Ignoring ‘downstream infection’ in the evaluation of harm reduction interventions for injection drug users

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Abstract. Harm reduction interventions to reduce blood-borne disease incidence among injection drug users (IDUs). A common strategy to estimate the long-term impact of such interventions is to examine short-term incidence changes within a specific group of individuals exposed to the intervention. Such evaluations may overstate or understate long-term program effectiveness, depending upon the relationship between short-term and long-term incidence and prevalence. This short paper uses steady-state comparisons and a standard random-mixing model to scrutinize this evaluation approach. It shows that evaluations based upon short-term incidence changes can be significantly biased. The size and direction of the resulting bias depends upon a simple rule. For modest interventions, such analyses yield over-optimistic estimates of program effectiveness when steady-state disease prevalence exceeds 50% absent intervention. When steady-state prevalence is below 50%, such analyses display the opposite bias.

Key words: Epidemiological modeling, Harm reduction, Hepatitis C, HIV, Injection drug use, Secondary infection

Abbreviations: HCV = Hepatitis C; HIV = Human immunodeficiency virus; IDU = Injection drug user

Introduction

Many interventions seek to slow the spread of infectious disease in settings that do not allow complete data regarding program impact or disease incidence and prevalence. A common strategy to estimate the long-term impact of such interventions is to examine short-term incidence changes within a specific group exposed to the intervention. An inherent shortcoming of such evaluation is that short-term analysis can either overstate or understate the impact of prevention interventions on long-run disease spread. Although these generic limitations of short-term analysis are well-known, their full implications are easily overlooked.

Harm reduction interventions for injection drug users (IDUs) provide an especially important application in which short-term analysis and naive intuition may be misleading. In simplest form, harm reduction seeks to prevent blood-borne diseases without altering the underlying pattern or intensity of substance use. Those who implement harm reduction hope that such interventions will induce some IDUs to enter treatment or to reduce their drug use. However, harm reduction is intended to slow disease spread even without such behavioral effects. Indeed the most widely-cited evaluation of syringe exchange programs (SEP) examines short-term changes in the proportion of infected needles, and then infers changes in disease incidence and prevalence assuming no underlying change in the frequency and duration of injection drug use.

This short paper uses steady-state comparisons and a random-mixing model to examine this evaluation approach. It shows that reliably-measured short-term changes in disease incidence can provide biased estimates of the long-run effectiveness of studied interventions. A simple rule describes the direction and size of the resulting bias.

Background

Given the covert nature of injection drug use, harm reduction is difficult to evaluate using standard methods. In principal, however, many researchers and policy makers take clinical trials as the point of departure in evaluating such interventions. Though study designs differ, the general strategy is to estimate infection rates per person per unit time among IDUs exposed to the intervention, and to compare these rates to observed patterns within a comparison group of other IDUs. The observed difference in short-term disease incidence is then used to compute policy-relevant measures such as the efficacy or the costs per averted infection associated with the intervention.

Such comparisons might arise from prospective randomized trials, or more commonly from
non-experimental comparisons with pertinent comparison groups. Such analyses might also be conducted based upon pre-post comparisons within the treated group itself. The development of novel incidence–estimation techniques such as the detuned assay test may increase the use of short-term incidence analysis in harm reduction program evaluation.

Such evaluations face many threats to internal and external validity: selection bias, cross-over effects, non-random attrition, inadequate power, questionable applicability of best-practice results to the widespread implementation of lower-quality interventions [1, 2]. IDUs are a hidden population whose health status and underlying risk behavior is difficult to observe. By now, these evaluation challenges are familiar to clinicians, to researchers, and to many policy makers.

Less widely-recognized is the fact that short-term comparisons may not capture the long-run impact of broadly-implemented prevention efforts. Short-term studies do not capture the full period that treated individuals face disease risk. Such evaluations may therefore fail to capture the possibility that treated individuals will become subsequently infected.

Regardless of specific design, most such evaluations observe a small fraction of the total population facing disease risk. Except in rare cases, evaluations cannot measure ‘secondary’ or ‘downstream’ infections attributable to members of the treated group. Even when such data are possible to collect, this effort requires prolonged and elaborate investigation that is often infeasible. Thus, downstream infections are generally ignored. Yet downstream infections are often important, and can amplify or reduce the ultimate impact of the studied intervention.

Vaccination that confers permanent immunity provides one clear example of such effects. Vaccinating one child protects her from illness. Yet vaccination also protects other children whom she might have otherwise infected [3]. Evaluation strategies that measure disease patterns within the immunized group while ignoring secondary infection can severely understate the benefits of vaccination [4].

Motivated by this example, one might think that ignoring downstream infections always understates the benefits of prevention efforts. Metzger et al. [5, 6] compare the incidence of human immunodeficiency virus (HIV) among methadone maintenance patients and among out-of-treatment injection drug users. One might assume that an expanded analysis that considers the safety of one’s sex and needle-sharing partners would yield even more favorable results.

This intuition is wrong when prevention interventions provide imperfect or temporary protection to treated individuals. In the case of vaccination, those with declining effectiveness over time can produce counterintuitive effects on disease spread [3]. In the case of substance abuse treatment, some methadone clients who remain uninfected during the study period will subsequently become infected and may then infect others. Because treatment merely delays infection for some treated individuals, short-term group differences in disease incidence can provide overly optimistic estimates of program effectiveness.

Epidemiological model

When, then, do evaluations that ignore downstream infection create large biases, and in which direction? A susceptible-infected model with random mixing among IDUs [7, 8, 9] provides one answer to this question. Within this simplified but empirically relevant framework, there is a constant-size population of $N$ active IDUs. Every week, some fraction $\delta$ will exit the population of active users due to death. At the same time, some number $\theta$ uninfected individuals are recruited into the population of active users. In steady-state, $N = \theta / \delta$. These population parameters are assumed to be fixed. They do not depend upon disease prevalence within the population.

The dynamics of disease spread are described by an equally simplified process. At any time $t$, some $I(t)$ active drug users are infected, and $\pi(t) = I(t)/N$ is the proportion of infected individuals within the drug-using population. Each IDU shares a needle with a randomly selected partner at a common rate of $\lambda$ times per week. If a susceptible comes into contact with an infected IDU, the probability of disease transmission is some constant $\kappa$. This reflects both disease biology and behavioral risks. This framework leads to the standard model

$$\frac{dI}{dt} = -\delta I(t) + \kappa \lambda N [1 - \pi(t)] \pi(t)$$

(Note that at time $t$, $N - I(t) = N [1 - \pi(t)]$ drug users remain susceptible to infection. These IDUs share needles $\lambda$ times per week. Under random mixing, they have probability $\pi(t)$ per encounter of sharing a needle with an infected person. If this does happen, they will become infected with probability $\kappa$. Putting this together, the number of new infections yields a standard expression for disease incidence under random mixing in a fixed population:

$$i(t) = N \kappa \lambda \pi(t) [1 - \pi(t)]$$

To simplify the analysis, we assume that steady-state comparisons accurately describe disease incidence and prevalence for policy modeling. One determines steady-state prevalence by setting $dI/dt = 0$, which yields:

$$\pi^* = 1 - \frac{\delta}{\kappa \lambda}$$

1 I thank an anonymous reviewer for this observation.