Optimizing Research Methods Used for the Evaluation of Antimicrobial Stewardship Programs

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Antimicrobial stewardship programs (ASPs) are an increasingly common intervention for optimizing antimicrobial therapy in healthcare settings. These programs aim to improve patient care and limit the emergence and spread of multidrug-resistant organisms by supporting prudent antimicrobial use. However, pressure from the current reimbursement climate necessitates that ASPs operate as cost-cutting programs rather than focus on patient outcomes. This has forced the research that is evaluating ASP interventions to concentrate heavily on economic outcomes. As the science of antimicrobial stewardship advances, it is essential that well-conducted evaluations, focused on patient and microbial outcomes, serve as the evidence base that directs optimal ASP intervention design and implementation. In this review, we provide guidance and recommendations for the design of studies to evaluate the impact of ASP interventions on patient and microbial outcomes.

Keywords. antibiotic stewardship programs; methodology; outcomes; evaluation.

Use of antimicrobial stewardship programs (ASPs) to optimize antimicrobial therapy in healthcare settings is rapidly becoming commonplace. These programs typically operate by implementing multiple interventions aimed at facilitating appropriate and prudent antimicrobial prescription to support effective patient care while minimizing collateral damage. Because of differences in patterns of antimicrobial use, patient characteristics, and healthcare resources, the complexity of ASP interventions and anticipated outcomes vary widely among institutions. Regardless of these variations, evaluations of these programs should draw on core methodological principles to determine their effectiveness. Here, we describe how to optimize epidemiological methods to design and conduct rigorous evaluations of ASPs, with an emphasis on patient and microbial outcomes. We discuss the predominant study designs and the factors that should be weighed in selecting the most appropriate design. We also emphasize the need to explicitly define the intervention and outcomes of interest before ASP implementation. In this review, we aim to provide methodological guidance for conducting such evaluations and representative examples rather than systematically review the literature on ASP evaluation.

OUTCOMES OF ANTIMICROBIAL STEWARDSHIP PROGRAMS

Theoretically, the first step in selecting an ASP intervention for implementation should be the identification of a target outcome that is informed by baseline data or a needs assessment. In reality, multiple factors drive the selection of these program interventions and associated target outcomes. Still, before designing the approach to evaluate an intervention, it is critical to identify the outcomes of interest. An explicitly defined outcome enables accurate assessment of the intervention’s effectiveness. Consequently, we describe the outcomes often targeted and assessed by ASP interventions and outcomes for which more data are needed. These outcomes can be divided into the following 3 general categories:

1. **Patient Outcomes:** These include measures related to patient morbidity and mortality, hospital-acquired conditions, and complications associated with antimicrobial therapy. Examples are infection-related mortality, hospital-acquired infections, and length of hospital stay.
2. **Microbial Outcomes:** These outcomes focus on the impact of ASPs on the incidence and prevalence of multidrug-resistant organisms. Important microbial outcomes include the incidence of infections due to multidrug-resistant organisms, changes in the antimicrobial resistance patterns of pathogens, and the proportion of patients experiencing successful antimicrobial therapy.
3. **Economic Outcomes:** These outcomes assess the cost-effectiveness of ASP interventions. Economic evaluations may include data on the costs of antimicrobial therapy, healthcare utilization, and the costs associated with the implementation and maintenance of the ASP. Examples include cost savings, cost-effectiveness ratios, and cost-utility analysis.
clinical outcomes, microbial or resistance outcomes, and process measures. Although not discussed in this review, researchers may also assess satisfaction with ASPs, such as user satisfaction regarding ASP informatics or educational intervention.

Improvement in clinical outcomes is the goal for ASPs, as with any healthcare intervention. Therefore, these outcomes are most important when they are being implemented and evaluated [1]. Potential clinical outcomes of ASPs include clinical cure or failure, mortality, hospital length of stay, and readmission to the hospital, as well as potential adverse events associated with antimicrobial therapy, including adverse drug effects and drug–drug interactions. Each outcome can be more precisely defined depending on the specific interest of the investigators and expected outcomes of the intervention. For example, a mortality outcome can be further specified by type (eg, all-cause or infection-associated mortality), quantified using temporal parameters (eg, 30-day mortality), setting (eg, in-hospital mortality), or a combination of these characteristics (eg, in-hospital mortality caused by ventilator-associated pneumonia). It is important to recognize that many ASP interventions are not expected to improve or worsen clinical outcomes; rather, they are expected to reduce collateral damage (eg, decrease multidrug-resistant organism [MDRO] acquisition) without changing clinical outcomes. In this scenario, studies should be planned to have sufficient statistical power to show that clinical outcomes do not differ before and after ASP interventions, similar to noninferiority trials for assessing new antimicrobial therapies. One limitation of the current evidence base is that most studies that show no significant difference in these outcomes do not have sufficient power to ensure that the interventions do not inadvertently affect patient care. Despite their importance in implementing and evaluating ASPs, a relatively small proportion of previous studies have assessed clinical outcomes. Additionally, much of the resulting data may be biased or underpowered because of suboptimal study design [2, 3]. Davey et al recently updated their Cochrane Collaboration systematic review and metaanalysis of studies evaluating interventions aimed at improving antimicrobial prescription in hospitalized patients. The authors concluded that interventions aimed at improving antimicrobial prescription for pneumonia among hospitalized patients are associated with significant reductions in mortality rate [2]. Furthermore, interventions aimed at decreasing excessive antimicrobial use did not significantly increase mortality rate [2]. However, more recent studies also did not find significant differences in mortality rate, number of readmissions, or length of stay after implementation [4, 5]. Although these data provide evidence supporting the effectiveness of some stewardship interventions, they touch on only a narrow scope of the range of interventions currently implemented in practice. Therefore, more work is needed to evaluate the impact of different ASP interventions on these clinical outcomes.

Microbial or resistance outcomes are strongly tied to ASP goals. They measure the incidence or prevalence of colonization or infection by an organism and may be assessed at the individual or population level. For example, rates of acquisition or healthcare–associated infection rates of important MDROs (eg, methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, extended-spectrum β-lactamase–producing gram-negative bacteria) are essential for measuring the effect of ASP interventions. For example, in one randomized control trial (RCT), investigators were able to attribute a 20% reduction in antimicrobial resistance, superinfections, or both to the implementation of a short-course empiric therapy regimen for patients with pulmonary infiltrates in the intensive care unit [6]. Although a primary goal of antimicrobial stewardship is limiting the spread of MDROs, the literature regarding ASP intervention evaluation does not reflect this because most studies have focused on economic or process measure outcomes. Although some studies have shown the potential for ASP interventions to decrease MDRO outcomes [7, 8], more effort is needed to identify best practices for achieving this goal [2]. Additionally, as a frequent, drug-associated adverse effect, rates of Clostridium difficile infection represent an important target for ASPs, and this outcome is being increasingly used in stewardship research. Recent studies have identified significant decreases in the incidence of C. difficile infection after implementation of ASPs [4, 5, 9]; however, a metaanalysis of 5 previous studies suggests a more attenuated effect [2]. These conflicting findings underscore the need for additional studies that evaluate the impact of interventions on C. difficile infection rates using optimal research methods.

Process measures, also referred to as quality or performance measures, assess the quality of healthcare delivery and are frequently used in studies of the effectiveness of ASPs [3, 10–12]. Process measures, such as antimicrobial days of therapy (DOT), represent the intermediate outcomes that ASP interventions directly influence. Process measure data are also typically less subjective and more easily attainable than clinical outcome measures. However, the association of these measures with clinical outcomes should be validated to demonstrate their value as an intermediate outcome. Valid process measures can be useful in understanding study findings that show limited intervention effects on clinical outcomes. Common process measures in evaluations of ASP interventions include overall or specific antimicrobial use, frequency and time to appropriate empiric or definitive antimicrobial therapy, and unnecessary or excess drug use. Several recent reviews describe the use of process measures in evaluating ASP interventions [3, 11, 12]. Cost-based or economic outcomes are another commonly assessed process measure. Reducing antimicrobial expenditures was the impetus
for many early ASPs and is still used to justify continued funding for these programs, especially given the inability to directly bill for these services in the United States [4, 5, 13–15]. Despite the relevance of economic outcomes, the importance and necessity of ASPs can be better proven by showing the impact of their interventions on clinical outcomes, as reduced cost does not always equate to improved patient care.

Regardless of the type of outcome selected for study, multiple factors influence the outcome rate and can result in considerable “background noise” that would complicate identification of the impact of an ASP. Thus, appropriate design or analytical approaches must be used to adjust for confounding factors and rule out alternate possible causes for any observed effects. These approaches are described further below.

**SPECIFYING THE INTERVENTION**

Once the outcomes of interest have been determined, investigators should clearly specify the interventions to be evaluated so that outcomes and study design can be selected and developed in a manner that best suits the intervention(s) under evaluation. Even in cases in which the desire is to assess the effect of the program as a whole, ASPs are often composed of multiple interventions. Although many ASPs consist of similar interventions across different institutions, substantial variation might exist. Consideration for what interventions are being implemented, how they are being implemented, and in what populations they are being implemented is critical for identifying the expected impact and what factors might attenuate that effect.

A common initial focus of new ASPs is the transition of patients taking parenteral antibiotics to oral antibiotics. One leading reason for the focus of this intervention is its large potential cost savings for pharmacy, though it does not generally aim to reduce DOT. However, transitioning patients to oral antibiotics can lead to earlier removal of central indwelling catheters, thereby possibly reducing patient risk for central line–associated infection and other adverse events—all of which could serve as potential outcomes of interest in a study evaluating parenteral-to-oral conversions. Additionally, the ability to perform such conversions and the risk of these outcomes are influenced by other patient-level factors, such as use of other medications, which should be accounted for as potential confounders.

Many stewardship interventions also focus on reducing unnecessary continuation of empirically prescribed agents (eg, vancomycin), excessive duration of therapy, or unnecessary double coverage. Ultimately, these interventions aim to reduce the evolutionary selective pressures that drive increasing MDROs. Studying the association between these interventions and reduction in MDRO acquisition and spread can require large sample sizes or longer follow-up periods; ultimately, such studies are essential for supporting the central tenets of stewardship. Furthermore, the effectiveness of these interventions may vary by both patient (eg, disease severity) and provider characteristics (eg, medical specialty).

Many stewardship interventions also include a direct and active education program intended to alter clinician behavior, for example, provider training coupled with new antimicrobial order set for community-acquired pneumonia. Still, other interventions may have an indirect educational effect such as a change in the electronic order entry system that requires use of a new extended infusion protocol but is implemented without simultaneous provider education efforts. In this scenario, providers may seek out the rationale for the extended infusion; if the electronic intervention is removed, use of extended infusion may continue. Thus, studies of interventions that are directly or indirectly educational should consider how expected outcomes might be impacted. For example, when implementing a new order set for community-acquired pneumonia, the expected changes in antibiotic ordering may occur gradually as teams are trained and use of the new order set increases. The duration of the study should then be planned to appropriately capture the effect of the intervention.

**STUDY DESIGN**

Study design must be balanced between both theoretical ideals and ethical and practical considerations. An understanding of these ideals and the principles surrounding the ability of each design to contribute to causal inference facilitates conduct of a study with a high likelihood for strong internal validity, that is, a study that provides unbiased and accurate evidence of the relationship between the intervention and the outcome. Ideally, study design should be determined a priori to allow for integration of design and analysis features that can further strengthen the evaluation of an ASP intervention. When designing a study, it is important to consider holistically the methodology (eg, inclusion/exclusion criteria, control group selection, or analysis plan). Key aspects that should be considered in designing evaluation studies of ASPs are listed in Figure 1. The following sections describe the common and appropriate study designs for evaluation of ASP interventions, strengths and limitations of each, and design features that can further support the internal validity of the study; these designs are also summarized in Table 1.

**Randomized Control Trials**

RCTs can provide strong evidence for attributing observed effects to ASP interventions because the process of randomization is generally highly effective at removing the effect of confounding factors that threaten the internal validity of nonexperimental studies. In determining the appropriateness and feasibility of an RCT for evaluating an ASP intervention, specification of the
<table>
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<th>Characteristic</th>
<th>Randomized Control Trial</th>
<th>Cluster Randomized Control Trial</th>
<th>Cluster-Randomized Crossover</th>
<th>Nonrandomized Controlled Trial</th>
<th>Interrupted Time Series</th>
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<tr>
<td><strong>General description</strong></td>
<td>Intervention randomized to patients or clinicians; outcomes compared between intervention and control groups</td>
<td>Intervention randomized to different clusters (e.g., units or hospitals); outcomes compared between intervention and control clusters, controlling for correlation and cluster sizes</td>
<td>Two-phase design in which clusters are randomized to receive either intervention in phase 1 and standard care in phase 2 or vice versa; outcomes compared between intervention and standard of care across clusters</td>
<td>Intervention is assigned to patients or clinicians without randomization; outcomes are compared between intervention and control groups, controlling for known potential confounders</td>
<td>Intervention is assigned to either all study patients or specific intervention groups; pre-intervention and post-intervention outcome rates are analyzed to identify immediate and gradual changes following implementation of intervention; control groups may be included</td>
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<tr>
<td><strong>Unit of intervention allocation</strong></td>
<td>Individual</td>
<td>Cluster (e.g., hospital or unit)</td>
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<td>Individual</td>
<td>Cluster (e.g., hospital or unit)</td>
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<td><strong>Major advantage</strong></td>
<td>Randomization generally controls for known and unknown confounders</td>
<td>Randomization generally controls for known and unknown confounders at the cluster level</td>
<td>Randomization generally controls for known and unknown confounders; cluster serves as own control</td>
<td>Interventions may be allocated in a manner that considers logistical or practical implementation issues</td>
<td>Allows for identification of immediate and gradual changes in outcomes over time compared with baseline rates and trends; typically lower cost/effort to implement</td>
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<td><strong>Potential limitations</strong></td>
<td>May be logistical or ethical barriers to implementation</td>
<td>Requires larger numbers of patients than RCT; may be difficult to standardize intervention across clusters; differences in cluster characteristics may be difficult to fully control in analysis</td>
<td>Requires larger numbers of patients than RCT; may be difficult to standardize intervention across clusters; differences in cluster characteristics may be difficult to fully control in analysis; interventions may have lasting effects even after removed; may necessitate washout periods between phases</td>
<td>Potential confounding effects need to be controlled for using design or analytical methods; cannot control for unknown confounders</td>
<td>Requires longer follow-up periods; controlling for confounders more difficult</td>
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Abbreviation: RCT, randomized control trial.
intervention and outcome is critical. We previously used an
RCT design to evaluate a computerized clinical decision-
support system (CDSS) for ASPs [16]. An active ASP was in
place but required labor-intensive chart review to identify op-
opportunities to optimize antimicrobial use. During the study,
randomization was used to determine which patients would
trigger automated CDSS alerts to guide the ASP team interven-
tions. In this scenario, an RCT design was feasible and ethical.
While the intervention was randomly allocated at the patient
level in our study, stewardship interventions are commonly im-
plemented at the provider level and may have direct or indirect
educational effects. Therefore, it is often not feasible to random-
ize at the patient level because the intervention might have also
adversely affected the control group. However, randomiza-
tion at the provider level might still be performed. In this sce-
nario, it is critical to recognize that when the outcome of
interest is at the patient or population level, randomization
might not sufficiently remove confounding effects because the
patient case mix seen by each provider is associated with that
provider’s characteristics (eg, discipline, specialty training,
ward/unit of service, shift time). Weighted or blocked random-
ization schemes may help to remove these effects by purposeful-
ly taking these provider differences into consideration; however,
doing so might be difficult depending on the size of the institu-
tion and number of providers to be enrolled. Alternatively, stan-
dard analytical techniques such as multivariable regression
might be used to control for known and suspected confounders.

Cluster Randomized Trials
Cluster randomized trials are a variation of the RCT design in
which the unit of randomization is a naturally occurring group
such as a hospital, clinic, or other healthcare facility. The
strength of this design lies in the use of randomization to reduce
threats to internal validity and the use of multiple healthcare
sites, which can increase external validity (ie, generalizability).
Despite the methodological similarities among standard pa-
tient-level RCTs, design and statistical analysis of cluster ran-
domized trials are more complex. Although detailed statistical
guidance for sample size determinations and statistical analysis
exists elsewhere [17–19], we provide relevant considerations
here for analysis of cluster randomized trials of ASP interven-
tions. For studies that evaluate effects on patient-level outcomes,
the correlation structure of the data must be assessed and, if
necessary, must be accounted for in the analysis by use of ap-
propriate modeling techniques. It might also be necessary to
weight observations in studies in which cluster sizes differ. Ad-
ditionally, for studies evaluating intervention effects on patient-
level outcomes, adjustment for confounding might still be
necessary. Recently, several groups successfully used this ap-
proach to evaluate stewardship interventions in non–acute
care settings. In these settings, stewardship interventions have
the same goals of supporting prudent antibiotic use, but the in-
terventions themselves are not typically implemented through a
stewardship team. A major focus in outpatient settings has been
the reduction of unnecessary antibiotic prescription for viral
acute respiratory tract infection (ARTI). Recent cluster random-
ized trials of primary care clinics have evaluated different strat-
egies to reduce unnecessary prescription for ARTIs, from
educational interventions coupled with audit/feedback [20] to
clinical decision-support systems [21, 22] to shared decision-
making aids [23]. Cluster randomized trials have also been
used to evaluate stewardship interventions in emergency de-
partments [24] and long-term care facilities [25, 26]. However,
this approach has been underused to evaluate stewardship inter-
ventions in acute care settings. Because ASP interventions are
already in place in many acute care facilities, willingness to par-
ticipate in a study that randomly allocates an intervention might
be limited. Parallels can be drawn to infection control research,
where, despite the commonplace nature of many interventions,
cluster randomized trials [27, 28] have shown an ability to drive
the evidence-based refinement of best practice. Because the evi-
dence base for many common ASP interventions is limited,
similar work is needed to identify stewardship best practices.

Cluster-Randomized Crossover Studies
The basic cluster-randomized crossover study is one in which
groups (eg, units or hospitals) are randomized to receive either
the intervention in phase 1 and standard care in phase 2 or the
reverse—with standard care in phase 1 and the intervention in
phase 2. The design can be modified to include additional phas-
es to compare multiple interventions or to include washout per-
iods to account for transient effects of removed interventions.
As with the RCTs and cluster randomized trials, the primary
analysis approach should be intention to treat in order to retain
the benefits of randomization (ie, control for known and un-
known confounders). Van Werkhoven and colleagues recently
published an overview of the cluster-randomized crossover
study in which they used their own study as an example [29].
The authors designed a 3-phase cluster-randomized crossover
trial to compare beta-lactam monotherapy, beta-lactam and
macrolide combination therapy, and fluoroquinolone mono-
therapy as empiric treatment regimens for hospitalized patients
with community-acquired pneumonia. While the trial results are
still pending, the published methods paper by van Werkhoven
et al provides details regarding study design and analysis specific
to cluster-randomized crossover studies [29].

Nonrandomized Controlled Studies
Nonrandomized controlled studies, also known as clinical con-
trolled trials, include both intervention and control groups, and
outcomes can be compared between groups. The intervention is
not randomly assigned. While the approach to this design is
similar to that of observational studies such as the cohort study, the key differentiating factor is the assignment of the intervention, albeit not randomly, to patients. Examples of this study design for the evaluation of antimicrobial stewardship interventions include a study by Toltzis et al in which investigators compared an assigned antibiotic cycling schedule in one neonatal intensive care unit with another neonatal intensive care unit that retained standard unrestricted use to determine the impact on colonization rates with antibiotic-resistant gram-negative bacilli [30]. The lack of randomization leaves the study vulnerable to confounding effects. Design and analytical techniques for controlling known confounders can be used, similar to cohort studies. These include strategies such as matching, stratification, and multivariable regression.

**Quasi-Experimental Studies**

Quasi-experimental studies are a family of study designs used to evaluate the effect of a group/population-level intervention. Often referred to as pre/post or before-and-after studies, this design is commonly used for quality improvement projects in acute care settings. In quasi-experimental studies, the outcome of interest is measured at the group/population level (e.g., DOT or infection rates); for data analysis, the time point at which the intervention is introduced should be specifically identified. Similar to experimental or observational studies, the strength of quasi-experimental studies in providing unbiased evidence of the effect of an intervention varies but can be meaningfully improved through the addition of higher-order design features (described below).

The different types of quasi-experimental study designs are described in detail elsewhere [31–33]. Here, we focus on the strongest design for causal inference—interrupted time series (ITS). ITS studies require repeated measurements of the outcome across evenly spaced time intervals before and after the intervention. For example, Aldeyab et al used the ITS design to evaluate an intervention to reduce use of antimicrobials associated with a higher risk of subsequent *C. difficile* infection [9]. Monthly rates of *C. difficile* infection were recorded in the pre-intervention and post-intervention periods and rates and trends in rates were compared [9]. The strength of this approach lies in the ability to identify both immediate and gradual effects of an intervention. Yet, this strength is lost if the data are not appropriately analyzed. As we have shown [34], the effect of an intervention might be either over- or underestimates if statistical regression models are not appropriately parameterized to detect changes in intercept and slope terms in the post-intervention period. In other words, the regression model must include not only an indicator variable to identify the pre- vs post-intervention periods but must also include a variable to indicate the time since study initiation and time since intervention initiation. These variables are all necessary to allow the model to identify immediate changes and/or gradual changes in the outcome following intervention implementation. Furthermore, the collected data will be correlated, and failure to account for this correlation will result in biased statistical tests. These more advanced statistical principles for analysis of time series data are beyond the scope of this review and described elsewhere [31, 34, 35]. However, we wish to emphasize a few principles for designing an ITS study such that the design supports the intended analysis. It is recommended that a minimum of 10 data points (i.e., outcome measurements) be collected before and after the intervention. If seasonal or other secular trends are anticipated, additional data points might be necessary to appropriately model such trends. For studies in which the outcome is expressed as a rate (i.e., events per time unit), consideration of the width of the time intervals used in analysis is important. Although using smaller time intervals might create more data points before and after the intervention, it can also result in periods with very low event rates—or even periods with zero observed events. To balance the need for sufficient data points with stability in rate estimates, outcome data should be collected with sufficient granularity to allow periods to be collapsed or divided, if necessary. While the study is being conducted, attention should be given to recording any coincident events that might affect the outcome, such as antibiotic shortages, outbreaks, or facility expansion. If the timing of these coincident events is recorded, their potential effect can be adjusted for if there is sufficient statistical power.

As with other study designs, alternate explanations must be ruled out in order to attribute any observed change in outcome to the intervention. The use of higher-order design features facilitates this goal. To those accustomed to the more traditional experimental and observational study designs, the most apparent design feature is the addition of a control group. In an ITS study, the ideal control group is one in which the intervention is not implemented but is subject to influences by the same external forces (e.g., drug shortages, staffing changes) as the intervention group. It is also possible to leverage the common practice of rolling out an intervention to compare different groups in which the intervention is implemented at the different phases. Ideally, rolling out the intervention would be sufficiently staggered to allow outcome trends to be tracked in each group at each phase of implementation. The expected pattern would be that similar intervention effects are observed in different groups (e.g., wards or units) with each subsequent implementation of the intervention. The strength of this approach lies in the complexity of the expected pattern. With rolling out an intervention, if the expected pattern were achieved, it would be difficult to attribute that pattern to alternative causes. A similarly complex pattern of intervention effects would be expected from introducing the intervention and then subsequently removing it. Demonstrating the effect and subsequent reversal
of effect using this design feature provides strong evidence that the observed pattern can be attributed to the introduction and removal of the intervention. Another design feature is the use of a nonequivalent dependent variable, which is an alternate dependent outcome not subject to influence by the intervention but by any coincident events or forces. Selection of a nonequivalent dependent variable when evaluating an ASP intervention can be challenging because these interventions often have broader indirect effects on antimicrobial use. When possible, consultation with an epidemiologist and/or statistician may be advantageous in developing the study design and analytic approach.

CONCLUSIONS

A strong evidence base is critical to ensuring that ASPs are successful at increasing prudent antimicrobial use and limiting the development and spread of MDROs. The nature of ASP interventions and the outcomes of importance to patients can complicate study design selection and methodology. However, well-designed studies aimed at evaluating ASP impact on MDRO control and patient outcomes are critical for maintaining efficient, high-quality patient care and promoting prudent antibiotic use. Randomization of patients may not always be appropriate because interventions are typically applied at the provider level, whereas outcomes of interest are at the patient level. Furthermore, randomization at the clinician or institution level could still result in residual confounding effects. Antimicrobial stewardship programs also often implement multiple interventions simultaneously. Although this might necessitate assessment of multiple relevant outcomes, interventions can have global effects on patterns of antimicrobial use and, therefore, affect simultaneously enacted interventions. Even an intervention that seems to be single might consist of a bundle of elements, often incorporating an educational component or integrating infection control and ASP practices. In this case, it is important to recognize that the observed intervention effect results from the implementation of the entire bundle and that the effect attributable to any one component cannot be ascertained. Regardless, this bundled approach is often the best method to increase the initial likelihood of obtaining the desired effect.

The ability to assess the effect of an ASP intervention is also often limited by external forces beyond the control of investigators. Drug shortages, outbreaks, changes in personnel, and expansion of facilities or services can have major influence on outcomes. It can be difficult to isolate the true intervention effect from these secular influences. It is also important to recognize that many ASPs do not have data management or statistical support for programmatic evaluation. Thus, the lack of these resources can be a major barrier to the conduct of high-quality evaluations of ASPs.

There is a specific need to evaluate different ASP interventions in a broad array of clinical settings. Although the overarching goals of prudent antimicrobial prescribing are the same in all healthcare settings, the approach to supporting prudent prescribing should be tailored to each setting. As described previously herein, efforts have been made to curtail inappropriate antimicrobial use in primary care settings, emergency departments, long-term care facilities, and other non–acute care settings. These interventions fall under the broad umbrella of stewardship; whenever possible, we should learn from the experience gained from studies in all healthcare settings. Practicing prudent antimicrobial use in all healthcare settings will best attain the overarching goals of improving patient outcomes and limiting MDROs.

Conduct of rigorous and methodologically sound evaluations of ASP interventions can inform best practice and policy. The findings of several recent studies have shown the positive impact that ASPs can have on MDRO transmission [36–39] and patient outcomes [2, 40, 41]; however, more work is needed to further inform the field by identifying effective and efficient stewardship interventions. To identify the most effective interventions and implementation strategies, studies evaluating ASP interventions should be carefully planned and conducted to minimize bias and maximize internal validity. Evaluations in a breadth of patient settings and populations are also necessary to ensure generalizability. Therefore, continued effort is needed to show the value of ASPs beyond simple cost savings and to increase the evidence base that informs best practices for stewardship in all healthcare settings.

Notes

Acknowledgments. Editorial support was provided by ApotheCom ScopeMedical (Yardley, Pennsylvania) and funded by Cubist Pharmaceuticals. Supplement sponsorship. This article appears as part of a supplement titled “Antimicrobial Stewardship: Patients Over Process,” sponsored by Cubist Pharmaceuticals. Potential conflicts of interest. Both authors: No reported conflicts. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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