Commentary: Back to the future with Sir Bradford Hill: statistical analysis with hospital-acquired infections

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In this issue of the IJE, Schumacher and colleagues1 present examples demonstrating some common and under-appreciated pitfalls when analysing observational cohort studies of hospital-acquired infections (HAIs). Specifically, the pitfalls stem from a failure to appropriately account for the risk period of the HAI, because HAIs may occur at any time during hospitalization. By discussing Sir Austin Bradford Hill and William Farr as epidemiological and statistical points of reference, the authors implicitly note that, in general, pitfalls occur when investigators do not realize that problems encountered in a modern milieu can be tackled by considering first principles. In this case, the first principles are: (i) selecting an appropriate study design and understanding its statistical implications; (ii) knowing the assumptions of candidate statistical methods; and (iii) recognizing when the assumptions are violated. Schumacher and colleagues1 consider two broad study designs: one in which the HAI is an exposure, and another in which HAI is the outcome. Below, we discuss issues of both designs through the lens of epidemiological and statistical first principles.

When studying HAI as an exposure that may lead to outcomes such as excess morbidity, mortality, hospital length of stay or cost, the authors focus on the problem of time-dependent bias and duration bias. These forms of selection bias are issues that often go unrecognized in studies of HAIs. Both types of bias occur primarily when the study design does not allow for flexible definitions of exposure, whereby individuals who are negative at admission and develop an HAI later during the hospital stay are either (i) assigned to the unexposed group for the duration of their follow-up based on their status assessed at admission, or (ii) assigned to the exposed group for the duration of their follow-up based on their subsequent HAI. To solve this problem, the authors encourage investigators to consider a multi-state model framework. However, this issue may be more clearly defined as that of time varying-exposure, which can be appropriately accommodated by accessible methods, such as the Cox model, as suggested by the authors.1 Alternatively, researchers can use log-linear regression to allow exposure covariates to be modelled flexibly and in a time-varying fashion (see, for example Jumanji et al.2). In an analysis with an exposure that is subject to lead-time bias, investigators must take care in defining baseline and appropriately accounting for the effects of HAI timing. Accessible methods based on the Cox model with inverse probability weighting are available.3

Researchers may encounter additional issues under less ideal circumstances. For example, to enhance feasibility, investigators often rely on the data collection procedures already in place at participating hospitals. As a result, HAI ascertainment does not occur continuously, and hence the timing of HAI may not be known with certainty. In this case, the exposure is operationalized as timing of HAI detection rather than timing of HAI onset. HAI onset, the presumed gold-standard exposure, therefore becomes an interval-censored observation, which means that HAI onset is known to occur within some window of time, but the exact time is unknown. Furthermore, the censoring may be informative in cases where ascertainment is of variable intensity, as might occur when specimens are more frequently cultured from sicker patients than from healthier patients. An associated problem is confounder adjustment. Because the timing of the exposure is unknown, an attempt to adjust for time-varying factors, such as severity of...
illness or colonization pressure, may lead to an adjustment for mediators rather than confounders.\textsuperscript{4-6}

When studying HAI as an outcome, the authors highlight the issue of competing risks, a problem in the context of randomized controlled trials, quasiexperimental\textsuperscript{7} and observational cohort studies. Oftentimes, researchers are under the misconception that the analysis might be simplified by defining the outcome as hospital acquired infection, rather than just ‘infection’. However, in the former case, hospital discharge is a competing risk, whereas in the latter case, hospital discharge is censoring (albeit likely dependent).\textsuperscript{8} To overcome the problem of competing risks, some researchers have opted for the logistically challenging ‘patient-centred’ design that involves following up with patients after their discharge for a pre-specified length of time.\textsuperscript{9} This approach is not always feasible, especially in the context of multisite trials with thousands of admissions. Thus, in HAI studies, competing risks are the rule rather than the exception.

Once again, when HAI is the outcome and risk factors are assessed, researchers may encounter additional challenges such as informative interval censoring\textsuperscript{10,11} when they rely on on-site data collection procedures. This problem is exacerbated when colonization with an infection-causing agent (e.g. methicillin-resistant \textit{Staphylococcus aureus}—MRSA), rather than infection, is the outcome. In the hospital setting, on-site procedures include surveillance culturing and clinical culturing. Surveillance cultures (e.g. nasal swabs for MRSA) are collected from patients without symptoms to detect prevalent colonization or incident acquisition, whereas clinical cultures (e.g. blood cultures) are collected to diagnose an active infection. In this case, relying on surveillance cultures may mitigate bias and increase variance due to censoring into wide intervals, but relying on clinical cultures may increase bias because patients who are cultured are those who are most likely to be colonized or infected.

The issues surrounding studies of HAIs are indeed epidemiologically and statistically challenging, but should not distract researchers from principles such as study design and understanding statistical assumptions. Reiterating—and paraphrasing—Sir Bradford Hill, the adroit researcher must understand the subject matter and context as well as the statistical and epidemiological methods. This task can be accomplished in modern settings by assembling multidisciplinary research teams and fostering communication between disciplines. The paper by Schumacher \textit{et al.}\textsuperscript{1} is a valuable step toward helping members of teams acquire a vocabulary, ask revealing questions and use the appropriate analytical approach. In other words, it can help researchers rediscover first principles for use in tackling modern problems.

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\textbf{References}


