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ISSUE BRIEF
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Trends in Antimicrobial Drug Prescribing During the COVID-19 Pandemic

KEY POINTS

- COVID-19 has impacted antimicrobial drug prescribing both directly, through COVID-19 treatment, and indirectly, through the reduced spread of illnesses for which antimicrobial drugs are commonly prescribed.
- Overall, antimicrobial drug prescriptions declined significantly during the COVID-19 pandemic, with the largest reductions in May and June 2020 relative to 2019 prescription levels.
- Prescriptions for azithromycin and ceftriaxone in long-term care facilities increased 63% and 25%, respectively, in April 2020 relative April 2019. After this early peak, these drugs were prescribed at rates comparable to 2019 levels through the remainder of 2020.
- Monthly prescriptions for antimicrobial drugs have slowly increased since their lowest point in 2020, and as of June 2021, have reached pre-pandemic levels.

INTRODUCTION

The COVID-19 pandemic disrupted healthcare in the U.S. in an unprecedented way. In the early months of the pandemic, effective treatments for COVID-19 were not known, and healthcare workers and researchers were still learning about the progression of the disease. Strategies that had been effective for other respiratory illnesses were repurposed to treat COVID-19 patients, including empiric treatment with antimicrobial[1] drugs.[2] At the same time, people began working from home, children stayed home from school, and many people limited their movements outside of the home to limit the spread of COVID-19. These behavioral changes, as well as other mitigation strategies such as mask wearing, reduced the spread of influenza and other respiratory viruses.[3,4,5] Use of telemedicine increased dramatically and in-person doctor visits declined.[6,7] All of these

[1] The term "antimicrobial" in this brief refers to drugs with antibacterial and/or antifungal properties.
[2] IDSA. Co-infection and antimicrobial stewardship. Available at: https://www.idsociety.org/covid-19-real-time-learning-network/disease-manifestations--complications/co-infection-and-Antimicrobial-Stewardship/, last accessed August 25, 2021.
[3] Olsen, S., Azziz-Baumgartner, E., Budd, A., Brammer, L., Sullivan, S., Pineda, R., Cohen, C., Fry, A. (2020). Decreased influenza activity during the COVID-19 pandemic – United States, Australia, Chile, and South Africa, 2020. *MMWR Morb Mortal Wkly Rep 69*: 1305-1309. doi: 10.15585/mmwr.mm6937a6
[4] Nolen, L., Seeman, S., Bruden, D., Klejka, J., Desnoyer, C., Tiesinga, J., Singleton, R. (2021). Impact of social distancing and travel restrictions on non-coronavirus disease 2019 (non-COVID-19) respiratory hospital admissions in young children in rural Alaska. *Clinical Infectious Diseases 72*(12): 2196-2198. doi: 10.1093/cid/ciaa1328
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[6] Patel, S., Mehrotra, A., Huskamp, H., Uscher-Pines, L., Ganguli, I., Barnett, M. (2021). Variation in telemedicine use and outpatient care during the COVID-19 pandemic in the United States. *Health Affairs 40*(2): 349-358. doi: 10.1377/hlthaff.2020.01786
[7] Tarazi W, Ruhter J, Bosworth A, Sheingold S, and De Lew N. (2021). The Impact of the COVID-19 Pandemic on Medicare FFS Beneficiary Utilization and Provider Payments: FFS Data for 2020 (Issue Brief No. HP-2021-13). Washington, DC: Office of the Assistant Secretary for

disruptions have had potential impacts on antimicrobial drug prescribing. For COVID-19 patients, numerous reports have identified potential over-prescribing of antimicrobial drugs, particularly in the early months of the pandemic when no treatments were available and the incidence of bacterial or fungal co-infection was unknown.[8,9] There were also concerns that increased use of telemedicine might increase inappropriate antimicrobial drug prescribing.[10,11] Conversely, reduced activity outside the home and resulting reduction in other illnesses may have simultaneously reduced antimicrobial drug prescribing in the outpatient setting.[12] Overuse of antimicrobial drugs can lead to the development of antimicrobial resistance, which is a significant public health threat leading to nearly 3 million infections and 35,000 deaths each year in the United States.[13]

This brief uses prescription claims data to explore trends in antimicrobial prescriptions dispensed from retail pharmacies as well as in long-term care facilities from 2019 to 2021, with the goal of understanding trends in antimicrobial prescribing during various phases of the COVID-19 pandemic and across different prescribing settings.

METHODS

This analysis was conducted using data from IQVIA's National Prescription Audit (NPA). The NPA dataset includes prescriptions dispensed through retail pharmacies (chain, independent, and food store pharmacies), mail service pharmacies, and long-term care facilities. The long-term care dataset encompasses nursing homes with in-house pharmacies, nursing home provider organizations and other pharmacies that serve a mixture of retail, nursing home and other institutional, long-term care patients. The final dataset included monthly prescriptions for antimicrobial drugs between January 2019 and June 2021.

Antimicrobial drugs were defined for the purpose of this analysis as any antibacterial or antifungal drug reported to the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) through the Antimicrobial Use option.[14] Antimicrobial drugs were further grouped by antimicrobial class, as defined by NHSN. Prescriptions for a given antimicrobial drug were summed across all product formulations and strengths. To evaluate trends in antimicrobial prescribing during the COVID-19 pandemic, total monthly prescriptions were compared to 2019 monthly totals.

Planning and Evaluation, U.S. Department of Health and Human Services. Available at: https://aspe.hhs.gov/reports/covid-19-medicare-ffs-utilization-payment, last accessed September 15, 2021.

[8] Russell, C., Fairfield, C., Drake, T., Turtle, L., Seaton, R., Wootton, D., *et al.* (2021). Co-infections, secondary infections, and antimicrobial use in patients hospitalised with COVID-19 during the first pandemic wave from the ISARIC WHO CCP-UK study: a multicentre, prospective cohort study. *The Lancet Microbe 2*(8), E354-E365. doi: 10.1016/S2666-5247(21)00090-2

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[12] Lepak, A., Taylor, L., Stone, C., Schulz, L., Anderson, M., Fox, B., Temte, J. (2021). Association of changes in seasonal respiratory virus activity and ambulatory antibiotic prescriptions with the COVID-19 pandemic. *JAMA Internal Medicine.* doi: 10.1001/jamainternmed.2021.2621

[13] CDC. Antibiotic resistance threats in the United States, 2019. Available at: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf, last accessed August 27, 2021.

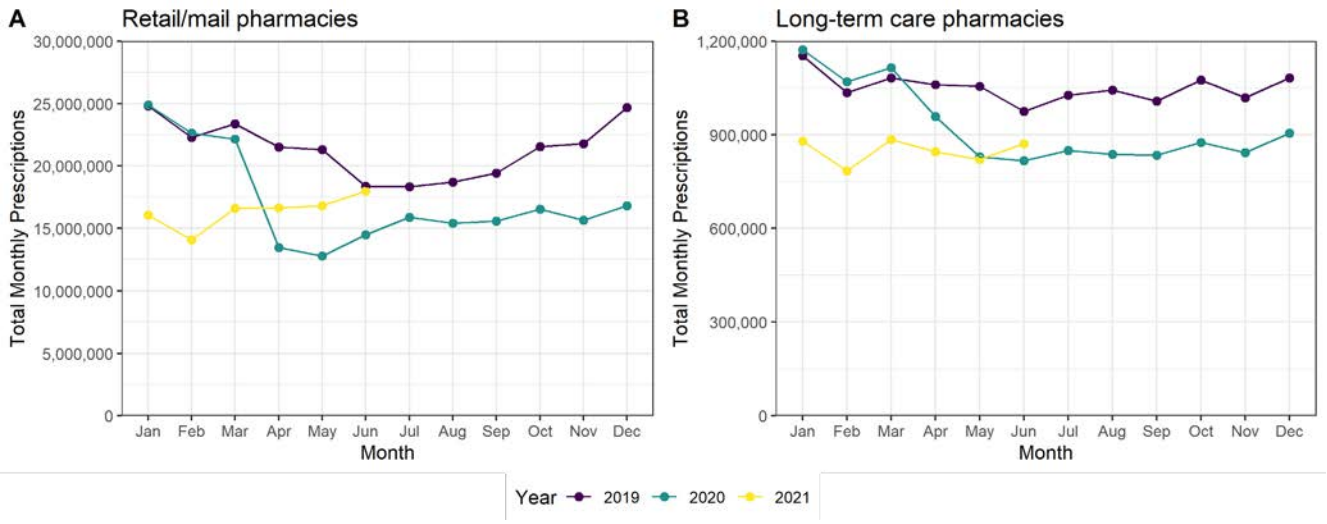
[14] CDC. National Healthcare Safety Network (NHSN): Antimicrobial Use and Resistance (AUR) Options. Available at: https://www.cdc.gov/nhsn/psc/aur/index.html, last accessed August 23, 2021. The list of eligible antimicrobials was last updated January 2021.

RESULTS

Overall trends in monthly antimicrobial prescriptions

Prescriptions for all antimicrobial drugs included in this study declined significantly during the COVID-19 pandemic (Figure 1). Across retail and mail settings, prescriptions for antimicrobial drugs were approximately 40% lower in April and May 2020 relative to the prior year (Figure 1A). Although total prescriptions increased slightly by July 2020, total monthly prescriptions remained well below 2019 levels until June 2021. Similar trends were observed in the long-term care setting, although the decline was smaller relative to 2019 prescribing levels (Figure 1B). In the long-term care setting, there was a modest decline in prescriptions for antimicrobials in April 2020 relative to April 2019 (-9.7%), followed by a larger decline in May 2020 relative to May 2019 (-21.5%). Since May 2020, antimicrobial prescriptions in the long-term care setting have remained 10-20% lower than 2019 levels. Of note, occupancy levels in nursing homes have declined slightly during the pandemic, which could have partly contributed to fewer prescriptions. Our results, however, are consistent with other studies that account for seasonal variability in antibiotic prescribing and declines in nursing home occupancy.[15]

Figure 1: Total Antimicrobial Drug Prescriptions from Retail/Mail and Long-Term Care Pharmacies



Notes: Points represent the total prescriptions per month for any antimicrobial drug, dispensed from a retail or mail pharmacy (A) or in the long-term care setting (B).
Source: IQVIA National Prescription Audit.

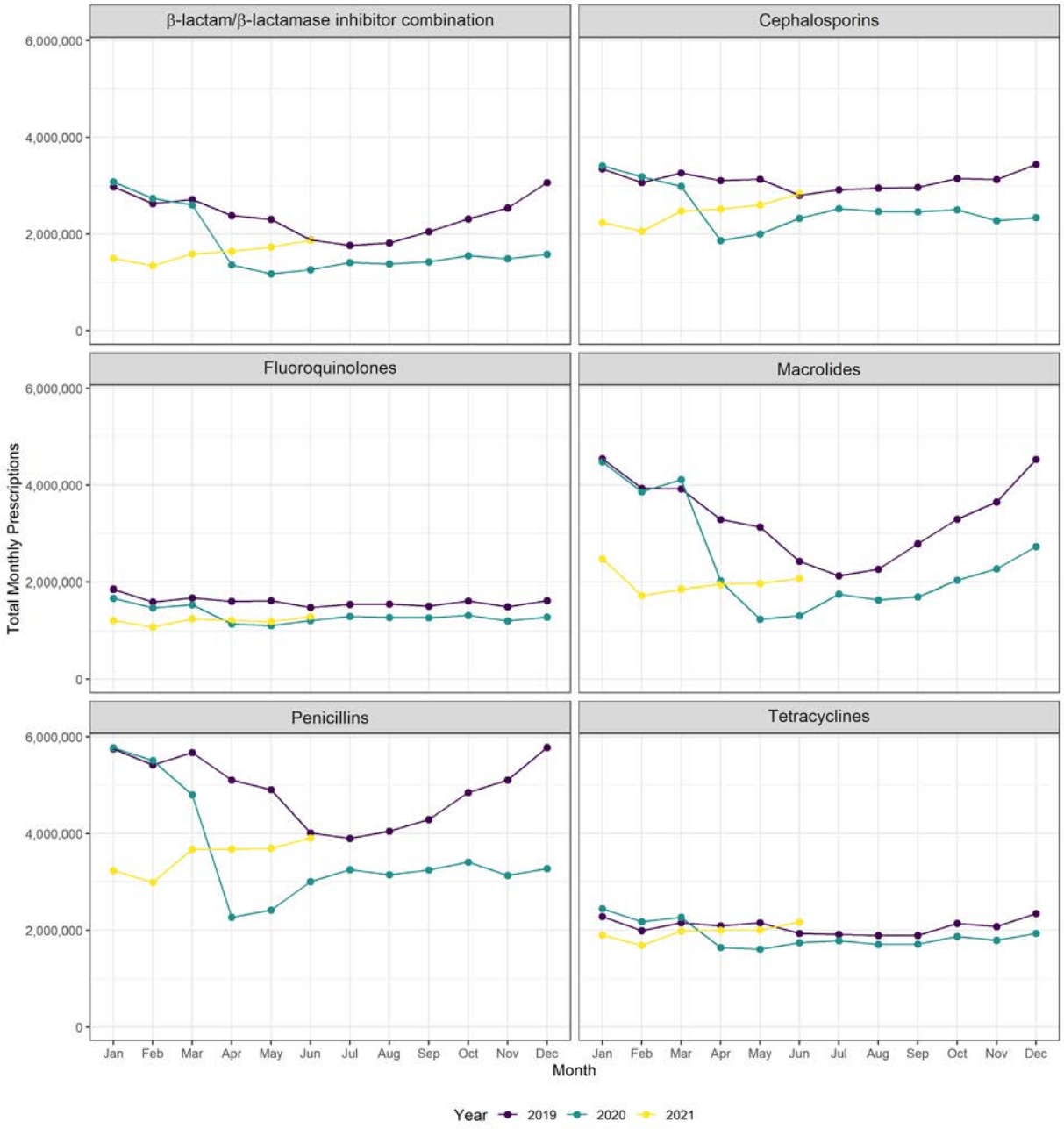
Antimicrobial prescription trends from retail/mail pharmacies

Among the most commonly prescribed antimicrobial drug classes, the largest changes relative to 2019 prescription levels were observed in penicillins and macrolides (Figure 2). Penicillins include drugs such as amoxicillin and ampicillin, whereas macrolides include azithromycin, clarithromycin, and erythromycin. Macrolide prescriptions reached their lowest level relative to 2019 in May 2020 (-60%), and have remained consistently lower than 2019 levels. Prescriptions for macrolides only modestly increased to follow the

[15] Gouin, K., Creasy, S., Beckerson, M., Wdowicki, M., Hicks, L., Lind, J., Geller, A., Budnitz, D., Kabbani, S. (2021). Trends in Prescribing of Antibiotics and Drugs Investigated for Coronavirus Disease 2019 (COVID-19) Treatment in US Nursing Home Residents During the COVID-19 Pandemic. *Clinical Infectious Diseases.* doi: 10.1093/cid/ciab225

seasonal trends in prescribing. Similarly, penicillin prescriptions reached their lowest level relative to 2019 in April 2020 (-55%), and a seasonal uptick in prescriptions was not observed in late 2020. However, penicillin prescriptions have slowly increased in 2021, and have now reached comparable levels to 2019 prescriptions. Similar, but less pronounced, trends were observed for the other 4 major antimicrobial classes. In general, seasonal trends were muted in late 2020, but increases in prescribing were observed for all antimicrobial classes such that June 2021 prescriptions reached pre-pandemic levels. There were no antimicrobial drugs dispensed from retail/mail pharmacies with a notable increase in prescriptions in the early months of the COVID-19 pandemic.

Figure 2: Monthly Prescriptions from Retail/Mail Pharmacies by Antimicrobial Drug Class

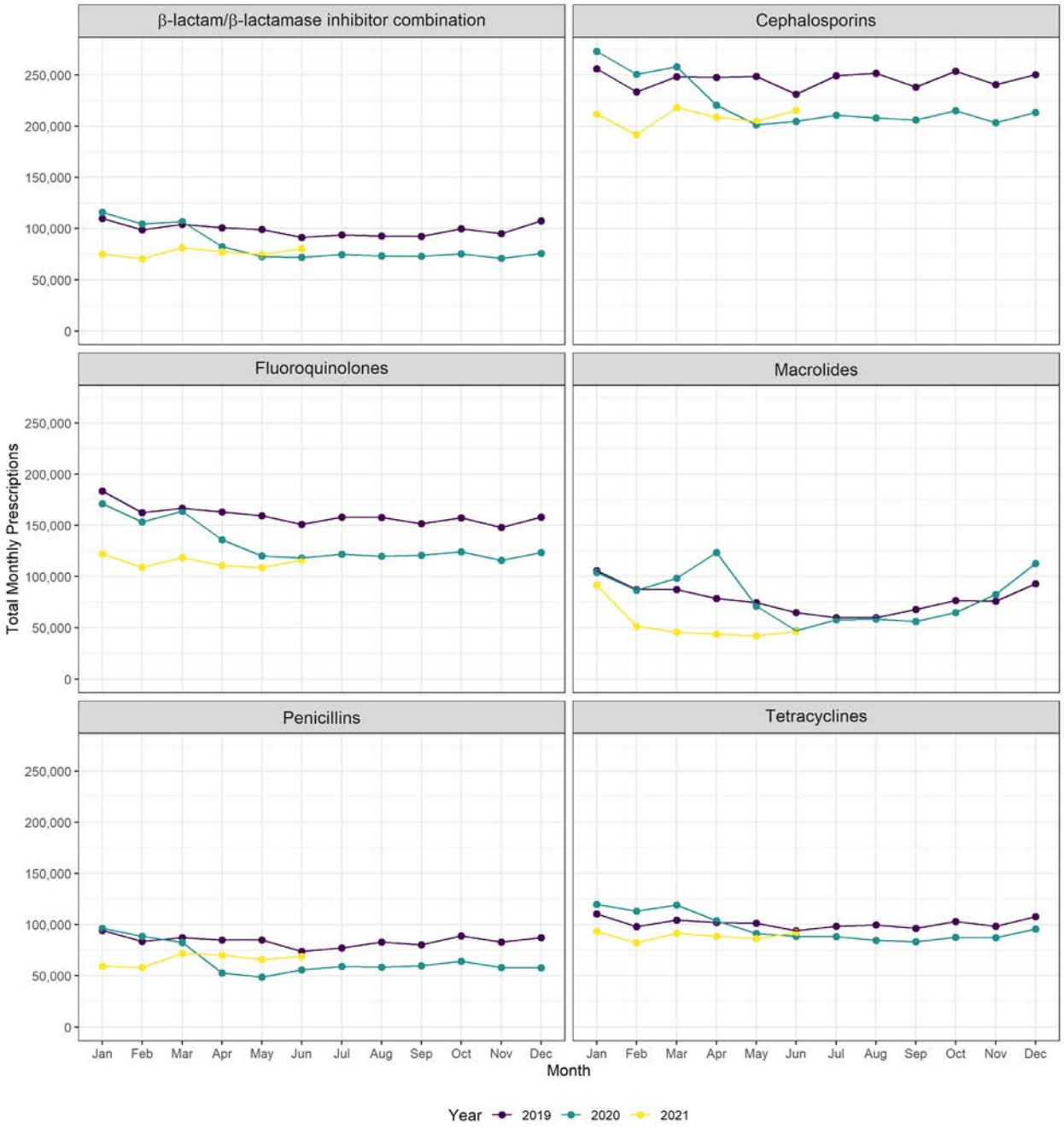


Notes: Antimicrobial drug classes were defined according to the National Healthcare Safety Network's list of antimicrobial drugs. This figure represents the six antimicrobial drug classes with the most prescriptions from 2019-2021. Points represent the total number of prescriptions for any drug in a given antimicrobial drug class.
Source: IQVIA National Prescription Audit.

Antimicrobial prescription trends in the long-term care setting

Although these antimicrobial drug classes showed similar trends in the long-term care setting, overall declines tended to be smaller, particularly in the early months of the pandemic (Figure 3). Unlike prescriptions dispensed from retail/mail pharmacies, not all antimicrobial drug classes declined in the early months of the COVID-19 pandemic: there was a 57% increase in macrolide prescribing in April 2020. Prescriptions for some classes reached 2019 levels by June 2021; notably, prescriptions for fluoroquinolones have consistently remained 20-30% lower than 2019 levels since May 2020.

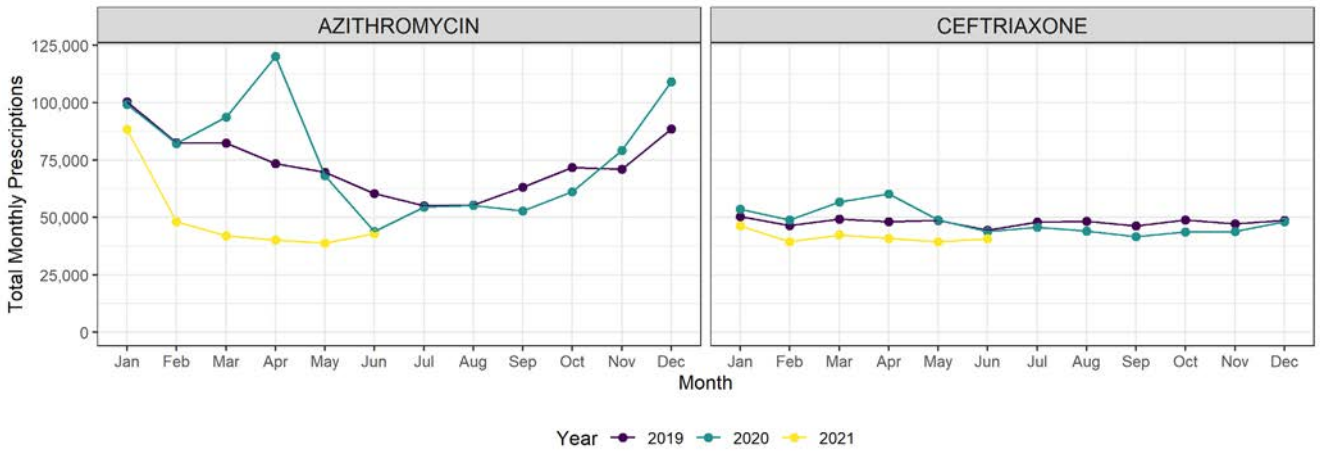
Figure 3: Monthly Prescriptions from Long-Term Care Settings by Antimicrobial Drug Class



Notes: Antimicrobial drug classes were defined according to the National Healthcare Safety Network's list of antimicrobial drugs. Points represent the total number of prescriptions for any drug in a given antimicrobial drug class.
Source: IQVIA National Prescription Audit.

Further exploration of these trends revealed increases in prescriptions for two antimicrobial drugs (Figure 4). Both of these drugs are commonly prescribed for respiratory infections and were also identified in a recent study as the mostly commonly prescribed antimicrobials for COVID-19 patients.[16] Azithromycin prescriptions were 14% and 63% higher than 2019 levels in March and April 2020, respectively. Similarly, ceftriaxone prescriptions were 15% and 25% higher than 2019 levels in March and April 2020, respectively. No other antimicrobial drugs increased significantly in the long-term care setting during the early months of the COVID-19 pandemic. Prescriptions for both azithromycin and ceftriaxone declined in the first half of 2021 and have remained below 2019 levels.

Figure 4: Antimicrobials with Increased Prescriptions in the Long-Term Care Setting during COVID-19



Notes: Points represent the total number of prescriptions for azithromycin or ceftriaxone, regardless of formulation or dosage.
Source: IQVIA National Prescription Audit

DISCUSSION

The COVID-19 pandemic, and its wide-ranging impacts on the healthcare system and health behaviors of individuals, relates to a variety of changes on antimicrobial drug prescribing. Our results show a net decline in antimicrobial prescriptions during the COVID-19 pandemic, with the sharpest drop corresponding to March through May 2020. Seasonal trends in antimicrobial prescribing were muted, or in some cases, eliminated almost entirely. However, prescriptions have slowly increased, and are now very close to 2019 levels. This likely reflects the lifting of many mitigation strategies that were in place due to COVID-19, such as mask mandates, school closures, and stay-at-home orders, as more of the general population became vaccinated against COVID-19. As people resume normal activities, there are greater opportunities for bacterial infections to develop and spread.

Several studies have found that antimicrobial drugs were commonly prescribed for COVID-19 patients, despite

[16] The Pew Charitable Trusts. Could Efforts to Fight the Coronavirus Lead to Overuse of Antibiotics? Available at: https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/03/could-efforts-to-fight-the-coronavirus-lead-to-overuse-of-antibiotics, last accessed August 23, 2021.

a lack of empirical evidence for their use.[17] A meta-analysis showed that approximately 75% of COVID-19 patients worldwide received antimicrobial drugs, despite estimated rates of bacterial co-infection of 8.6%.[18] This was particularly common during the earliest months of the pandemic, when it was unknown what treatments might be effective, or whether secondary infections with bacteria or fungi would be common in patients with COVID-19. Prescribing of azithromycin increased following a small, non-randomized study that identified azithromycin, coupled with hydroxychloroquine, as an effective treatment for COVID-19.[19] However, subsequent studies found no benefit of azithromycin alone or in conjunction with hydroxychloroquine.[20,21] Outbreaks of drug-resistant bacteria and fungi have occurred in facilities treating COVID-19 patients,[22,23] which may be linked to inappropriate antimicrobial prescribing.[24]

Antimicrobial use is a particular challenge in long-term care settings. Antimicrobials are commonly prescribed in long-term care facilities, but inappropriate or unnecessary prescribing is estimated to make up 40-75% of antimicrobials prescribed in long-term care settings.[25] Overprescribing of antimicrobials poses risks to individual patients, through potential adverse events, colonization by *Clostridioides difficile*, and development of drug resistance; in turn, the emergence of new drug-resistant strains can have impacts on others in the facility or the population at-large. Long-term care facilities were also disproportionately affected by early outbreaks of COVID-19.[26] Although our data do not definitively link the increase in antimicrobial use to treatment of COVID-19, our findings align with other studies that have found increased use of azithromycin and ceftriaxone in COVID-19 patients.[27,28] Encouragingly, our study does not show sustained elevated prescribing for antimicrobials, which reflects how treatment practice evolved as the medical community

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[17] Russell, C., Fairfield, C., Drake, T., Turtle, L., Seaton, R., Wootton, D., *et al.* (2021). Co-infections, secondary infections, and antimicrobial use in patients hospitalised with COVID-19 during the first pandemic wave from the ISARIC WHO CCP-UK study: a multicentre, prospective cohort study. *The Lancet Microbe 2*(8), E354-E365. doi: 10.1016/S2666-5247(21)00090-2

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[23] Prestel, C., Anderson, E., Forsberg, K., Lyman, M., de Perio, M., Kuhar, D., Edwards, K., Rivera, M., Shugart, A., Walters, M., Dotson, N. (2021). *Candida auris* outbreak in a COVID-19 specialty care unit – Florida, July-August 2020. *MMWR Morb Mortal Wkly Rep 70*: 56-57. doi: 10.15585/mmwr.mm7002e3

[24] Patel, A., Emerick, M., Cabunoc, M., Williams, M., Preas, M., Schrank, G., Rabinowitz, R., Luethy, P., Johnson, J., Leekha, S. (2021). Rapid spread and control of multidrug-resistant gram-negative bacteria in COVID-19 patient care units. *Emerging Infectious Diseases 27*(4): 1234-1237. doi: 10.3201/eid2704.204036

[25] CDC. Core Elements of Antibiotic Stewardship for Nursing Homes. Available at: https://www.cdc.gov/longtermcare/prevention/antibiotic-stewardship.html, last accessed August 24, 2021.

[26] McMichael, T., Clark, S., Pogosjans, S., *et al.* (2020). COVID-19 in a long-term care facility – King County, Washington, February 27-March 9, 2020. *MMWR Morb Mortal Wkly Rep 69*: 339-342. doi: 10.15585/mmwr.mm6912e1

[27] The Pew Charitable Trusts. Could efforts to fight the coronavirus lead to overuse of antibiotics? Available at: https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/03/could-efforts-to-fight-the-coronavirus-lead-to-overuse-of-antibiotics, last accessed August 25, 2021.

[28] CDC. COVID-19 and Antibiotic Resistance. Available at: https://www.cdc.gov/drugresistance/covid19.html, last accessed August 25, 2021.

learned more about COVID-19. However, the observation that azithromycin and ceftriaxone remain at levels similar to 2019, while other antimicrobials were prescribed at much lower levels than 2019, suggests that some amount of these antimicrobials may have continued to be prescribed for treatment of COVID-19 in long-term care facilities. Importantly, other antimicrobials that are commonly prescribed in the long-term care setting, such as fluoroquinolones, stabilized well below 2019 levels and unlike the trends in the retail setting, have not returned to their pre-pandemic levels. Future work should explore whether there are any lessons to be learned about infection prevention and control in the long-term care setting that might be helpful in reducing antimicrobial use. For example, a recent study found significant reductions in inappropriate azithromycin prescribing for COVID-19 patients after implementing a multispecialty clinical guidance team.[29]

CONCLUSION

The long-term impacts of COVID-19 on antimicrobial resistance are not yet fully understood. The effects appear to be mixed, due to increased use of certain antimicrobials in COVID-19 patients but decreased use of antimicrobials in the outpatient setting. Nevertheless, these changes to antimicrobial prescribing represent an opportunity to identify and learn from practices that may have reduced unnecessary antimicrobial prescribing, particularly in the long-term care setting. Future work should explore these trends further, including specifically in COVID-19 patients, as well as by sub-national geographies and diverse patient populations.

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