European Journal of Epidemiology **17**: 391–395, 2001.

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

Harold A. Pollack
University of Michigan School of Public Health, SPH II, 109 Observatory, Ann Arbor, MI 48109-2029, USA

Accepted in revised form 24 August 2001

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-appreciated 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][1]. 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 over-optimistic estimates of program effectiveness.

[1]I thank an anonymous reviewer for this observation.

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 δ will exit the population of active users due to death. At the same time, some number θ 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 λ times per week. If a susceptible comes into contact with an infected IDU, the probability of disease transmission is some constant κ. This reflects both disease biology and behavioral risks. This framework leads to the standard model

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

Note that at time t, $N - I(t) = N[1 - \pi(t)]$ drug users remain susceptible to infection. These IDUs share needles λ 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 κ. Putting this together, the number of new infections yields a standard expression for disease incidence under random mixing in a fixed population:

$$\iota(t) = N\kappa\lambda\pi(t)[1 - \pi(t)] \quad (2)$$

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:

$$\pi^* = 1 - \frac{\delta}{\kappa\lambda} \quad (3)$$

Throughout, we assume that π^* is positive to avoid algebraic complications associated with zero prevalence. Steady-state incidence is then

$$\iota = N\kappa\lambda\pi^*(1-\pi^*) = \theta\left[1-\frac{\delta}{\kappa\lambda}\right] \quad (4)$$

Suppose that one devises a modest harm reduction intervention which reduces the rate of needle sharing from l time per week to $\lambda - e$. Since the product $\kappa\lambda$ is the critical factor for disease spread, an identical analysis could be done of interventions that reduce κ. This analysis therefore captures features of many interventions [10]. SEP reduces the frequency of needle-sharing [11]. Bleach provision might be thought of as reducing infectivity [12]. Outside the immediate model, methadone maintenance or incarceration can be modeled as reducing disease incidence by raising the exit rate δ from active drug use.

Given these assumptions, well-implemented evaluation will capture short-term incidence changes by measuring changes in ι within the treated group. When study participants are a small subgroup of the overall population and the intervention occurs over a short period compared with the dynamics of disease spread, researchers typically regard population prevalence as a constant unaffected by the intervention itself.

Modest interventions

In many cases, one seeks to examine the efficacy and cost-effectiveness of interventions that have small behavioral or epidemiological effects – in other words interventions where e is very small. Examining modest interventions, a well-implemented study would capture the change in disease incidence over a period in which population prevalence may be takes as constant. Under these assumptions, the short-term reduction in disease incidence are given by Δ_1 in Equation (5) below:

$$\begin{aligned}\Delta_1 &= e\left(\frac{\partial}{\partial\lambda}N\kappa\lambda\pi^*(1-\pi^*)\right)_{\pi^*} \\ &= eN\kappa\pi^*(1-\pi^*) = e\frac{\theta}{\lambda}\left(1-\frac{\delta}{\kappa\lambda}\right)\end{aligned} \quad (5)$$

A more complete analysis considers that prevalence itself changes as a consequence of the intervention. Given a sufficiently long time-series or the correct application of a steady-state epidemiological model, a widely-provided intervention would change disease prevalence. The intervention would therefore reduce steady-state incidence ι by the effectiveness (e) multiplied by the total derivative of ι with respect to λ:

$$\begin{aligned}\Delta_2 &= e\frac{\mathrm{d}\iota}{\mathrm{d}\lambda} = \Delta_1 + e\left(\frac{\partial\iota}{\partial\pi^*}\right)_{\lambda}\frac{\mathrm{d}\pi^*}{\mathrm{d}\lambda} \\ &= \Delta_1 + eN\kappa\lambda[1-2\pi^*]\frac{\mathrm{d}\pi^*}{\mathrm{d}\lambda}\end{aligned} \quad (6)$$

If $\Delta_1 < \Delta_2$, short-term incidence comparisons understate the intervention's steady-state impact on disease spread. Comparing equations, this happens exactly when the last term in Equation (6) is positive. The same analysis understates the true treatment effect when $\Delta_1 > \Delta_2$.

When does this happen? When prevalence is positive, straightforward calculation shows that π^* strictly increases with λ. So $\Delta_2 > \Delta_1$ exactly when $N\kappa\lambda[1-2\pi^*]$ is positive. This happens when $\pi^* < 0.5$. The opposite result holds when π^* exceeds this threshold.

Thus, for small interventions, short-term incidence analysis understates long-term program effectiveness exactly when steady-state prevalence is below 50%. Although some beneficiaries of the intervention will become infected after the period of observation, these long-run effects are outweighed by the number of secondary infections prevented as a result of the intervention. In like fashion, short-term incidence analysis overstates program effectiveness exactly when π^* exceeds 50%. In this case, many IDUs who derive immediate protection are eventually infected, and so short-term analysis exaggerates the long-run effect.

Manipulating Equations (5) and (6), the relative error in short-term incidence analysis is given by $(\Delta_1 - \Delta_2)/\Delta_2 = (2\pi^* - 1)/(1-\pi^*)$. As shown, ignoring downstream infection can cause large bias when steady-state prevalence diverges from the 50% point. When π^* is below 20%, short-term incidence comparisons understate program effectiveness by more than 75%. Applying the calculations in Figure 1 for a prevalence of 70%, short-term incidence comparisons are predicted to overstate program effectiveness by more than 100%.

Substantial interventions

The above findings were derived using calculus for modest interventions. Building on [9] one can derive a

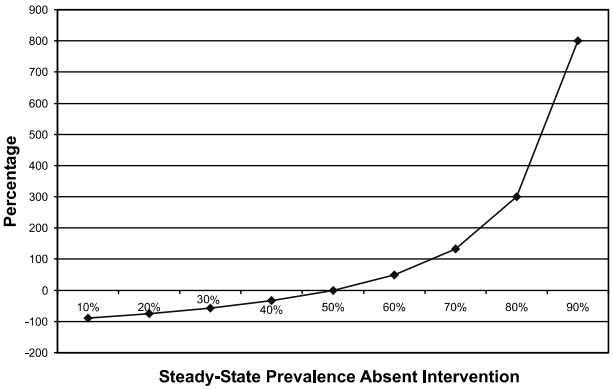

Figure 1. Bias in short-term incidence estimation for modest interventions (negative values indicate understatement of program effect).

similar approach for more extensive interventions. When the fraction (e/λ) is large, the short-term incidence analysis remains unchanged. Holding prevalence constant, the incidence is proportional to λ, and so Equation (5) continues to hold even for large interventions. However, when one considers the resulting change in steady-state prevalence, the resulting change in steady-state incidence is

$$\Delta_3 = \theta\left(1 - \frac{\delta}{\kappa\lambda}\right) - \theta\left(1 - \frac{\delta}{\kappa(\lambda - e)}\right) = \frac{\delta\theta e}{\kappa\lambda(\lambda - e)} \tag{7}$$

Comparing Equations (5) and (7), short-term incidence analysis overstates long-run effects when $\Delta_1 > \Delta_3$. After algebra, one can show that this happens when steady-state prevalence absent intervention is sufficiently great:

$$\pi^* > \frac{1}{2 - (e/\lambda)} \tag{8}$$

Since e is non-negative, short-term analysis always understates long-term program effectiveness when the steady-state prevalence absent intervention, is below 50%. When steady-state prevalence far exceeds 50%, however, short-term analysis will generally overstate the long-run effects of typical interventions. For example, if steady-state prevalence is 75%, short-term incidence analysis will overstate steady-state effects for interventions that cause a proportional reduction in needle-sharing (e/λ) of less than 2/3.

Previous analysis based upon the New Haven, Ct. SEP provides one empirically pertinent example of a substantial intervention [7, 8, 9, 11]. Pollack considers an intervention in which $\delta = 1/(4000$ days), $\lambda = 0.142$, and $\kappa = 0.005$. These parameters yield a steady-state prevalence of 65% – a prevalence that matches observed data prior to SEP intervention. In a population of $N = 2000$ IDUs, these parameters indicate steady-state incidence of 0.325 new infections per week.

The work of Kaplan and collaborators indicates an estimated program effectiveness of $e = 1/3$. Given these parameters, short-term incidence analysis indicates an incidence reduction of 0.1083 infections per week associated with the intervention. Applying Equation (7) to obtain steady-state values, we find a reduction of 0.0875 infections per week. In this example, steady-state prevalence was close to the threshold defined by Equation (8). Short-term analysis and steady-state analysis therefore yield similar results.

In contrast to this example, high steady-state prevalence yields more pessimistic results. Raising the presumed value of κ from 0.005 to 0.01 raises steady-state prevalence to 82.5%, with a steady-state incidence of 0.413 new infections per week. In this case, short-term incidence analysis indicates that SEP reduces disease incidence by 0.1375 infections per week. Steady-state analysis indicates a reduction of only 0.0438 infections per week. Thus, failure to consider long-run effects leads one to overstate SEP effectiveness by more than 200%. Data from hospital needlestick accidents indicates much higher estimates of κ for HCV – highlighting the difficulty of short-term incidence analysis in examining measures to prevent a highly infectious disease.

Discussion

Practicality dictates that infectious disease prevention efforts are often evaluated based upon their short-term effects. Given other challenges to validity and generalizability, one might overlook the fact that short-term incidence measures can provide a biased account of long-run treatment effects.

This paper explores these biases using steady-state analysis of a random-mixing model. The paper derives simple rules to quantify the size and direction of the resulting bias. Short-term incidence comparisons always understate long-run program effectiveness when steady-state prevalence is below 50% absent intervention. For modest interventions, the same analyses yield over-optimistic results where steady-state population disease prevalence exceeds 50%. The resulting bias can be quite large when steady-state prevalence is far above or far below 50%. Analogous findings hold for substantial interventions.

The present results depend on a specific model with important limitations. Perhaps most important, we assume random mixing. Other types of models may yield different results [13, 14]. Heterogenous populations, such as those with a highly active core group, raise issues outside the scope of the present analysis. Steady-state analysis also has limited application to slowly changing epidemics that begin far from long-run values [9]. Specific calculations suggest that steady-state calculations work well in analyzing HCV.

The present analysis is not applicable to interventions that provide permanent protection to treated subjects (the case $e/\lambda = 1$) [15]. It is striking, however, that the major vaccinatable diseases have very high prevalence absent intervention ([3], p. 88). The present analysis highlights the comparative advantage of vaccination in curbing these ailments.

Despite specific limitations of the current analysis, its main conclusions highlight broader concerns. Within homogeneous populations, the number of 'discordant' contacts between infected and uninfected individuals is maximized at 50% prevalence. When initial prevalence is below 50%, measures that reduce current prevalence will also reduce the number of subsequent discordant contacts that generate further infections. Downstream infections therefore amplify short-term treatment effects. When steady-state prevalence exceeds 50%, however, the opposite dynamic occurs. Short-term prevention slightly in-

creases the number of subsequent discordant pairs. This partially offsets the benefits of the intervention. Because prevalence is a concave function of λ, this intuition must be slightly modified for more substantial interventions. Yet the basic argument holds.

One consequence of the above analysis is to highlight the challenge to harm reduction posed by hepatitis B and C, and by other highly infectious agents. Although HIV and HCV arise from similar behavioral risks, the high infectivity of hepatitis leads to extremely high prevalence, even in IDU populations that maintain low prevalence of HIV [16]. In much of the United States, Europe, and Australia, more than 70% of active IDUs are apparently infected with HCV [16–18]. Because intervention merely delays infection for many members of the treated group, short-term incidence analysis is likely to produce over-optimistic estimates of steady-state effects [19, 20].

On a more optimistic note, the same calculations imply that short-term analysis understates the long-term effectiveness of prevention interventions in low-prevalence populations. Tacoma, Sydney, and other cities have maintained HIV prevalence of 10% or lower among active IDUs [20]. Short-term analysis of SEP in such low-prevalence environments may understate the capacity of modest interventions to maintain low HIV prevalence.

The particular application is to harm reduction for IDUs. However, the same factors are pertinent to other interventions and settings. When an intervention reduces, but does not eliminate disease risk, short-term incidence analysis likely overstates long-run program effectiveness in curbing highly-infectious agents. Short-term analysis will likewise understate the long-run effectiveness of interventions that curb diseases with low steady-state prevalence absent intervention. In both cases, policy modeling of public health interventions requires well-considered epidemiological analysis to link observed short-term results to the underlying dynamics of infectious disease spread.

References

1. Rossi P, Freeman H. Evaluation. Sage, Newbury Park, London, New Delhi, 1993.
2. Currie J. Welfare and the Well-Being of Children. Harwood Academic, Switzerland, 1995.
3. Anderson RM, May RM. Infectious Diseases of Humans. Oxford University Press, Imperial College, London 1992.
4. Koopman J, Little R. Assessing Imperial College London HIV Vaccine Effects. Am J Epidemiol 1995; 142(10): 1113–1120.
5. Metzger D, Woody G, De Philippis D, McLellan A, O'Brien C, Platt J. Risk factors for needle sharing among methadone-treated patients. Am J Psychiat 1991; 148(5): 636–640.
6. Metzger D, Woody G, McLellan AT, et al. Human immunodeficiency virus seroconversion among intravenous drug users in- and out-of-treatment: An 18-month prospective follow-up. J Acquired Imm Deficiency Syndromes and Human Retrovirology 1993; 6(9): 1049–1056.
7. Kaplan EH. Needles that kill: Modeling human immunodeficiency virus transmission via shared needle injection equipment in shooting galleries. Rev Infect Dis 1989; 11(2): 289–298.
8. Kaplan E, Heimer R. A model-based estimate of HIV infectivity via needle sharing. J Acquired Imm Deficiency Syndromes and Human Retrovirology 1992; 5: 1116–1118.
9. Pollack HA. "The cost-effectiveness of harm reduction in preventing hepatitisis C among injection drug users." Medical Decision Making 2001; 21(5): 357–367.
10. Holtgrave DR (ed). Handbook of HIV Prevention Policy Analysis. Plenum, 1998.
11. Kaplan EH, Heimer R, "A circulation theory of needle exchange." AIDS 1994; 8(5): 567–74.
12. Titus S, Marmor M, Des Jarlais D, Kim M, Wolfe H, Beatrice S. Bleach use and HIV seroconversion among New York city injection drug users. J AIDS 1994; 7(7): 700–704.
13. Kretzschmar M, Wiessing L. Modelling the spread of HIV in social networks of injecting drug users. AIDS 1998; 12(7): 801–811.
14. Morris M. Social Networks and HIV. AIDS 1997; 11(Suppl A): S209–S216.
15. Mather D, Crofts N. A computer model of the spread of hepatitis C virus among injecting drug users. Eur J Epidemiol 1999; 15: 5–10.
16. Coutinho R. HIV and Hepatitis C among injecting drug users: Success in preventing HIV has not been mirrored for hepatitis C. Br Med J 1998; 317: 424–425.
17. Garfein R, Doherty M, Monterroso E, Thomas D, Nelson K, Vlahov D. Prevalence and incidence of hepatitis C virus infection among young injection drug users. J Acquired Imm Deficiency Syndromes and Human Retrovirology 1998; 18(Suppl 1): S11–S19.
18. Crofts N, Nigro L, Oman K, Stevenson E, Sherman J. Methadone maintenance and hepatitis C virus infection among injecting drug users. Addiction 1997; 92(8): 999–1005.
19. Pollack HA. Can we protect drug users from hepatitis C? J Policy Anal Manag 2001; 20(2): 358–364.
20. Des Jarlais D, Hagan H, Friedman S, et al. Maintaining low HIV prevalence in populations of injecting drug users. J Am Med Assoc 1995; 274(15): 1226–1231.

Author for correspondence: Harold A. Pollack, University of Michigan School of Public Health, SPH II, 109 Observatory, Ann Arbor, MI 48109-2029, USA
Phone: +1-734-936-1298; Fax: +1-734-764-4338
E-mail: haroldp@sph.umich.edu