Sources of Error

Background

The HIV epidemic in the United States began in the 1980's through three major sources of transmission: anal sexual intercourse, viral contamination of blood and blood products, and passage of virus through sharing and re-use of needles, syringes and other drug-use paraphernalia ("works") by injection drug users (IDU). As surveillance data and epidemiologic studies identified the key role of injection drug use in the spread of HIV, proposals to increase the availability of sterile injection supplies to reduce HIV transmission — a strategy characterized as "harm reduction" — emerged. Although Canada and a number of European countries experimented with "needle-exchange" programs (NEP) as a way of reducing the sharing of infectious needles and syringes, this strategy has been a highly controversial issue in the United States, where NEP are often prohibited by state laws and where the U.S. Congress has forbidden the use of federal funding for such programs.

Much of the controversy has centered around the concern that NEP send a "mixed message" about drug use and undermines the prohibitionist-stance of U.S. drug policy, thereby encouraging drug use. Controversy has also existed over whether NEP do in fact reduce HIV transmission. A fall 1993 report commissioned by the U.S. Centers for Disease Control concluded from studies available at that time that NEP were likely to reduce HIV transmission without increasing drug use rates, but the report was suppressed until the *Washington Post* obtained it in February 1995 (Lurie, 1997). A Congressionally-mandated report by the National Academy of Sciences reached a similar conclusion in September 1995, though three studies raising doubts about NEP effectiveness had not yet been published.

The first of these three studies appeared in the December 15, 1997 issue of the *American Journal of Epidemiology* (Bruneau J, Lamothe F, Franco F, Lachance N, Desy M, Soto J, Vincelette J, "High rates of HIV infection among injection drug users participating in needle exchange programs in Montreal: results of a cohort study", *Amer J Epidemiol* 146(12):994-1002), accompanied by an invited commentary by Peter Lurie ("Le mystere de Montreal") and a response from the authors. As the authors carefully note, their cohort study of active IDU in Montreal began a year prior to the introduction of NEP in Canada and was not designed for the purpose of evaluating NEP. Preliminary analyses of the data, however, indicated a possible increase in seroincidence of HIV in NEP users, so the authors carried out an extensive analysis of the relationship. This exercise is based largely on data from the Bruneau *et al.* study.

Abstract from Bruneau et al.: Needle exchange programs (NEPs) are designed to prevent human immunodeficiency virus (HIV) transmission among injection drug users. Although most studies report beneficial effects in terms of behavior modification, a direct assessment of the effectiveness of NEPs in preventing HIV infection has been lacking. A cohort study was conducted to assess the association between risk behaviors and HIV seroprevalence and seroincidence among injection drug users in Montreal, Canada. The association between NEP use and HIV infection was examined in three risk assessment scenarios using intensive covariate adjustment for empirical confounders: a cross-sectional analysis of NEP use at entry as a determinant of seroprevalence, a cohort analysis of NEP use at entry as a predictor of subsequent seroconversion, and a nested case-control analysis of NEP participation during follow-up as a predictor of seroconversion. From September 1988 to January 1995, 1,599 subjects were enrolled with a baseline seroprevalence of 10.7%. The mean follow-up period was 21.7 months. The adjusted odds ratio for HIV seroprevalence in injection drug users reporting recent NEP use was 2.2 (95% confidence interval 1.5-3.2). In the cohort study, there were 89 incident cases of HIV infection with a cumulative probability of HIV seroconversion of 33% for NEP users and 13% for nonusers (p<0.0001). In the nested case-control study, consistent NEP use was associated with HIV seroconversion during follow-up (odds ratio = 10.5, 95% confidence interval 2.7-41.0). Risk elevations for HIV infection associated with NEP attendance were substantial and consistent in all three risk assessment scenarios in our cohort of injection drug users, despite

extensive adjustment for confounders. In summary, in Montreal, NEP users appear to have higher seroconversion rates than NEP nonusers. *Amer J Epidemiol* 146(12):994

1. *Random error: sample size, precision, and standard error*

The study enrolled 1,599 persons who had injected drugs during the preceding six months principally through self-referral or a detoxification facility. One hundred seventy one (10.7%) were HIV seropositive at baseline. How precise is the estimate of 10.7% HIV seropositivity at baseline?

If Montrealers who have injected drugs during the six months before the study recruitment period are the population of interest and we assume simple random sampling, we can use introductory statistics to compute a confidence interval around this estimate of HIV seroprevalence. The width of this interval quantifies the variability inherent in selecting a sample of a given size. The narrower the interval, the more precision the estimate.

Complete the following table by computing the standard errors and corresponding confidence intervals for the estimate of 10.7% if the sample size had been 900 or 2,500. Describe the relationship between the sample size and relative width of the intervals. (The standard error is the square root of the variance of the estimate of a proportion [p(1-p)/n]. The large sample formula for the 95% confidence interval for a proportion (p) estimated from a simple random sample of size *n* from a large population is:

$$p \pm 1.96 \sqrt{p(1-p)/n}\quad)$$

Sample size *n*	$\sqrt{n}$	Prevalence p	p(1-p)	Standard error $\sqrt{[p(1-p)/n]}$	95% confidence limits Lower	Upper
900	30	0.107				
1,600	40	0.107	(0.107)(0.893)	0.309113/40	0.092	0.122
2,500						

2.   *Nonresponse bias*

As noted above, the results of this study have been highly controversial. There are several potential sources of bias, one of which is differential response rates. **Suppose** that the following table shows the injection drug-using population of Montreal at the time the Bruneau *et al.* study began, the HIV seroprevalences for men and women in that population, by treatment status, and their rates of participation in the study (e.g., 20% of the 3,620 male injection drug users not in treatment participated in the study):

	Population HIV seroprevalence	Population size	Participation rate	Participants	Observed HIV seroprevalence
Total				*1,599*	*0.107*
Males	0.109	4,406		*1,274*	0.121
Females	0.042	2,746		*325*	0.050
In treatment					
Males	0.150	786	0.70	550	0.150
Females	0.090	72	0.80	58	0.090
Not in treatment					
Males	0.100	3,620	0.20	724	0.100
Females	0.041	2,674	0.10	267	0.041

* All numbers in the table are **hypothetical** except those in *italics*.

Under this scenario, what would the crude seroprevalence be in the IDU population of Montreal? Explain why the seroprevalence estimate from the Bruneau study differs from this hypothetical seroprevalence. (Hint: The crude HIV seroprevalence is a weighted average of the seroprevalence for each subgroup, weighted by the proportionate subgroup sizes.)

3. Loss to follow-up

Of the 1,351 participants who were seronegative at baseline, 974 were followed up. Median duration of follow-up was 15.4 months. 89 seroconversions were noted, for an overall incidence of 5.1 per 100 person-years. (Note: the 15.4 months is a <u>median</u>, not a mean, so 89/(974*15.4/12) does not equal 5.1 per 100. The appropriate analysis of these data is based on person-time, but for simplicity the following questions ask for incidence proportions.)

    a. What was the cumulative incidence [proportion] of seroconversion among those not lost to follow-up?

The 377 initially-seronegative participants who were lost to follow-up differed from the 974 participants with follow-up data in several respects (given as % in those lost vs. % in those followed), including gender (81% vs. 74% male), income (11.5% vs. 21% reported lower income), and getting syringes and needles from a drug dealer (57% vs. 33%). However, the participants lost to follow-up were no more or less likely to have attended a NEP. (Note: the remaining 77 baseline participants were excluded since they had been recruited too late in the study to have at least three months of follow-up.)

Suppose that the cumulative HIV sero-incidence in the 377 participants lost to follow-up was twice that in the 974 participants with follow-up, and that this ratio held for both NEP users and nonusers.

    b. Under these assumptions, what was the actual cumulative incidence of seroconversion among the 377 + 974 initially-seronegative participants?

    c. Under these assumptions, was the seroconversion ratio for NEP attenders to non-attenders biased by the loss to follow-up? Explain (if you prefer arithmetic to algebra, try using the hypothetical numbers in the following table):

	Subjects with follow-up data			Subjects lost to follow-up		
	Baseline	Incident cases	CI	Baseline	Incident cases	CI
NEP attenders	322	50	0.155	125	39	0.312
Non-attenders	652	39	0.060	252	30	0.119
Total	974	89	0.091	377	69	0.183

4. Berkson's bias

Switching gears, consider a case-control study to see whether diabetes is a risk factor for pneumonia. Cases are persons hospitalized for viral pneumonia (bacterial, viral, or mycoplasma). Controls (N=220) case are selected by random-digit dialing. Suppose that the number of persons with and without diabetes in the population and the number of new cases of pneumonia that develop during one year are:

	Entire population	Incidence rate per 10,000 py	Rate of hospitalization	Hospitalized for pneumonia
Persons with diabetes	10,000		_____	_____
Develop pneumonia	200	200	0.40 or 0.80	
Persons without diabetes	100,000		_____	_____
Develop pneumonia	1,000	100	0.40	400

   a. What is the incidence rate ratio (i.e., the IDR) for pneumonia comparing persons with and without diabetes?

   b. What odds ratio would be obtained by the above-described case-control study if 40% of all pneumonia cases are hospitalized (in computing the odds of exposure in the control group, use the entire population figures).

   c. Suppose that primary care physicians are twice as likely to hospitalize a pneumonia patient who also has diabetes, so that 80% of pneumonia patients with diabetes are hospitalized. What odds ratio would the case-control study estimate in this scenario?

   d. Would the odds ratios in b. and c. be greater or lower if controls had instead been selected from hospitalized persons admitted for reasons other than infection (e.g., cardiovascular, genito-urinary, gynecological, and trauma patients)?

5. Accuracy and precision*

Lead intoxication is one of the most studied phenomena in occupational and environmental toxicology. Children are especially susceptible to this metal. Blood lead levels as low as 10 μg/100g of blood can affect their development and behavior. Levels above 40 μg/100g blood in occupational settings are indicative of excess exposure, and a value above 60 μg/100g blood requires removal from exposure according to OSHA standards.

Laboratories maintain internal and inter-laboratory quality control programs to ensure the accuracy of their analyses, as well as to know the limits and advantages of their methods. The method (A) recommended by NIOSH to quantify lead in blood has a working range between 5 to 150 μg of lead per 100g of blood. The accuracy of the method is ± 10.8%, and relative standard deviation (precision) of 0.05. Consider another method (B) to determine the same chemical with the following characteristics: optimum working range of 0.05 to 50 μg/100g blood, accuracy of 7.6%, and relative standard deviation of 0.10.

1. Which method gives better accuracy in lower blood level ranges?

2. Which method is more precise?

3. Which method would be more indicated for use in a study that evaluated workers in a very contaminated plant? Why?

4. Which method would be more indicated for use in a study of the association between IQ test and environmental exposure of elementary school children? Why?

*These questions were developed by Mina Kato