

# Primary Care Physicians' Attitudes and Perceptions Towards Antibiotic Resistance and Antibiotic Stewardship: A National Survey

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**Background.** Outpatient antibiotic stewardship is needed to reduce inappropriate prescribing and minimize the development of resistant bacteria. We assessed primary care physicians' perceptions of antibiotic resistance, antibiotic use, and the need for stewardship activities.

**Methods.** We conducted a national online survey of 1550 internal, family, and pediatric medicine physicians in the United States recruited from an opt-in panel of healthcare professionals. Descriptive statistics were generated for respondent demographics and question responses. Responses were also stratified by geographic region and medical specialty, with a  $\chi^2$  test used to assess for differences.

**Results.** More respondents agreed that antibiotic resistance was a problem in the United States (94%) than in their practice (55%) and that inappropriate antibiotic prescribing was a problem in outpatient settings (91%) than in their practice (37%). In addition, 60% agreed that they prescribed antibiotics more appropriately than their peers. Most respondents (91%) believed that antibiotic stewardship was appropriate in office-based practices, but they ranked antibiotic resistance as less important than other public health issues such as obesity, diabetes, opioids, smoking, and vaccine hesitancy. Approximately half (47%) believed they would need a lot of help to implement stewardship. Respondents indicated that they were likely to implement antibiotic stewardship efforts in response to feedback or incentives provided by payers or health departments.

**Conclusions.** Primary care physicians generally did not recognize antibiotic resistance and inappropriate prescribing as issues in their practice. This poses a challenge for the success of outpatient stewardship. Healthcare stakeholders will need to explore opportunities for feedback and incentive activities to encourage stewardship uptake.

**Keywords.** antibiotics; antibiotic resistance; antimicrobial stewardship; primary care.

Antibiotic effectiveness is being threatened by the spread of antibiotic-resistant bacteria [1, 2]. Antibiotic use is the primary driver of the development of resistant bacteria. In the United States, the majority of antibiotic use occurs in outpatient settings [3]. A recent study showed that, although there was a 5% decrease in the overall outpatient antibiotic prescribing rate from 2011 to 2016, this decrease stopped in 2014 [4]. Studies have shown that a large proportion of outpatient antibiotic prescriptions are inappropriate, most often for treatment of acute respiratory conditions that do not require antibiotics [5–8].

In addition, the coronavirus disease 2019 (COVID-19) is likely to impact antibiotic prescribing practices due to clinical uncertainties surrounding these infections. Early studies of patients hospitalized with COVID-19 have shown that a significant majority of these patients received antibiotics [9]. There is potential for a similar increase in antibiotic prescribing in outpatient settings. In addition, antibiotic use could be impacted by how ambulatory healthcare is delivered during the pandemic with increased utilization of telemedicine, a model that has been associated with higher rates of outpatient antibiotic prescribing [10, 11]. Antibiotic stewardship efforts during and after the pandemic will be critical for fully addressing the threat of antibiotic resistance.

Leaders in infectious diseases and antibiotic stewardship have been calling for the implementation of robust stewardship programs for years, resulting in the number of hospitals with stewardship programs almost doubling from 2014 to 2017 [12–14]. Similar efforts to expand antibiotic stewardship into outpatient settings through the implementation of the Centers for Disease Control and Prevention's (CDC) outpatient stewardship

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guidelines are needed [15]. A better understanding of primary care physicians' (PCPs) attitudes towards antibiotic resistance, use, and stewardship is needed to identify barriers to stewardship uptake. In addition, a better understanding of PCPs' perceptions of different stewardship activities and policies implemented by healthcare stakeholders is needed to identify strategies for tailoring effective interventions. In support of this, we conducted a national survey of PCPs in the United States.

## METHODS

We conducted an online national survey of PCPs in the United States from August through October 2018. This study was reviewed and deemed exempt by the Chesapeake IRB (now known as Advarra).

### Questionnaire Development

The study team, in collaboration with M3 Global Research (M3)—a medical market research firm—developed a 20-minute online questionnaire (see [Supplementary Material](#)). The survey began with 4 questions aimed at gathering additional information beyond what was captured in the survey screener (questions D1, D2a–c). The second section included 8 questions on respondents' knowledge, attitudes, and perceptions around antibiotic resistance (questions 1–4) and prescribing (questions 5–8). The final section of the questionnaire included 26 questions aimed at evaluating perceptions on the acceptability and impact of different antibiotic stewardship approaches. These questions included asking respondents how helpful they would find it for external organizations to provide them with support for stewardship activities (question 9), how likely they would be to support stewardship implementation in their practices in response to external stakeholder activities (question 10a–j), and whether stewardship is appropriate for office-based medical practices (question 14). The majority of questions utilized 5-point Likert scales ranging from the following: “strongly agree” to “strongly disagree”; “very high pressure” to “no pressure at all”; “extremely helpful” to “not at all helpful”; “extremely likely” to “not at all likely”; and “extremely appropriate” to “not at all appropriate.”

This questionnaire underwent an initial online pretest among 20 physicians. Each participant was interviewed by an independent moderator to assess whether the questions were being understood, whether the response options provided were adequate, and any other issues that arose when completing the survey. Minor changes were made to the questionnaire based on the pretest interviews. The data from the pretest were not included in the final sample. Pretest participants received \$155 to compensate them for their time.

### Survey Population and Recruitment

Study participants were recruited by M3 from an opt-in, nonprobability panel of healthcare professionals that they

maintain. This panel includes physicians who are recruited to participate on the panel via various mechanisms—such as direct mail, online recruitment, and professional conferences. These physicians are verified against other physician databases to ensure that panel members accurately represent physicians in practice. Only physicians in the United States were surveyed for this study.

For our survey, we prescreened potential participants to meet the following inclusion criteria: self-report of board certification in pediatrics, family medicine (FM), or internal medicine (IM); being a full-time physician (excluding residents and fellows) practicing in a primary care outpatient office setting; and spending  $\geq 50\%$  of medical practice time in direct patient care. Potential participants were excluded if they reported (1) being  $\geq 65$  years-old, (2) being board-certified in a subspecialty outside of primary care, or (3) having worked at their current practice location for less than 1 year. Physicians practicing in Vermont and Maine were not included in the sample due to state regulations on research incentives.

Participants were screened for eligibility, and they were sent an introductory email directing them to an informed consent webpage with information about the study sponsor and purpose. Potential participants were informed that, by continuing to the survey, they would be providing consent to participate in this study. Each participant received \$43 to compensate for their time.

### Data Analysis

We used a quota-based sampling strategy to recruit an adequate sample size for stratified analysis and a balanced number of participants by geographic region (defined as the US Census regions: Northeast, Midwest, South, West) and specialty. Specifically, our recruitment targets were 129 participants per stratum (ie, FM physicians in the Northeast, IM physicians in the Northeast, etc). Our targets were 130 participants for pediatricians in the Northeast and FM physicians in the South to meet our overall target of 1550 participants. These targets were selected to ensure an adequate sample size for analyzing the data when stratifying the data by region or specialty.

To account for over- and undersampling of participants due to the sampling strategy, we weighted the results by geographic region and medical specialty to mirror actual distribution of US physicians according to these characteristics. The American Medical Association's Physician Masterfile was used to identify true population estimates.

We generated descriptive statistics for demographic and practice characteristics of survey respondents, as well as for individual question responses (only weighted results presented). Responses were also stratified by geographic region of practice and medical specialty. For this stratified analysis, responses were collapsed into positive (strongly agree or agree, extremely likely, very likely, or likely, etc), neutral

(where applicable), and negative responses (strongly disagree or disagree, not at all likely, or not very likely, etc). We used the  $\chi^2$  test to assess for differences in responses according to these characteristics. We considered  $P < .05$  to be significant. Any questions with fewer than 5 respondents in a given cell were excluded from stratified analysis. All analyses were conducted using Stata v.14.2.

## RESULTS

Overall, 12 987 M3 panel members received invitations to participate in the survey, 4892 opened the invitation, and 1550 passed the screener and completed the survey. An additional 141 respondents were either in a stratum that had already reached its quota or did not complete the survey. Finally, 25 respondents from the initial 1550 sample had low-quality responses with inconsistencies between their age and the year they completed their medical residency. These 25 respondents were removed from the sample and replaced with additional respondents to fill the final 1550 sample. Demographics and practice characteristics of respondents are summarized in [Table 1](#) and [Supplementary Table 1](#).

### Antibiotic Resistance

The questionnaire asked respondents to rank antibiotic resistance compared with other public health issues in order of impact on their patients in their daily practice (question 1; [Figure 1](#)). The IM and FM physicians were presented with the same 5 issues and had very similar response patterns. Overall, they ranked obesity, diabetes, smoking, and opioid misuse as more important problems than antibiotic resistance. Only 26% of IM and FM respondents ranked antibiotic resistance among their top 3 public health issues.

Pediatricians were asked to rank the same health issues, with the addition of vaccine hesitancy. Overall, 73% of pediatricians ranked antibiotic resistance within their top 3 public health issues. Obesity and overweight was ranked highest—with 99% of respondents ranking it within their top 3—followed by vaccine hesitancy (83% ranked in top 3).

Respondents were asked questions to assess their knowledge and attitudes around antibiotic resistance ([Figure 2](#)). Approximately all (94%) agreed that antibiotic resistance is a problem in the United States (question 3). There were small but statistically significant differences based on specialty—with higher agreement among pediatricians ( $P = .0045$ ). However, only 55% agreed that resistance is a problem in their practice (question 2). In addition, most respondents (65%) had seen an increase in resistant infections among their patients (question 4). Responses were mixed when asked whether they agreed that resistance is more of a problem in hospitals and less important in outpatient settings (question 13c). A larger proportion

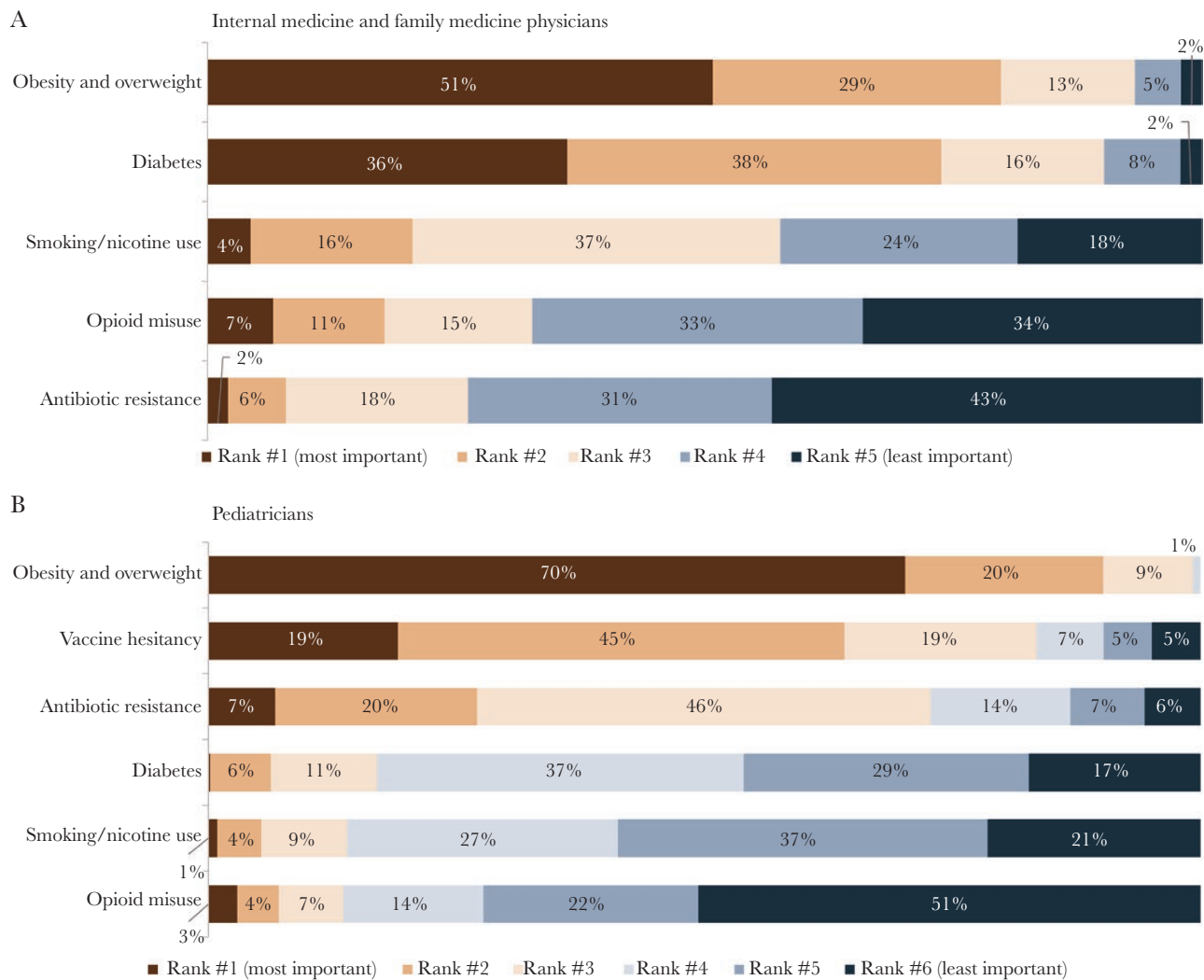
**Table 1. Demographic and Practice Characteristics of Survey Respondents (N = 1550)**

Demographic and Practice Characteristics	Percent (Weighted)
<b>Age</b>	
25- to 34-year-olds	12%
35- to 44-year-olds	27%
45- to 54-year-olds	32%
55- to 64-year-olds	29%
<b>Gender</b>	
Male	58%
Female	42%
<b>Geographic Region</b>	
Northeast	18%
Midwest	23%
South	35%
West	24%
<b>Medical Specialty</b>	
Family Medicine	43%
Internal Medicine	35%
Pediatrics	22%
<b>Primary Practice Setting</b>	
Physician's office, solo practice	18%
Physician's office, 2 physician practice	9%
Group practice	72%
<b>Medical Practice Ownership</b>	
Private, independently (physician)-owned practice	55%
Hospital or healthcare system-owned practice—community-based practice location	39%
Hospital or healthcare system-owned practice—hospital-based practice location	7%
<b>Years at Current Practice Location</b>	
1–5 years	28%
6–10 years	18%
10 years or longer	54%

of pediatricians (59%) disagreed with this statement than IM (44%) and FM (49%) physicians ( $P < .001$ ). Overall, 93% of respondents agreed that inappropriate outpatient prescribing accelerates the emergence of antibiotic-resistant bacteria (question 5).

### Antibiotic Use

Responses to questions on antibiotic use were similar to those on resistance ([Figure 2](#)). Overall, 91% of participants agreed that inappropriate outpatient prescribing was a problem (question 6). However, only 37% of respondents agreed when asked whether inappropriate prescribing was a problem within their own practice (question 7; 44% in the West compared to 37% in the Midwest, 36% in the South, and 30% in the Northeast [ $P = .021$ ]). Pediatricians were less likely to agree that this was a problem in their practice (27%) compared with IM (38%) and FM (42%) physicians ( $P < .001$ ). Finally, 60% of respondents agreed that they prescribe antibiotics more appropriately than their peers (question 13e). Pediatricians were more likely to agree (71%) than IM (59%) and FM (56%) physicians ( $P < .001$ ).



**Figure 1.** Ranking of public health issues in order of impact on patients and daily practice.

Forty-seven percent of respondents indicated that they experience moderate pressure to prescribe antibiotics, with 37% saying they experience high or very high pressure and 16% saying they experience low or no pressure at all (question 8; [Supplementary Figure 1](#)). Only 20% of pediatricians experienced high or very high pressure, compared to 43% of IM and 41% of FM physicians ( $P < .001$ ).

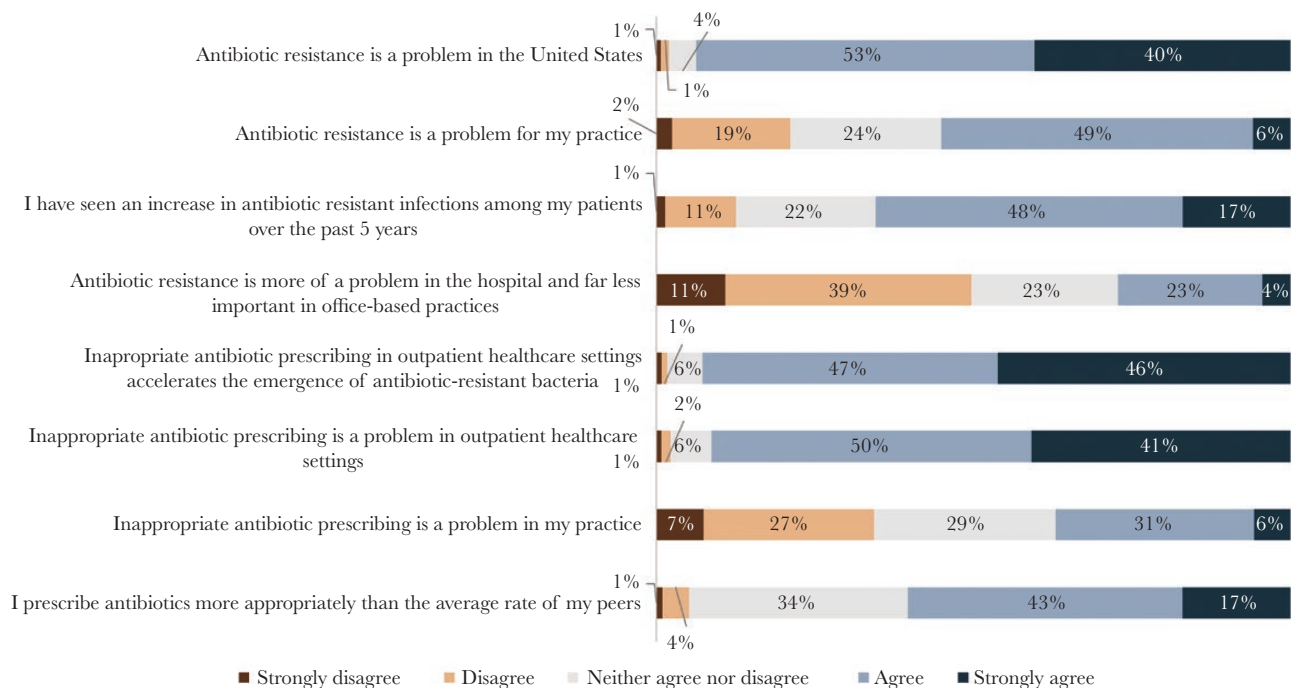
#### Antibiotic Stewardship

Antibiotic stewardship was defined for respondents as activities aimed at ensuring antibiotics are prescribed appropriately. Example activities included staff and patient education, clinician-level antibiotic prescribing feedback, and communications training on how to discuss antibiotic prescribing with patients. Respondents were then asked to respond to a series of questions about the value and feasibility of stewardship and how to encourage stewardship uptake.

#### Perceived Value of Antibiotic Stewardship

Overall, 72% of respondents agreed that antibiotic stewardship programs are needed in healthcare settings to address the threat of antibiotic resistance (question 13d; [Figure 3](#)). This was highest for pediatricians (77%) and lowest for IM physicians (68%) ( $P = .024$ ). Ninety-one percent of respondents indicated that they believed stewardship programs were appropriate for office-based medical practices (question 14; [Supplementary Figure 2](#)), which varied only slightly by geographic region of practice (87% South, 89% Northeast, 95% West/Midwest;  $P < .001$ ).

Many respondents thought patients and families should be the primary focus of stewardship efforts. Seventy-nine percent of respondents agreed that stewardship efforts would be ineffective unless paired with efforts aimed at educating patients and parents (question 13a; [Figure 3](#)). In addition, 53% believed that all they need to do to support stewardship efforts is to talk with



**Figure 2.** Primary care physician perceptions on antibiotic resistance and antibiotic use.

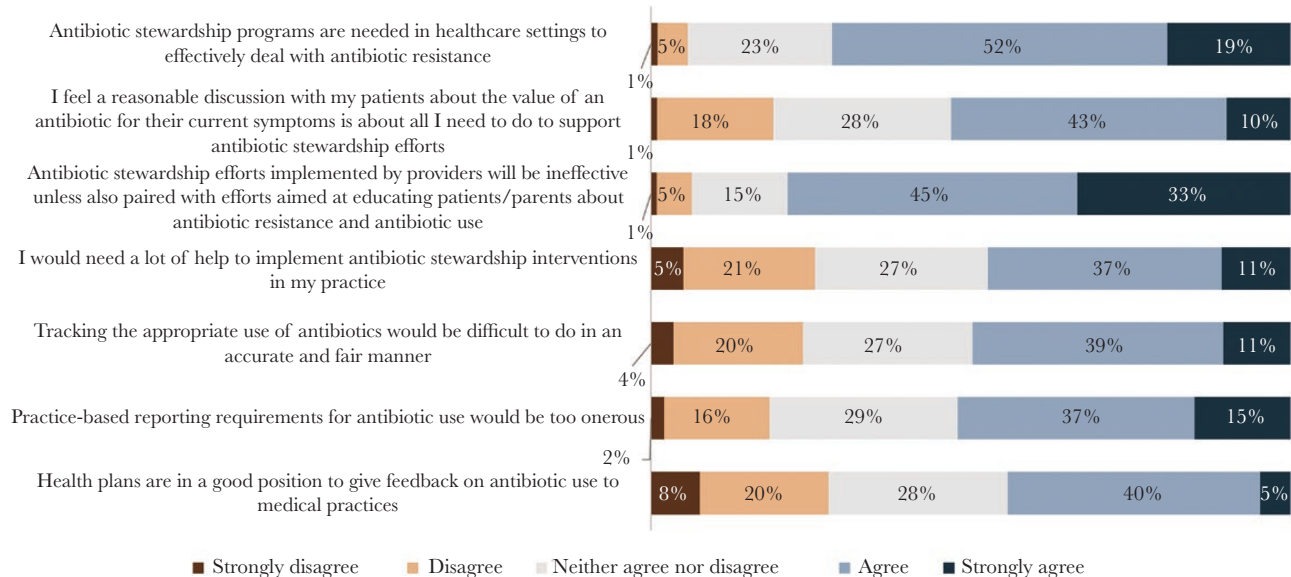
their patients about the value of an antibiotic for their symptoms (question 13g; [Figure 3](#)).

### Feasibility of Antibiotic Stewardship

Slightly less than half of respondents (47%) believed they would need a lot of help to implement stewardship efforts within their practices (question 13f; [Figure 3](#)), including 52% of IM physicians, 47% of FM physicians, and 40% of pediatricians

( $P = .0029$ ). In addition, 59% of respondents indicated they could provide input on implementing antibiotic stewardship in their practice, but the final decision would be made by practice leadership (question 11).

Half of participants agreed that tracking appropriate antibiotic use would be difficult to accomplish (question 13b; [Figure 3](#)). This agreement was higher for IM (54%) and FM (50%) physicians than for pediatricians (42%) ( $P = .0192$ ).



**Figure 3.** Primary care physician perceptions on antibiotic stewardship.

In addition, 52% of respondents believed that practice-based antibiotic use reporting requirements would be too onerous (question 13h), and 44% believed that health plans were in a good position to provide prescribing feedback (question 13i).

When asked which healthcare organizations they trusted to provide accurate antibiotic prescribing feedback (question 12), IM and FM physicians favored their own practice or health system (75% ranked first or second) and the state department of health (68%) followed by commercial payers (30%), Medicare (22%), and Medicaid (4%). The same pattern was seen among pediatricians, with 88% of respondents ranking their own practice or health system first or second followed by the state department of health (75%), commercial payers (27%), and Medicaid (10%) (Supplementary Figure 3).

Respondents were asked how useful they would find it for different external organizations to provide resources and technical assistance to support stewardship implementation (question 9a–d; Supplementary Figure 4). Local and state departments of health and a national public health agency were seen as most helpful compared with public and commercial payers (79% and 77% vs 67% and 64%).

### Incentivizing Antibiotic Stewardship

Participants were presented with a range of stewardship activities that could be implemented by healthcare stakeholders to spur stewardship uptake and were asked to indicate how likely they would implement stewardship interventions in response to these activities (question 10a–j; Table 2). The activities with the strongest likelihood to spur stewardship adoption included the state department of health publishing reports on local antibiotic resistance patterns (82%) and a public or private payer creating a standalone quality incentive program on antibiotic stewardship (80%) or including antibiotic stewardship as an option to fill a requirement within a broader quality incentive program (76%).

### DISCUSSION

We conducted a national survey of PCPs in the United States to better understand their attitudes towards antibiotic resistance, antibiotic use, and antibiotic stewardship, as well as perceptions of stewardship activities and policies. Although most participants recognized that antibiotic resistance and inappropriate outpatient prescribing is a problem in the United States, there was less recognition that these were problems within their own practices. This finding is consistent with previous quantitative

**Table 2. Primary Care Physicians' Likelihood of Implementing Stewardship in Response to Feedback and Incentive Activities (N = 1550)**

Healthcare Stakeholder Activities	Not at All Likely	Not Very Likely	Likely	Very Likely	Extremely Likely	Differences by Medical Specialty*	Differences by Region†
The state department of health publishes a report on antibiotic resistance patterns in your geographic area	5%	13%	42%	28%	12%	Peds: 85%; FM: 82%; IM: 79%; P = .0413	NS
A public or private payer creates a standalone quality incentive program where participating physicians would receive additional reimbursement for performing antibiotic stewardship	6%	14%	38%	28%	14%	Peds: 86%; FM: 78%; IM: 78%; P = .0099	NS
A public or private payer includes antibiotic stewardship as an option to fulfill a requirement for a quality incentive program	6%	18%	42%	25%	8%	NS	NS
A "report card" from the state department of health/health plans that measures the rates of antibiotic-associated adverse events for your patients compared with other providers in your state or region	7%	19%	42%	23%	9%	NS	NS
A report card from the state department of health/health plans on quality measures for antibiotics compared with other providers in your state or region	8%	19%	43%	23%	8%	NS	NS
The state department of health publishes results of quality measures for appropriate antibiotic use for all practice locations	7%	20%	45%	21%	7%	NS	NS
A letter from the state department of health or a health plan notifying you that you or your practice is a "high prescriber" of antibiotics compared with other providers in your state/region	8%	21%	42%	22%	8%	NS	S: 67%; NE: 71%; MW: 72%; W: 77%; P = .0207
The state department of health publicly reports "high prescribing" practices	10%	23%	38%	21%	8%	NS	NS
The state department of health publishes aggregate data on the volume of outpatient antibiotic prescribing in your state	7%	26%	44%	17%	6%	NS	NS
The state department of health creates an "honor roll" recognizing practices that have demonstrated high levels of appropriate antibiotic prescribing on the state department of health website	8%	26%	37%	19%	9%	Peds: 72%; FM: 65%; IM: 62%; P = .0184	S: 60%; MW: 67%; W: 68%; NE: 70%; P = .0268

Abbreviations: FM, family; IM, internal medicine physicians; MW, Midwest; NE, Northeast; NS, not significant; Peds, pediatricians; S, South; W, West.

\*Percentages are the sum of responses for likely, very likely, and extremely likely.

†Percentages are the sum of responses for likely, very likely, and extremely likely.

and qualitative studies that found high levels of awareness among clinicians of antibiotic resistance and prescribing as national issues, with less recognition as issues within their own practice [16–21]. This lack of recognition of physicians' own contributions to inappropriate prescribing presents a barrier to encouraging widespread stewardship uptake.

Although there was strong agreement among respondents that stewardship was needed in healthcare settings and appropriate for office-based facilities, there was less consensus on the feasibility of applying stewardship activities to their practice. Approximately half of participants believed that tracking appropriate antibiotic use would be difficult to do in an accurate and fair manner and that antibiotic use reporting would be a significant burden for their practice. Antibiotic use measurement and reporting is a key aspect of antibiotic stewardship, and individualized feedback on antibiotic prescribing has been shown to be effective at improving prescribing [22–24]. However, healthcare stakeholders will need to work to address these concerns to effectively implement these types of activities.

Respondents also indicated that they perceive patient education as critical to stewardship. Approximately half of respondents believed that all they needed to do to support stewardship efforts was to discuss antibiotic prescribing decisions with their patients. There are resources available to support these efforts. For example, the CDC has developed an online training program on antibiotic stewardship for healthcare professionals that includes a module on how to communicate prescribing decisions to patients that could help minimize the burden on physicians when pushing back against perceived patient demand [25]. In addition, time constraints on physicians have been highlighted as contributing to inappropriate prescribing [26–30]. Addressing these time constraints on PCPs may help support these conversations with patients.

This survey found consistent differences in participant responses according to medical specialty. There was higher recognition among pediatricians about the issue of antibiotic resistance at the national level. However, pediatricians were less likely to agree that inappropriate antibiotic prescribing was a problem in their practices, and they were more likely to agree that they prescribe antibiotics more appropriately than their peers. Pediatricians also expressed stronger agreement with the need for stewardship programs, as well as a stronger likelihood of stewardship implementation in response to some of the proposed activities. Although these results may appear contradictory, this could reflect the fact that pediatricians are largely driving the recent decrease in outpatient antibiotic prescribing in the United States [4]. Pediatricians both acknowledge the importance of the problem while recognizing that they are taking the steps needed to address the issue within their practices. Although our research did not assess why pediatricians have been successful at decreasing their antibiotic prescribing rates, the reasons are likely multifactorial. For example, strict

diagnostic criteria for acute otitis media could have minimized the number of these diagnoses, resulting in fewer antibiotic prescriptions [4]. In addition, early educational efforts from the CDC focused on improving antibiotic prescribing in children, which could have led to greater awareness within the pediatric community [4].

Another notable finding was the difference between pediatricians and IM and FM physicians in their perceptions of the intensity of patient pressure to prescribe antibiotics. Fewer pediatricians indicated they believed high or very high pressure compared to IM and FM physicians. Past studies have shown that patient demand is seen as an important driver of inappropriate prescribing [26–29, 31–34]. Our survey expands on past research by showing that pressure may not be believed equally across specialties. This could also be contributing to the decrease in pediatric antibiotic prescribing.

This study has limitations. Although a large number of PCPs from across the United States participated in this survey, participants were recruited from a physician panel maintained for research purposes. The physicians who were recruited and who participated in the final survey may be different than the general PCP population, limiting generalizability. In addition, this study was limited to only internal and FM physicians and pediatricians, and it did not include other outpatient clinicians, such as nurse practitioners, physician assistants, and providers in urgent care, retail clinics, and telemedicine. Nurse practitioners and physician assistants represented approximately 27% of outpatient antibiotics in 2017 [35]. Additional research will be needed to assess attitudes of these clinicians. Finally, this study could only assess the knowledge and attitudes of the respondents and not the quality of their antibiotic prescribing practices.

To our knowledge, this research is the first to survey PCPs' perceptions of specific activities designed to incentivize outpatient antibiotic stewardship. This study has broad implications for how healthcare stakeholders can support PCPs in developing and implementing stewardship activities in their practice. Although the tracking and reporting of antibiotic use is a core element of outpatient stewardship according to the CDC, this survey shows that PCPs have some skepticism around the feasibility of antibiotic use measurement [15]. There is also varying amounts of trust in healthcare organizations that might be able to provide PCPs with prescribing feedback—namely, lower levels of trust in both private and public payers. However, PCPs did express a greater amount of trust in state health departments. Partnerships between payers and public health entities around providing antibiotic prescribing feedback may enhance the impact of measurement activities. Public health agencies could provide subject matter expertise in support of these partnerships and serve as a trusted source of information for healthcare professionals. An example of this is a partnership between one payer and public health officials to send feedback letters to prescribers [36].

Finally, this study highlighted activities that can be implemented by healthcare stakeholders to incentivize stewardship uptake. These activities included the implementation of quality incentive programs and reporting of antibiotic use quality measures. Our study did not assess the perceived impact of specific quality measures, such as antibiotic use measures included in the Healthcare Data and Information Set managed by the National Committee for Quality Assurance or those included in the Centers for Medicare & Medicaid Services Merit-based Incentive Payment System [37–39]. However, these existing measures can be leveraged for these types of activities. In addition, although implementation of stewardship is needed across primary care, healthcare stakeholders may consider prioritizing these activities among IM and FM physicians. Our survey highlighted that resistance is not viewed as a priority health issue for these physicians. However, quality incentive programs or the provision of local antibiotic resistance data may help escalate the issue.

## CONCLUSIONS

There has been significant progress in recent years on the implementation of antibiotic stewardship within hospitals, largely driven by the antibiotic stewardship and infectious diseases communities. A 2019 report from the CDC found fewer infections and deaths caused by resistant pathogens since 2013, which was attributed in part to these activities [1]. However, this report also showed an increase in resistant community-associated infections, highlighting the increased need for community-based efforts [1]. This will require collaboration between the antibiotic stewardship community and key outpatient healthcare stakeholders to support implementation and ensure that this issue is prioritized by PCPs. Considering the potential impact of COVID-19 on antibiotic prescribing, these efforts are even more critical for ensuring recent progress is not lost and driving improved prescribing moving forward.

## Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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**Author contributions.** R. M. Z. led the development of the study concept and design, participated in the analysis and interpretation of data, and drafted the manuscript. D. Y. H. provided supervision in the development of the study concept and design, participated in the analysis and interpretation of the data, and provided critical revision of the manuscript. A. M. G., J. N. D., J. S. G., and J. A. L. all provided input in the development of the study concept and design, participated in the interpretation of data, and provided critical revision of the manuscript.

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