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Review

Interventions to control nosocomial infections: study designs and statistical issues

M. Wolkewitz [a,*], A.G. Barnett [b], M. Palomar Martinez [c], U. Frank [d], M. Schumacher [a] for the IMPLEMENT Study Group

[a] Institute of Medical Biometry and Medical Informatics, University of Freiburg, Freiburg, Germany
[b] Institute of Health and Biomedical Innovation and School of Public Health and Social Work, Queensland University of Technology, Queensland, Australia
[c] Hospital Arnau de Vilanova, Lleida, Universitat Autonoma de Barcelona, Barcelona, Spain
[d] Department of Infectiology, Heidelberg University Hospital, Heidelberg, Germany

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SUMMARY

There is a wide range of potential study designs for intervention studies to decrease nosocomial infections in hospitals. The analysis is complex due to competing events, clustering, multiple timescales and time-dependent period and intervention variables. This review considers the popular pre–post quasi-experimental design and compares it with randomized designs. Randomization can be done in several ways: randomization of the cluster [intensive care unit (ICU) or hospital] in a parallel design; randomization of the sequence in a cross-over design; and randomization of the time of intervention in a stepped-wedge design. We introduce each design in the context of nosocomial infections and discuss the designs with respect to the following key points: bias, control for non-intervention factors, and generalizability. Statistical issues are discussed. A pre–post-intervention design is often the only choice that will be informative for a retrospective analysis of an outbreak setting. It can be seen as a pilot study with further, more rigorous designs needed to establish causality. To yield internally valid results, randomization is needed. Generally, the first choice in terms of the internal validity should be a parallel cluster randomized trial. However, generalizability might be stronger in a stepped-wedge design because a wider range of ICU clinicians may be convinced to participate, especially if there are pilot studies with promising results. For analysis, the use of extended competing risk models is recommended.

Introduction

The effective control of nosocomial infections (NIs) is one of the most important priorities in hospitals. There are many interventions that are effective at controlling infections including those caused by antibiotic resistant organisms. Examples include implementation of guidelines, controlled antibiotic stewardship, improved hygiene practices, isolation of infected patients, and universal screening at hospital admission. The use of strategic bundles of evidence-based procedures has had some success in reducing NIs – for instance, in controlling catheter-related bloodstream infections in the intensive care unit (ICU).[1]

Proving that an intervention is successful is rather challenging and requires at least one study with an appropriate

* Corresponding author. Address: Institute of Medical Biometry and Medical Informatics, Stefan-Meier-Str. 26, 79104 Freiburg, Germany. Tel.: +49 761 2037703; fax: +49 761 2037700.
E-mail address: wolke@imbi.uni-freiburg.de (M. Wolkewitz).

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design. Shardell *et al.* have produced an overview of quasi-experiments to antimicrobial resistance intervention studies.[2] In this review, we extend their approach and discuss several aspects of randomization: randomization of the cluster (ICU or hospital) in a parallel design; randomization of the sequence in a cross-over design; and randomization of the timing in a stepped-wedge design.

Outcome definition

There are several definitions of outcome in NI intervention studies. A well-established definition is the incidence rate of infection which is collected in monthly records [e.g. number of new meticillin-resistant *Staphylococcus aureus* (MRSA) infections per 1000 patient-days]. The most suitable denominator is often patient-days, but others are also suitable depending on the outcome of interest, e.g. number of patients, catheter-days for catheter-related bloodstream infections, or ventilation-days for ventilator-associated pneumonia. In the following, we use the term 'infection rates' for incidence rates of infection.

Even though the primary interest is in incidence rates of infections, one should keep in mind that discharge from the hospital and dying in the hospital without NI are competing events for NI.[3,4] Thus, the collection of monthly records of discharge or mortality rates without NI is necessary. Ideally, data should be available on the patient-individual rather than on the aggregated level.

Level of inference

Even though randomized trials at a patient level exist in this field, it is often not feasible to measure intervention effects at the individual patient level due to potentially complex transmission patterns.[5] Therefore, we assume that trials are intended to evaluate interventions at the hospital or at the ICU level. In the following, we use the term 'cluster' for hospital or ICU. From a statistical point of view, clusters require special attention since individual patients within a hospital are correlated and thus not independent.

Bias in intervention studies to control NI

Intervention studies to control NIs have a specific challenge, namely the Hawthorne effect: healthcare workers might improve their behaviour (e.g. in hygiene practices) simply in response to being studied and not in response to the intervention. For instance, Kohli *et al.* explored the Hawthorne effect with respect to hand hygiene performance.[6] This effect is a problem in all designs which only consider within-cluster comparisons. It could be addressed by adding a control group and assuming that the Hawthorne effect acts on the intervention as well as on the control group with the same intensity.

The choice of a control group can be inappropriate in the sense that the intervention and the control group are not comparable. This selection bias can be avoided if the groups are similar in all important respects such as the baseline infection rate, the size of cluster (number of beds in the ICU/hospital), specialty of the cluster (surgical or medical ICU), overall patient-days, average length of stay, and mortality rates.

Another challenge is to control for non-intervention factors which have an impact on the outcome (e.g. incidence rate of infection). Examples are a general better understanding of NI infections (which usually increases with time) and an implementation of new guidelines to control NI (which is independent of the intervention of interest). Thus, the minimum requirement to control for non-intervention factors is by adjusting for period effects.

Designs

Figure 1 presents the five designs: pre–post intervention, pre–post intervention with control, parallel, cross-over, and stepped-wedge cluster randomized.

Design A: pre–post intervention

The most popular approach is a pre–post quasi-experimental design without any type of randomization (Figure 1A). There is a control period during which baseline data of monthly records of infection rates are collected (pre-intervention data). Then, after a certain time (usually about 12 until 36 months), there is the intervention at the cluster level. After the intervention, post-treatment data are collected for a certain period (usually about the same period as before the intervention). These data are best analysed with interrupted time-series regression models.[2] Interrupted time-series studies allow researchers to estimate whether and how much an intervention changed the infection rates. They are suitable to show whether these effects occurred immediately after the intervention or with delay, and whether effects are long term.[7] They are particularly useful for interventions in outbreak settings and recommended by the ORION (Outbreak Reports and Intervention studies Of Nosocomial infection) statement.[8]

Control for bias and non-intervention factors

In this design inference is made by a within-cluster comparison. This has the advantage that it controls for cluster-specific factors [such as hospital size, average length of stay (or patient-days as the combination of both), mortality rates, etc.] since each cluster is its own control. However, it should be checked (and reported) whether these factors changed during the study period, especially when the intervention could influence these factors.

The main disadvantage is that it is not clear whether an estimated intervention effect was actually due to the Hawthorne effect or to calendar-time-related factors such as an increased awareness with respect to the NI.

One major disadvantage is the limited generalizability. Often only a small number (between one and three) of clusters is used. In this case – and assuming that there are no calendar-time-related factors – inference is only valid for these clusters (which might be enough for, e.g. a large hospital) but there is a lack of generalizability. That means that a significant intervention effect is not in principle generalizable to others: the intervention might work for this specific cluster but not for others. One reason for a lack of generalizability might be the variation in baseline infection rates.

Possible improvements

An example of a thorough analysis of an interrupted time-series is the study made by Fowler *et al.*[9] They investigated