease upon admission to the hospital. It is reasonable to anticipate that superinfections will occur in an appreciable minority of critically ill, hospitalized patients, as risk factors for nosocomial infections such as advanced age, underlying systemic diseases, mechanical ventilation, and prolonged hospital and ICU stays are prominent features of severe disease [14, 29]. Susceptibility to infections may be abetted by immune dysregulation coinciding with acute respiratory distress. The use of corticosteroids, tocilizumab (anti–IL-6 monoclonal antibody) or other immunomodulatory agents for treatment of COVID-19 could have unintended consequences for secondary infections. Adherence to rigorous infection prevention practices will be crucial in limiting nosocomial infections.

Bacterial and fungal pneumonias, especially ventilator-associated pneumonias, will likely be the most common superinfections; patients will also be susceptible to bloodstream and urinary tract infections. Microbiology and AMR patterns are likely to be consistent with institutional ecology. Hospitals and regions with high prevalence of AMR should be prepared for potential upswings in numbers of infections by these pathogens. Early indications are that *Aspergillus* species and other fungi may play prominent roles at certain centers. Broad-spectrum antimicrobial use is likely to be prevalent in critically ill patients, both as empiric and pathogen-directed therapy. Managing antimicrobial usage will be a stewardship challenge. A stewardship issue we have observed is that sample collection for therapeutic drug monitoring may be limited, impacting use of agents like vancomycin. As always, patients receiving antimicrobials should be observed for *Clostridioides difficile* infection and invasive candidiasis. Clinicians, hospitals, microbiology laboratories, and public health organizations must be vigilant in monitoring the potential impact of increased antimicrobial consumption on emergence of resistance in individual patients and at the institutional and regional levels. As the COVID-19 pandemic unfolds, availability of specific antimicrobials may be limited if there are disruptions in global manufacturing or supply chains, especially at possible choke points for raw materials and active pharmaceutical ingredients in China and India, respectively [34]. Local evolution of AMR will occur against the backdrop of larger, ongoing trends, such as the remarkable growth of pandrug-resistant *A. baumannii* and metallo-β-lactamase–producing Enterobacteriaceae in Asia, and ESBL-producing Enterobacteriaceae in the United States (US) [6, 35].

BEFORE COVID-19: ANTIMICROBIAL REIMBURSEMENT AND DEVELOPMENT

COVID-19 has emerged at a crucial time for antimicrobial development. Realizations in the early 2000s that the antibiotic pipeline was inadequate to meet the challenge of AMR prompted public and private investments to support drug development [36, 37]. As a result of these "push" incentives, 15 antimicrobials with activity against top priority, antimicrobial-resistant pathogens gained US Food and Drug Administration (FDA) approval during 2014–2019 [38]. However, most of these agents have had negligible US sales [39]. The pipeline is the most robust it has been in decades, with > 60 agents, including novel biologics, in development against priority bacteria and fungi [40, 41]. At the same time, many pipeline agents have overlapping spectra of activity. For example, 6 antibiotics that are active against carbapenem resistant Enterobacteriaceae (CRE) have been approved since 2015, and there are 9 CRE-active agents in the pipeline. While incremental improvements of pipeline agents over existing antimicrobials may have significant clinical utility [42], economic prospects for these drugs are uncertain. If companies consistently fail and/or the pipeline is not replenished, hard-won gains may be squandered, and next-generation drugs may not be available against future AMR threats. There is a small window of time to rectify the antimicrobial marketplace and development model.

Several proposals for reforming the marketplace and bolstering sustainability of antimicrobial development have been advanced [43, 44]. Details and potential strengths and limitations of various models are listed in Table 2. Reforms have already been enacted by the US Centers for Medicare and Medicaid Services (CMS), as part of their 2020 Final Rule for reimbursing hospitals [45, 46]. These measures were not meant to fix the broken marketplace, but rather to ameliorate financial pressures on hospitals that stem from use of newly approved antimicrobials. Despite their shortcomings, CMS's actions were important federal recognition of a need to address present inadequacies of antimicrobial reimbursement.

Like CMS reforms, most proposals target the existing for-profit, private industry model through "pull" incentives that assure revenue after FDA approval of a drug. Payment to US hospitals by Medicare for care of an individual is made as a bundled disbursement, based on the diagnosis-related group (DRG) classification of the case. Since all services and treatments are subsumed under the DRG, use of higher-cost new antimicrobials in hospitals may be disincentivized. The DISARM (Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms) Act is bipartisan legislation in the US Congress that would codify and extend CMS reforms by carving out designated antimicrobials from the DRG, and reimbursing

Table 2. Models for Reform of Antimicrobial Reimbursement and Sustainable Antimicrobial Development

Type of Model	Model [Reference]	Features	Potential Strengths	Potential Weaknesses
Reimbursement reform	CMS reforms [45, 46]	Final Rule modifications: increase hospital payments for QIDP antimicrobials; waive "substantial clinical improvement" criterion for QIDP antibiotics to be eligible for add-on payments (NTAPs); *ICD-10* codes modified to increase complexity of DRG codes relevant to AMR.	Reforms directly impact hospital reimbursement for use of new antibiotics active against AMR pathogens. CMS require hospitals to implement stewardship programs. CMS reforms do not require Congressional legislation.	Add-on payments (NTAPs) last only 3 years and do not cover full cost of drugs. NTAP applications are burdensome, and prior to CMS reforms, many hospitals did seek add-on payments. Reimbursement tied to per-unit use of antibiotic (no de-linkage).
	DISARM Act [45]	Bipartisan bill in US Congress would codify and extend CMS reforms by carving out QIDP antimicrobials from DRG, and reimbursing hospitals for use at or slightly above cost.	Reforms directly impact reimbursement for use of new antimicrobials active against AMR pathogens in all hospitalized patients. Bill requires hospitals to run stewardship programs and to report on antimicrobial usage. Potentially gives immediate boost to small companies, which may stave off imminent failures.	No de-linkage of payments. Even with DISARM, US market for drugs against many AMR pathogens is too small to support more than a few new agents. For sustainability in mid- to long-term, this model likely would need to be coupled with another reform. Requires Congressional approval. DRG carve-outs for antibiotics may create unwelcome precedent for other drugs. Removed from final version of CARES Act passed by Congress in March 2020.
Transfer of intellectual property rights	Market exclusivity voucher [44]	Companies with FDA approval of specific novel antibiotics receive 12-month market exclusivity extension voucher, which could be used for existing brand name drug or sold.	Precedent for TIPR models over 3 decades in many types of drug development. Does not require spending line item by Congress.	Societal costs of delaying genericization of expensive drugs. Financial reward is not linked to societal benefit. Financially inefficient, compared to direct award to antibiotic developers. REVAMP Act proposing this model did not pass Congress in 2018.
Market entry reward	Fully de-linked MER [43]	Direct prize awarded to companies that introduce a priority antimicrobial, which can be given as series of payments and serve as main revenue stream.	Provides predictable revenue to companies. Units sold at contractually agreed-upon price with conditions on stewardship, access, and transparency.	Necessary payments likely to be > $1 billion per drug. Financially unsustainable without accompanying method of revenue generation, such as tax on existing generics.
	Partially de-linked MER [43]	Direct prize with smaller awards than fully delinked model, designed to augment revenue especially as antimicrobial establishes market.	Provides predictable revenue to companies. Can work within existing reimbursement models. Market disruptions are lower than fully de-linked MER or exclusivity voucher models. Can still have conditions attached.	Companies will need to generate sustainable revenue stream based on unit sales.
Government procurement	Subscription ("Netflix") [9, 43, 46]	Governments pay companies guaranteed revenue per year (subscription fee) to ensure access to certain quantity of an antibiotic within a defined time period. Antibiotic pilots initiated in UK and Sweden; hepatitis C program in Louisiana. PASTEUR Act supporting US subscription model drafted in Congress, April 2020.	De-linkage model. Provides predictable revenue to companies. Countries could pay for their "fair share" of antimicrobial development, as part of global or G20 initiative. Can be structured to help support sustainable R&D (as in UK), as well as assure access to drugs in event of need.	UK will implement roll-out with only 2 agents. Sweden's model includes any antibiotic meeting qualification standards, but is not designed to stimulate R&D. Will need time to ramp up, and validation in pilot projects.
	National stockpile [47]	Government purchases stockpile of agent(s) that might be necessary if AMR pathogen becomes widely disseminated.	De-linkage model. Provides revenue to companies who have invested in producing antimicrobials against high-priority pathogens. BARDA has precedent with purchasing bioterrorism antibiotics.	Need criteria for assessing risks and prioritizing antibiotics. Need decision-making body. BARDA and other government bodies also support drug development, creating potential conflicts of interest in selecting stockpile agents.
Pharmaceutical industry mandates	"Pay to play" [9, 46]	Large pharmaceutical companies would be required to engage in antimicrobial development or pay fine that could be applied to support antimicrobial development initiatives.	Acknowledges societal value of antimicrobials, and central role in modern medicine of preventing and treating infection.	Potential for gaming by companies, with token antimicrobial development programs enacted in lieu of paying fine. Concept has been politically unpalatable in the US.
Noncommercial	Nonprofit research and development [48]	Nonprofit entity(ies) would discover and develop agents against high-priority pathogens, modeled after programs for TB and malaria.	Removes pressure to maximize return to investors or profit. Can complement, rather than replace, for-profit model.	No more likely than for-profits to successfully develop agents or pick winners. Concerns about numbers of new agents and innovation if for-profit companies are displaced. Antibiotic model must address multiple pathogens, unlike TB or malaria models. Even without profit imperative, entities still need to generate some revenue and face substantial fixed pre- and postapproval costs.

Abbreviations: AMR, antimicrobial resistant/resistance; BARDA, United States Biomedical Advanced Research and Development Authority; CARES, Coronavirus Aid, Relief and Economic Security Act; CMS, United States Centers for Medicare and Medicaid Services; DISARM, Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms Act; DRG, diagnosis-related group; FDA, United States Food and Drug Administration; G20, Group of 20; *ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; MER, market entry reward; NTAP, new technology add-on payment; PASTEUR, Pioneering Antimicrobial Subscriptions to End Upsurging Resistance; QIDP, qualified infectious diseases product; R&D, research and development; REVAMP, Re-Valuing Anti-Microbial Products Act; TB, tuberculosis; TIPR, transfer of intellectual property rights; UK, United Kingdom; US, United States.

hospitals for use of these drugs at or slightly above cost [45]. DISARM sets stewardship criteria for hospitals and mandates reporting of data on antimicrobial use. For both CMS reforms and DISARM, reimbursement is still linked to per-unit drug use, which creates tension between tying revenue to prescription volume and responsible stewardship. Moreover, these reforms do not address the biggest challenge in the market, which is that numbers of antimicrobial-resistant infections requiring a new drug are currently insufficient in the US to support more than a few agents. For example, we estimated that the annual US market for new anti-CRE drugs is only approximately $300 million, even with full reimbursement [10, 45]. Other models propose to de-link revenue from use, thereby attempting to compensate the societal or insurance value of antibiotics against antimicrobial-resistant pathogens [12]. De-linkage models are often described using a fire extinguisher analogy: You pay for a fire extinguisher in case you need it, rather than trying to find or manufacture one after a fire starts [9, 46]. The costs of these models are paid upfront, which may present challenges in securing funding.

An alternative model proposes that a nonprofit entity or entities, funded by government and/or foundation seed grants, replace or operate alongside entrepreneurial companies [48]. Reducing the need to maximize revenue may lower drug costs. A nonprofit model would be less able to leverage financial resources of investment markets, which would almost certainly mean fewer products reaching the clinic and may lessen innovation. A counterargument is that there are already too many drugs in certain spaces, such as anti-CRE and anti–methicillin-resistant *Staphylococcus aureus* agents. Nonprofits have developed tuberculosis and malaria drugs, but their ability to sustain a successful pipeline against multiple pathogens and to respond to newly emergent threats is unproven. In addition to drug discovery and development expenses, nonprofits that brought a new agent to market themselves would face formidable postapproval costs for manufacturing, regulatory compliance, and pharmacovigilance (at least $350 million over the first 10 years) [49]. Failure to enact antimicrobial reimbursement reforms may lead to a nonprofit model by default.

COVID-19 AND ANTIMICROBIAL DEVELOPMENT: WHAT CAN WE EXPECT?

Medical and economic devastation wrought by COVID-19 has drawn much-needed attention to threats posed by emergent infections and the importance of investing in public health. Within policy discussions and debates on these issues, there is unprecedented opportunity to also reconsider AMR and antimicrobial development. Prior to COVID-19, there was steadily growing appreciation of the importance of these issues by governments and policy groups. The US Congress passed the first pull incentive in 2012. The GAIN (Generating Antibiotic Incentives Now) Act granted 5 years of additional market exclusivity for new antibiotics, but its impact was undermined by the unprofitability of these drugs [43]. New market exclusivity legislation, the REVAMP (Re-Valuing Anti-Microbial Products) Act, failed to pass Congress in 2018. REVAMP proposed a 12-month exclusivity extension for any brand-name drug, if a company brought a novel antibiotic to approval. DISARM has circulated for 2 years in the current Congress, and it was included in the original Senate version of the CARES (Coronavirus Aid, Relief and Economic Security) Act that was drafted in response to COVID-19. The bill was removed, however, from the final $2.3 trillion legislation passed by Congress and a $500 billion relief package that followed.

At least 1 other large COVID-19 relief bill will likely be considered by Congress. Groups endorsing antibiotic reform are advocating for DISARM or an antibiotic subscription model, along the lines of programs being piloted in the United Kingdom and Sweden [9, 46]. Details of the PASTEUR (Pioneering Antimicrobial Subscriptions to End Upsurging Resistance) Act were being finalized as this manuscript was written. Since subscription models propose that government pays companies a fee to ensure unfettered access to specified antibiotics in event of need, the legislation may fit within broader calls for investment in infectious diseases and public health preparedness in the aftermath of COVID-19. However, given competition between funding priorities and the scale of economic disruption imposed by the pandemic, prospects for enacting antimicrobial market reform are uncertain.

If DISARM or PASTEUR are not included in comprehensive COVID-19 response legislation, the issues of AMR and antimicrobial development will likely not be considered again until the new US Congress in 2021. In the interim, legislative priorities will be impacted by the course of COVID-19 and the November 2020 US elections. Another year without some reform to the marketplace will undoubtedly lead to more companies failing, and to further chilling of investor enthusiasm for new antibiotic development. As time passes, more drastic measures may be needed to salvage antibiotic development even as AMR increases.

CONCLUSIONS

As the COVID-19 pandemic proceeds, prospective studies are needed to systematically collect epidemiologic, clinical, microbiologic and AMR data on superinfections. Particular attention should be paid to high-risk patient populations, such as transplant recipients and other immunosuppressed hosts. The linking of immune profiling data from COVID-19 patients with infections is also a priority. Results from carefully designed studies early in the pandemic can be used to inform rational antimicrobial treatment and stewardship strategies, and to develop diagnostic criteria for superinfections. Furthermore, accurate information on antimicrobial usage and AMR over the duration of the pandemic can guide future efforts at market and drug development reform.

Notes

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