Trends in antibiotic use before and during the coronavirus disease 2019 (COVID-19) pandemic across an integrated health system with different antimicrobial stewardship program models trends in antibiotic use by ASP model

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Abstract
Changes in antimicrobial use during the pandemic in relation to long-term trends in utilization among different antimicrobial stewardship program models have not been fully characterized. We analyzed data from an integrated health system using joinpoint regression and found temporal fluctuations in prescribing as well as continuation of existing trends. (Received 1 December 2021; accepted 25 February 2022)

Methods
This study was conducted at 12 hospitals that are part of an inte- grated health system in Iowa. Data for antibiotic days of therapy (DOT) and days present were extracted from a centralized database. Only medical–surgical and intensive care units (ICUs) were included. The antibiotics most frequently prescribed at our facilities were selected for analysis: meropenem, piperacillin–tazobactam, cefepime, ceftriaxone, vancomycin, azithromycin, doxycycline, and levofloxacin. None of the antibiotics included are subject to preauthorization. We collected data from January 1, 2019, to February 28, 2021, which encompasses a period prior to the widespread availability of vaccines and preceding the circulation of the δ (delta) and δ (omicron) variants. The prepandemic period was defined as January 1, 2019, to February 29, 2020, and the pandemic period was defined as March 1, 2020, to February 28, 2021. During the first year of the pandemic, the state of Iowa experienced 2 significant increases in community spread with commensurate increase in hospitalizations for COVID-19. The first peak occurred in early May 2020 (peak number of patients hospitalized, 417) and the second peak occurred in mid-November 2020 (peak number of patients hospitalized, 1,510).

Antimicrobial stewardship program models
The daily antimicrobial stewardship activities and the composition of the staff performing them varied by site. Stewardship activities remained unchanged throughout the study period. The...
characteristics of the hospitals supported by each ASP model, as well as the ASP members and workflow are described in Table 1.

**Statistical analysis**

We examined the trends in antibiotic DOT per 1,000 days present among the 3 different ASP models. We used jointpoint regression to determine the number of joinpoints, the monthly percentage changes (MPCs), and the average monthly percent changes (AMPCs). The joinpoints are points at which the trend changes. The MPC characterizes changes in trends in antibiotic DOT rates occurring at any point during the entire observation period. The AMPC summarizes the trend over prespecified fixed intervals, which in our study were the prepandemic period (January 2019–February 2020) and the pandemic period (March 2020–February 2021). Models were fit to log-transformed antibiotic DOT rates, and permutation analysis was used to select the best-fit model. An autocorrelated error structure was selected to account for autoregression in prescribing rates over time. Analyses were conducted on the Joinpoint Regression Program version 4.7 software (National Cancer Institute, Bethesda, MD).

**Results**

**Facilities using antimicrobial stewardship model A**

In these facilities, estimates of the MPC for the entire observation period showed significant changes in trend of use of piperacillin–tazobactam, ceftriaxone, azithromycin, and doxycycline (Table 2, Supplementary Figs 1B, 1D, 1F, and 1G). During the prepandemic period, AMPC estimates showed monthly increases in the use of ceftriaxone, piperacillin–tazobactam, and vancomycin, and a decrease in azithromycin use (Table 2 and Supplementary Fig. 2C and 2F). For the prepandemic period, AMPC estimates showed monthly increases in the use of meropenem, cefepime, ceftriaxone, vancomycin, and azithromycin, and a decrease in levofloxacin use (Supplementary Table 1). For the pandemic period, AMPCs showed monthly increases in the use of meropenem, ceftriaxone and vancomycin, and a decrease in levofloxacin use (Supplementary Table 1). The AMPCs for meropenem (+2.3; 95% CI, 0.8–3.8; P < .01), ceftriaxone (+1.0; 95% CI, 0.2–1.7; P = .02), vancomycin (+2.4; 95% CI, 1.0–3.5; P < .01), and levofloxacin (−2.4; 95% CI, −3.3 to −1.5; P < .01) remained the same for the prepandemic and pandemic periods, reflecting long-standing trends.

**Facilities using antimicrobial stewardship model C**

In these facilities, the MPC estimates for the entire observation period indicated multiple significant fluctuations in the use of meropenem, cefepime, azithromycin, doxycycline, and levofloxacin (Table 2 and Supplementary Figs 3A, 3C, 3F, 3G and 3H). For the prepandemic period, the AMPCs showed monthly increases in the use of meropenem, piperacillin–tazobactam, ceftriaxone, and doxycycline, and a decrease in the use of vancomycin and levofloxacin (Supplementary Table 1). For the pandemic period, the AMPC showed monthly increases in the use of piperacillin–tazobactam and ceftriaxone, and doxycycline, and a decrease in the use of vancomycin and levofloxacin (Supplementary Table 1).

**Discussion**

Across hospitals using different ASP models, we identified multiple fluctuations in the rates of antibiotic use throughout the study period. In most cases, the average monthly percent changes reflected trends that preceded the COVID-19 pandemic. Up to 75% of patients with COVID-19 are prescribed antibiotics, and rates of prescribing have decreased throughout the pandemic. Our assessment of longitudinal trends in prescribing...
Table 2. Monthly Percent Change in Antibiotic Days of Therapy Per 1,000 Days Present According to Antimicrobial Stewardship Program (ASP) Model, January 1, 2019, to February 28, 2021

| Variable                   | Monthly Change, % (95% CI) | P Value |
|----------------------------|-----------------------------|---------|
| **ASP model A**            |                             |         |
| Meropenem                  |                             |         |
| January 2019–February 2021 | −0.2 (−1.3 to 1.1)          | .70     |
| Piperacillin–Tazobactam    |                             |         |
| January 2019–July 2019     | 5.1 (1.8 to 8.6)            | .04     |
| July 2019–January 2020     | −3.4 (−7.4 to 8.6)          | .10     |
| January 2020–February 2021 | 1.3 (0.3 to 2.6)            | .01     |
| Cefepime                   |                             |         |
| January 2020–February 2021 | 3.2 (2.4 to 3.9)            | <.01    |
| Ceftriaxone                |                             |         |
| January 2019–November 2019 | 1.6 (0.5 to 2.8)            | .01     |
| November 2019–April 2020   | 7.3 (2.4 to 12.7)           | .01     |
| April 2020–July 2020       | −5.2 (−24.2 to 17.4)        | .60     |
| July 2020–February 2021    | 1.5 (−0.3 to 4.6)           | .10     |
| Vancomycin                 |                             |         |
| January 2019–February 2021 | 0.4 (0.01 to 0.7)           | .04     |
| Azithromycin               |                             |         |
| January 2019–August 2019   | −1.9 (−5 to 1.3)            | .20     |
| August 2019–February 2020  | 9.6 (4.3 to 15)             | .03     |
| February 2020–May 2020     | −15.7 (−45.7 to 31.1)       | .40     |
| May 2020–August 2020       | 13.1 (−20.9 to 61.8)        | .50     |
| August 2020–February 2021  | −0.8 (−4.5 to 3.2)          | .70     |
| Doxycycline                |                             |         |
| January 2019–January 2020  | −0.6 (−4.3 to 3.3)          | .80     |
| January 2020–April 2020    | 57.9 (−31.7 to 264.9)       | .30     |
| April 2020–August 2020     | −25.1 (−43.8 to −2.6)       | .03     |
| August 2020–February 2021  | 6.3 (−5 to 25.7)            | .20     |
| Levofloxacin               |                             |         |
| January 2019–June 2020     | −3.0 (−3.9 to −2)           | <.01    |
| June 2020–February 2021    | 2 (−1.5 to 5.6)             | .30     |
| **ASP model B**            |                             |         |
| Meropenem                  |                             |         |
| January 2019–February 2021 | 2.3 (0.8 to 3.8)            | <.01    |
| Piperacillin–tazobactam    |                             |         |
| January 2019–February 2021 | 0.1 (−0.5 to 0.8)           | .70     |
| Cefepime                   |                             |         |
| January 2019–March 2020    | 7.0 (2.6 to 9)              | <.01    |
| March 2020–June 2020       | −25.0 (−74.4 to 120.1)      | .60     |
| June 2020–February 2021    | 7.0 (−1.0 to 9.0)           | .10     |
| Ceftriaxone                |                             |         |
| January 2019–February 2021 | 1.0 (0.2 to 1.7)            | .02     |
| Vancomycin                 |                             |         |
| January 2019–February 2021 | 2.4 (1.0 to 3.5)            | <.01    |

(Continued)
revealed fluctuations that, in most instances, did not reach a statistically significant deviation from the existing trend. There is a need for development of ASPs in settings with both limited access to the expertise of infectious diseases specialists, particularly during the COVID-19 pandemic, as well as a lack of reports of stewardship practices. Our study contributes to the literature on this

| Variable | Monthly Change, % (95% CI) | P Value |
|----------|-----------------------------|---------|
| January 2019–December 2020 | 2.2 (0.7 to 3.7) | <.01 |
| December 2020–February 2021 | −36.5 (−84.2 to 154.3) | .50 |

### Doxycycline

| January 2019–November 2019 | −8.1 (−17 to 1.8) | .10 |
| November 2019–April 2020 | 29.2 (−16.8 to 100.7) | .20 |
| April 2020–February 2021 | −10.7 (−17.9 to −2.9) | .10 |
| January 2019–February 2021 | −2.4 (−3.3 to −1.5) | <.01 |

### ASP model C

#### Meropenem

| January 2019–January 2020 | 2.5 (0.6 to 4.5) | .01 |
| January 2020–April 2020 | 19.1 (−23.1 to 84.3) | .40 |
| April 2020–September 2020 | −7.1 (−16.2 to 3) | .10 |
| September 2020–December 2020 | 13.9 (−23.4 to 69.2) | .50 |
| December 2020–February 2021 | −16.6 (−47.2 to 31.6) | .40 |

#### Piperacillin–tazobactam

| January 2019–February 2021 | 0.6 (0.2 to 1.0) | <.01 |

#### Cefepime

| January 2019–December 2019 | −1.7 (−2.9 to −0.4) | .01 |
| December 2019–March 2020 | 12.2 (−13.7 to 43.2) | .40 |
| March 2020–July 2020 | −7.8 (−18.3 to 4) | .20 |
| July 2020–December 2020 | 8.3 (2.1 to 15) | <.01 |
| December 2020–February 2021 | −16.6 (−36.4 to 9.3) | .20 |

#### Ceftriaxone

| January 2019–February 2021 | 0.9 (0.4 to 1.3) | <.01 |

#### Vancomycin

| January 2019–February 2021 | −0.3 (−0.5 to −0.1) | .05 |

#### Azithromycin

| January 2019–July 2019 | 5.3 (−8.2 to −2.3) | <.01 |
| July 2019–April 2020 | 7.2 (5.2 to 9.2) | <.01 |
| April 2020–August 2020 | −18.2 (−34.2 to 1.6) | .1 |
| August 2020–November 2020 | 19.7 (10.2 to 29.9) | <.01 |
| November 2020–February 2021 | −16.8 (−23.9 to −9.1) | .04 |

#### Doxycycline

| January 2019–May 2020 | 1.6 (0.2 to 3) | .03 |
| May 2020–February 2021 | −3.6 (−7 to 0.1) | .03 |

### Levofloxacin

| January 2019–July 2019 | −3.6 (−5.6 to −1.6) | <.01 |
| July 2019–January 2020 | 0.7 (−2.1 to 3.5) | .60 |
| January 2020–October 2020 | −3.3 (−4.7 to −1.9) | <.01 |
| October 2020–February 2021 | 2.6 (−2.5 to 7.9) | .30 |
topic by describing 3 ASP models in urban and semirural areas and by describing trends of use of key antibiotic agents under different stewardship practices.

The limitations of our study include use of registry-type data obtained from a centralized database in which accuracy depends on appropriate capture of data in the medication administration record. This aspect is mitigated by previous reviews on the accuracy of this data performed by clinical pharmacists. Also, we did not have data for the precise indication of antibiotic prescribing, which precluded us from evaluating changes in trends used specifically for respiratory infection. Furthermore, we did not assess the role of individual tools for mitigating antimicrobial use such as procalcitonin trends.

In conclusion, across 3 different ASP models, the core stewardship activities were maintained during the COVID-19 pandemic. Changes in antibiotic use were limited to temporal fluctuations and, for most agents, longstanding trends continued. Continued support and development of ASPs in accordance with local resources is crucial to their success.

Supplementary material. For supplementary material accompanying this paper visit https://doi.org/10.1017/ash.2022.39

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