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Research Methods in Healthcare Epidemiology and Antimicrobial Stewardship—Quasi-Experimental Designs

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Quasi-experimental studies evaluate the association between an intervention and an outcome using experiments in which the intervention is not randomly assigned. Quasi-experimental studies are often used to evaluate rapid responses to outbreaks or other patient safety problems requiring prompt, nonrandomized interventions. Quasi-experimental studies can be categorized into 3 major types: interrupted time-series designs, designs with control groups, and designs without control groups. This methods paper highlights key considerations for quasi-experimental studies in healthcare epidemiology and antimicrobial stewardship, including study design and analytic approaches to avoid selection bias and other common pitfalls of quasi-experimental studies.

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BACKGROUND

The fields of healthcare epidemiology and antimicrobial stewardship (HE&AS) frequently apply interventions at a unit level (eg, the intensive care unit [ICU]). These interventions are often rapid responses to outbreaks or other patient safety problems requiring prompt, nonrandomized interventions. Quasi-experimental studies evaluate the association between an intervention and an outcome using experiments in which the intervention is not randomly assigned.[1,2] Quasi-experimental studies can be used to measure the impact of large-scale interventions or policy changes in which data are reported in aggregate and multiple measures of an outcome over time (eg, monthly rates) are collected.

Quasi-experimental studies vary widely in methodological rigor and can be categorized into 3 types: interrupted time-series designs, designs with control groups, and designs without control groups. The HE&AS literature contains many uncontrolled before-and-after studies (also called pre-post studies), but advanced quasi-experimental study designs should be considered to overcome the biases inherent in uncontrolled before-and-after studies.[3] In this article, we highlight methods to improve quasi-experimental study design, including the use of a control group that does not receive the intervention[2] and the use of the interrupted time series study design, in which multiple equally spaced observations are collected before and after the intervention.[4]

ADVANTAGES AND DISADVANTAGES

The greatest advantages of quasi-experimental studies are that they are less expensive and require fewer resources than individual randomized controlled trials (RCTs) or cluster randomized trials (Table 1). Quasi-experimental studies are appropriate when randomization is deemed unethical (eg, in studies of the effectiveness of hand hygiene protocols).[1] With IRB approval as appropriate, quasi-experimental studies are often performed at a population level rather than an individual level; thus, they can include patients who are often excluded from RCTs, such as those too ill to give informed consent or urgent surgery patients.[5] Quasi-experimental studies are also pragmatic because they evaluate the real-world effectiveness of an intervention implemented by hospital staff rather than the efficacy of an intervention implemented by research staff under research conditions.[5] Therefore, quasi-experimental studies may also be more generalizable and have better external validity than RCTs.

The greatest disadvantage of quasi-experimental studies is that randomization is not used, which limits the study's ability to reveal a causal association between an intervention and an outcome. A practical challenge to quasi-experimental studies may arise when some hospital units are encouraged to introduce an intervention, while other units retain the standard of care and may feel excluded.[2] Importantly, researchers need to be aware of the biases that may occur in quasi-experimental studies that may lead to a loss of internal

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TABLE 1. Advantages, Disadvantages, and Important Pitfalls in Using Quasi-Experimental Designs in Healthcare Epidemiology Research

Advantages	Notes
Less expensive and time-consuming than RCTs or cluster randomized trials	Do not need to randomize groups
Pragmatic	Includes patients that are often excluded in RCTs; tests effectiveness more than efficacy; may have good external validity
Can retrospectively analyze policy changes	Even if policy implementation is out of the researcher's control
Meets some requirements of causality	Quasi-experimental studies meet some requirements for causality including temporality, strength of association, and dose response.[2]
Designs can be strengthened with control groups, multiple measures over time, and crossovers.	Not the gold standard of establishing causation but can be next level below RCT if well designed
Disadvantages	**Notes**
Retrospective data is often incomplete or difficult to obtain	Needs processes to assess availability, accuracy, and completeness during baseline phase before implementation
Not randomized	Nonrandomized designs tend to overestimate effect size.[3] Does not meet all requirements to determine causality Lack of internal validity
Potential pitfalls	**Notes**
Selection bias	When group receiving the intervention differs from the baseline group[2]
Maturation bias	Maturation bias can occur when natural changes over the passage of time may influence the study outcome.[1] Examples include seasonality, fatigue, aging, maturity or boredom.[2]
Hawthorne Effect	Could bias quasi-experimental studies in which baseline rates are collected retrospectively and intervention rates are collected prospectively, because the intervention group could be more likely to improve when they are aware of being observed[3]
Historical bias	Historical bias is a threat when other events occur during the study period that may have an effect on the outcome.[2]
Regression to the mean	Regression to the mean is a statistical phenomenon in which extreme measures tend to naturally revert back to normal.[2]
Instrumentation bias	Instrumentation bias occurs when a measuring instrument changes over time (eg, improved sensitivity of laboratory tests) or when data are collected differently before and after an intervention.[2]
Ascertainment bias	Systematic error or deviation in the identification or measurement of outcomes
Reporting bias	Reporting bias is especially prevalent in retrospective quasi-experimental studies, in which researchers only publish quasi-experimental studies with positive findings and do not publish null or negative findings.
Need advanced statistical analysis when using more complex designs	With time-series designs, interrupted time-series analysis should be used, not just single measurements before and after a response to an outbreak. Should account for intracluster correlation in power calculations

NOTE. RCT, randomized controlled trial.

validity, especially selection bias in which the intervention group may differ from the baseline group.[2] Types of selection bias that can occur in quasi-experimental studies include maturation bias, regression to the mean, historical bias, instrumentation bias, and the Hawthorne effect.[2] Lastly, reporting bias is prevalent in retrospective quasi-experimental studies in which researchers publish only quasi-experimental studies with positive findings and do not publish null or negative findings.

PITFALLS AND TIPS

Key study design and analytic approaches can help avoid common pitfalls of quasi-experimental studies. Quasi-experimental studies can be as small as an intervention in a single ICU or as large as implementation of an intervention in multiple countries.[6] Multisite studies generally have stronger external validity. Subtypes of quasi-experimental study designs are shown in Table 2 and the Supplemental Figure.[1,2,7] In general, the higher numbers assigned to the designs in the table are associated with more rigorous study designs. Quasi-experimental studies meet some requirements for causality, including temporality, strength of association, and dose response.[1,8] The addition of concurrent control groups, time-series measurements, sensitivity analyses, and other advanced design elements can further support the hypothesis that the intervention is causally associated with the outcome. These design elements aid in

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TABLE 2. Major Quasi-Experimental Design Types and Subtypes

Type and Subtype	Description	Notation
A. INTERRUPTED TIME-SERIES QUASI-EXPERIMENTAL DESIGNS		
15	Interrupted time series that uses switching replications and a control group	A1c A2c A3c X A4t A5t A6t removeX A7c A8c A9c A10c B1c B2c B3c B4c B5c B6c X B7t B8t B9t B10t
14	Interrupted time series with repeated treatment design[13]	A1c A2c A3c X A4t A5t removeX A6c A7c X A8t A9t
13	Interrupted time series removing the treatment at a known time	A1c A2c A3c A4c X A5t A6t A7t A8t removeX A9c A10c
12	Interrupted time series with a nonequivalent dependent variable[14]	($A1c^{v}$, $A1c^{n}$) ($A2c^{v}$, $A2c^{n}$) ($A3c^{v}$, $A3c^{n}$) X ($A4t^{v}$, $A4t^{n}$) ($A5t^{v}$, $A5t^{n}$)
11	Interrupted time series with an untreated control group[12]	A1c A2c A3c A4c A5c X A6t A7t A8t A9t A10t B1c B2c B3c B4c B5c B6c B7c B8c B9c B10c
10	Simple interrupted time series[11,15]	A1c A2c A3c A4c A5c X A6t A7t A8t A9t A10t
B. QUASI-EXPERIMENTAL DESIGNS THAT USE CONTROL GROUPS		
9	The control group design that uses dependent pretest and posttest samples and switching replications	A1c X A2t removeX A3c B1c B2c X B3t
8	The untreated-control group design that uses dependent pretest and posttest samples and a double pretest	A1c A2c X A3t B1c B2c B3c
7	The untreated control group design that uses dependent pretest and posttest samples	A1c X A2t B1c B2c
6	The posttest-only design that uses an untreated control group	X A1t B1c
C. QUASI-EXPERIMENTAL DESIGNS THAT DO NOT USE CONTROL GROUPS		
5	The repeated-treatment design	A1c X A2t removeX A3c X A4t
4	The removed-treatment design	A1c X A2t A3t removeX A4c
3	The 1-group, pretest-posttest design that uses a nonequivalent dependent variable	($A1c^{v}$, $A1c^{n}$) X ($A2t^{v}$, $A2t^{n}$)
2	The 1-group, pretest-posttest design that uses a double pretest	A1c A2c X A3t
1	The 1-group, pretest-posttest design	A1c X A2t

NOTE. Classification types adapted prior publications[1,2]; A = primary group of interest; B = control group; 1,2,3, etc. = observations for a Group; X = intervention; remove X = remove intervention; ^{v} = variable of interest; ^{n} = non-equivalent dependent variable; t = treatment group; c = no treatment. Time moves from left to right. Citations are published examples from the literature.

limiting the number of alternative explanations that could account for the association between the intervention and the outcome.[2]

Quasi-experimental studies can use observations that were collected retrospectively, prospectively, or a combination thereof. Prospective quasi-experimental studies use baseline measurements that are calculated prospectively for the purposes of the study, then an intervention is implemented and more measurements are collected. It is often necessary to use retrospective data when the intervention is outside the researcher's control (eg, natural disaster response) or when hospital epidemiologists are encouraged to intervene quickly in response to external pressure (eg, high central-line–associated bloodstream infection [CLABSI] rates).[2] However, retrospective quasi-experimental studies are at a higher risk of bias than prospective quasi-experimental studies.[2]

The first major consideration in quasi-experimental studies is the addition of a control group that does not receive the intervention (Table 2, subtypes 6–9, 11, and 15). Control groups can assist in accounting for seasonal and historical biases. If an effect is seen among the intervention group but not the control group, then causal inference is strengthened. Careful selection of the control group can also strengthen causal inference. Detection bias can be avoided by blinding those who collect and analyze the data to which group received the intervention.[2]

The second major consideration is designing the study to reduce bias, either by including a non-equivalent dependent variable or by using a removed-treatment design, a repeated treatment design, or a switching replications design. Non-equivalent dependent variables should be similar to the outcome variable except that the non-equivalent dependent

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variable is not expected to be influenced by the outcome (Table 2, subtypes 3 and 12). In a removed-treatment design, the intervention is implemented then taken away, and observations are made before, during, and after implementation (Table 2, subtypes 4, 5, and 13). This design can only be used for interventions that do not have a lasting effect on the outcome that could contaminate the study. For example, once staff members have been educated, that knowledge cannot be removed.[2] Researchers must clearly explain before implementation that the intervention will be removed; otherwise, this can lead to frustration or demoralization by the hospital staff implementing the intervention.[2] In the repeated-treatment design (Table 2, subtypes 5 and 14) interventions are implemented, removed, then implemented again. Similar to the removed-treatment design, the repeated-treatment design should only be used if the intervention does not have a lasting effect on the outcome. In a switching replications design, also known as a crossover design, one group implements the intervention while the other group serves as the control. The intervention is then stopped in the first group and implemented in the second group (Table 2, subtypes 9 and 15). The crossovers can occur multiple times. If the outcomes are only impacted during intervention observations but not in the control observations, then there is support for causality.[2]

A third key consideration for quasi-experimental studies with an interrupted time-series design is to collect many evenly spaced observations during both the baseline and intervention periods. Multiple observations are used to estimate and control for underlying trends in data, such as seasonality and maturation.[2] The frequency of the observations (eg, weekly, monthly, or quarterly) should have clinical or seasonal meaning so that a true underlying trend can be established. There are conflicting recommendations regarding the minimum number of observations needed for a time-series design, but they range from 20 observations before and 20 after intervention implementation to 100 observations overall.[2–4,9] The interrupted time-series design is the most effective and powerful quasi-experimental design, particularly when supplemented by other design elements.[2] However, time-series designs are still subject to biases and threats to validity.

The final major consideration is ensuring an appropriate analysis plan. Time-series study designs collect multiple observations of the same population over time, resulting in auto-correlated observations.[2] For instance, carbapenem-resistant *Enterobacteriaceae* (CRE) counts collected 1 month apart are more similar to one another than CRE counts collected 2 months apart.[4] Basic statistics (eg, χ^2 test) should not be used to analyze time-series data because they cannot take into account trends over time and they rely on an independence assumption. Time-series data should be analyzed using either regression analysis or interrupted time-series analysis (ITSA).[4] Linear regression models or generalized linear models can be used to evaluate the slopes of the observed outcomes before and during implementation of an intervention. However, unlike regression models, ITSA relaxes the independence assumption by combining a correlation model and a regression model to effectively remove seasonality effects before addressing the impact of the intervention.[2,4] ITSA assesses the impact of the intervention by evaluating the changes in the intercept and slope before and after the intervention. ITSA can also include a lag effect if the intervention is not expected to have an immediate result, and additional sensitivity analyses can be performed to test the robustness of the findings. We recommend statistician consultation while designing the study to choose the most appropriate model and to help perform power calculations that account for correlation.

Key considerations for designing, analyzing, and writing a quasi-experimental study can be found in the Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) statement and are summarized in Table 3.[10]

EXAMPLES OF PUBLISHED QUASI-EXPERIMENTAL STUDIES IN HE&AS

Recent quasi-experimental studies illustrated strengths and weaknesses that require attention when employing this study design.

A recent prospective quasi-experimental study (Table 2, subtype 10) implemented a multicenter bundled intervention to prevent complex *Staphylococcus aureus* surgical-site infections.[11] The study exemplified the strengths of quasi-experimental design using a pragmatic approach in a real-world setting that even enabled identification of a dose response to bundle compliance. To optimize validity, the authors included numerous observation points before and after the intervention and used time-series analysis. This study did not include a concurrent control group, and outcomes were collected retrospectively for the baseline group and prospectively for the intervention group, which may have led to ascertainment bias.

Quach et al[12] performed a quasi-experimental study (Table 2, subtype 11) to evaluate the impact of an infection prevention and quality improvement intervention of daily chlorhexidine gluconate (CHG) bathing to reduce CLABSI rates in the neonatal ICU. The primary strength of this study was that the authors used a non-bathed concurrent control group. Given that the baseline rates of CLABSI exceeded the National Healthcare Surveillance Network (NHSN) pooled mean and that the observation that the concurrent control group did not see a reduction in rates post-intervention, the treatment effect was more likely due to the treatment than to regression to the mean, seasonal effects, or secular trends.

Yin et al[13] performed a quasi-experimental study (Table 2, subtype 14) to determine whether universal gloving reduced HAIs in hospitalized children. This retrospective study compared the winter respiratory syncytial virus (RSV) season during which healthcare workers (HCWs) were required to wear gloves for all patient contact and the

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TABLE 3. Checklist of Key Considerations When Developing a Quasi-Experimental Study

CONSIDERATIONS FOR RETROSPECTIVE AND PROSPECTIVE QUASI-EXPERIMENTAL STUDIES
1. Determine PICO: population, intervention, control group, outcomes (specify primary vs secondary outcomes)
2. What is the hypothesis?
3. Is it ethical or feasible to randomize patients to the intervention?
4. Will this be a retrospective or prospective study or a combination of both?
5. What are the main inclusion and exclusion criteria?
6. Will anyone (participants, study staff, research team, analyst) be blinded to the intervention assignment?
7. Consider options for control group
8. Consider options for nonequivalent dependent variable
9. How will the observations (outcomes) be measured?
10. How many observations can be measured before and after intervention?
11. How should the observations be spaced to account for seasonality? Weekly? Monthly? Quarterly?
12. Do you hypothesize that the intervention will diffuse quickly or slowly? (Eg, are changes in the outcomes expected right away or only after a phase-in period?)
13. Do you hypothesize that the intervention will have a lasting effect on the outcome? (If yes, do not use crossover design.)
14. What is the analysis plan? (Consult a statistician.)
15. If the unit of analysis differs from the unit of assignment, what analytical method will be used to account for this (eg, adjusting the standard error estimates by the design effect or using multilevel analysis)?
16. What sample size is needed to be powered to see a significant difference? (Consult a statistician.)
17. Will the analysis strategy be intention to treat or how will noncompliers be treated in the analysis?
ADDITIONAL CONSIDERATIONS FOR QUASI-EXPERIMENTAL STUDIES WITH PROSPECTIVE COMPONENTS
18. What will be the unit of delivery (eg, individual patient or unit or hospital)?
19. How will the units of delivery be allocated to the intervention?
20. Who will deliver the intervention (eg, study team or healthcare workers)?
21. How and when will the intervention be delivered?
22. How will compliance with the intervention be measured?
23. Will there be activities to increase compliance or adherence (eg, incentives, coaching calls)?

non-winter, non-RSV season when HCWs were not required to wear gloves. Because the study period extended many calendar years, the design facilitated multiple crossovers removing the intervention as well as the use of time-series analysis. This study did not have a control group (another hospital or unit that did not require universal gloving during RSV season) nor did it have a nonequivalent dependent variable.

MAJOR POINTS

Quasi-experimental studies are less resource intensive than RCTs; they test real-world effectiveness; and they can support a hypothesis that an intervention is causally associated with an outcome. These studies are subject to biases that can be limited by carefully planning the design and analysis. Several key strategies to limiting bias should be considered: including a control group, including a non-equivalent variable or removed-treatment design, collecting adequate observations before and during the intervention, and using appropriate analytic methods (ie, ITSA).

CONCLUSION

Quasi-experimental studies are important for HE&AS because practitioners in those fields often need to perform nonrandomized studies of interventions at the unit level of analysis. Quasi-experimental studies should not always be considered methodologically inferior to RCTs because quasi-experimental studies are pragmatic and can evaluate interventions that cannot be randomized due to ethical or logistic concerns.[10] Currently, too many quasi-experimental studies are uncontrolled before-and-after studies using suboptimal research methods. Advanced techniques such as use of control groups and non-equivalent dependent variables, as well as interrupted time-series design and ITSA should be used in future research.

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SUPPLEMENTARY MATERIAL

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