

Do Needle Syringe Programs Reduce HIV Infection Among Injecting Drug Users: A Comprehensive Review of the International Evidence

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This first international review of the evidence that needle syringe programs reduce HIV infection among injecting drug users found that conservative interpretation of the published data fulfills six of the nine Bradford Hill criteria (strength of association, replication of findings, temporal sequence, biological plausibility, coherence of evidence, and reasoning by analogy) and all six additional criteria (cost-effectiveness, absence of negative consequences, feasibility of implementation, expansion and coverage, unanticipated benefits, and application to special populations). The Bradford Hill criteria are often used to evaluate public health interventions. The principal finding of this review was that there is compelling evidence of effectiveness, safety, and cost-effectiveness, consistent with seven previous reviews conducted by or on behalf of U.S. government agencies. Authorities in countries affected or threatened by HIV infection among injecting drug users should carefully consider this convincing evidence now available for needle syringe programs with a view to establishing or expanding needle syringe programs to scale.

Keywords Bradford Hill criteria; bridge populations; cost-effective; cost-saving; criminal justice approach; harm reduction; HIV; public health approach; risk factor; safe; zero tolerance

Introduction

By 2010, the global epicenter of the HIV epidemic is expected to shift from sub-Saharan Africa, where injecting drug use has made a negligible contribution, to Asia, home to half the world's population and a region where injecting drug use has made a substantial contribution. Central and Eastern Europe and the countries comprising the former Soviet Union is another region where HIV beginning among injection drug users (IDUs) has resulted in an explosive epidemic now spreading to the general population. Injecting drug use is an important risk factor for HIV in 7 of the 10 UNAIDS regions (UNAIDS, 2002), which account for 90% of the world's population. In many countries around the world, IDUs have contributed to HIV epidemics out of all proportion to the size of the drug injecting population.

It did not take long after recognition in 1981 of the epidemic soon to be called "AIDS" for public health practitioners around the world to start thinking about measures that could control HIV. The first needle and syringe program (NSP) was established in Amsterdam, the Netherlands, in 1981 in response to a hepatitis B outbreak among IDUs (Burns et al. 1996). Soon afterward, researchers and policymakers began to appreciate the immense

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Table 1
Reviews of NSPs by or on behalf of U.S. government agencies 1991–2001

Number	Author and year	Name of institution	Year	Prevents HIV?	Increases IDU?
1	National Commission on AIDS, 1991	National Commission on AIDS	1991	Yes	No
2	Lurie and Reingold, 1993	Centers for Disease Control and Prevention	1993	Yes	No
3	General Accounting Office, 1993	General Accounting Office	1994	Yes	No
4	Office of Technology Assessment of the U.S. Congress, 1995	Office of Technology Assessment of the U.S. Congress	1995	Yes	No
5	NIH, 1997	National Institutes of Health Consensus Panel	1997	Yes	No
6	Satcher, D, Surgeon General, 2000	U.S. Dept of Health & Human Sciences	2001	Yes	No
7	Institute of Medicine of the National Academy of Science, 2001	Institute of Medicine of the National Academy of Science	2001	Yes	No

potential threat of HIV epidemics and the centrality of injecting drug use in HIV control for communities. In most developed countries where there were large numbers of IDUs, NSPs were established in the 1980s and then expanded rapidly to prevent the spread of HIV among and from drug-injecting populations.

By the beginning of the 1990s, evidence of the effectiveness and safety of NSPs in reducing HIV spread among IDUs was already compelling and well summarized in seven previous reviews conducted by or on behalf of U.S. government agencies (Table 1). The failure of these reviews to influence the policymaking process in the United States has to be considered from the perspective of an unusual national drug policy sustained over many decades (McAllister, 2000; MacCoun and Reuter, 2001; McCoy, 2003).

Authorities, especially in developing and transitional countries, have often resisted implementation of NSPs lest any support for effective harm reduction strategies might be considered to undermine their entrenched commitment to global drug prohibition. This situation still prevails today despite copious high-quality data supporting the effectiveness, safety, and cost-effectiveness of NSPs.

In drug policy and HIV prevention, as in numerous other areas, many developing and transitional countries still look to the United States for leadership. However, HIV incidence and prevalence in the United States is the highest in the developed world, and IDUs comprise at least a third of all new HIV infections (Centers for Disease Control and Prevention, 1996). HIV/AIDS prevalence in the United States in 2003 was estimated to be 950,000 (470,000–1,600,000) or 0.6% (0.3–1.1%) (UNAIDS, 2004).

Adoption of NSPs in the United States has been late and implementation slow because of explicit rejection of harm reduction and strong support for a zero tolerance approach to drugs. A vociferous debate has been conducted in many countries between supporters of a public health approach based on evidence and a criminal justice approach supposedly based on the international drug treaties. However, even the International Narcotics Control Board has conceded that “Article 14 of the 1988 Convention requires parties to adopt appropriate measures aimed at eliminating or reducing illicit demand for narcotic drugs and psychotropic substances, with a view to reducing human suffering” and noted significantly that “The ultimate aim of the conventions is to reduce harm” (International Narcotics Control Board, 2004). The International Narcotics Control Board also commissioned a review of the legal status of harm reduction interventions which found that NSPs and other harm reduction interventions, with the possible exception of pill testing, did not infringe on the international treaties (Legal Affairs Section, United Nations International Drug Control Programme, UNDCP, 2002).

An appraisal of the published evidence for NSPs conducted for the World Health Organization as part of an “Evidence for Action” HIV/AIDS series (Wodak and Cooney, 2004) represents the first international review of this subject. This review encompassed needle and syringe decontamination strategies; needle and syringe exchange; pharmacy, vending machines, and other distribution program; needle and syringe disposal; and injecting paraphernalia legislation. This article reports only the findings of the review of evidence regarding the effectiveness of NSPs in reducing the spread of HIV infection among IDUs.

Methodology

An extensive and systematic literature search was conducted. Evidence was evaluated according to the Bradford Hill (1965) criteria attempting to disprove the relevant null hypothesis. Randomized controlled trials are often regarded as the gold standard in clinical

Table 2
Summary of results

Type of assessment	Criteria	Criterion fulfilled
Bradford-Hill	Strength of association	Yes
	Replication of findings	Yes
	Specificity of association	No
	Temporal sequence	Yes
	Biological plausibility	Yes
	Biological gradient	No
	Experimental evidence	No
	Reasoning by analogy	Yes
	Coherence of evidence	Yes
Extended criteria	Cost-effectiveness	Yes
	Absence of negative consequences	Yes
	Feasibility of implementation, expansion, and coverage	Yes
	Unanticipated benefits	Yes
	Application to special populations	Yes

biomedical research, although there is a vigorous debate about their universal application in diverse circumstances, especially public health interventions. No randomized controlled trial of NSPs has been reported to date, and the only known attempt to conduct such a trial (in Alaska) appears to have been abandoned. Conducting a randomized controlled trial of an NSP is probably not feasible and would now be considered unethical in most parts of the world. In cities or countries where NSPs are still illegal, conducting a randomized controlled trial faces self-evident and insuperable problems. In cities or countries where NSPs are now legal, randomization of subjects or locales and reducing contamination of groups to acceptable levels would be virtually impossible.

To assess inferences of causality from epidemiological studies of association, the noted English epidemiologist, Bradford Hill, devised (1965) a set of criteria (strength of association, replication of findings, specificity of association, temporal sequence, biological plausibility, biological gradient, experimental evidence, reasoning by analogy, and coherence). The Bradford Hill criteria, now also widely used as a standard framework to assess the strength of evidence for public health interventions, were used in this review and extended by additional criteria (cost-effectiveness; absence of negative consequences; feasibility of implementation, expansion, and coverage; unanticipated benefits; and application to special populations).

Many public health practitioners, noting the strength of evidence supporting NSPs, have struggled to understand the reluctance of NSP critics to accept this evidence. Supporters of NSPs, arguing from a consequentialist perspective, rely heavily on empirical data while disdaining discussion of perceived moral values of NSPs. In contrast, critics of NSPs often show little interest in empirical data and prefer to emphasize what they regard as the moral messages of NSPs (Buchanan et al., 2003).

There is no recognized acceptable method for deciding whether a specific null hypothesis has been disproved and thus a specific Bradford Hill criterion has been fulfilled.

Table 3a
Efficacy of needle syringe programs. NSP use and HIV seroprevalence or seroconversion as outcomes: studies with positive findings

Study	Respondents	Outcome variables	Results
Ljungberg et al., 1991 Skane province, Sweden; observational study	182 "active participants" of NSP	Seroprevalence in south Sweden compared with Scandinavian subpopulations with comparable drug problems	HIV seroprevalence among IDU in south Sweden maintained at ~1% contrasted with up to 60% in other Scandinavian subpopulations
Heimer et al., 1993 New Haven, CT, USA	Random sample of returned syringes at the New Haven NSP	Percentage of syringes containing HIV	Within 3 months of initiating syringe exchange, percentage of syringes containing serum with HIV declined by one third
Des Jarlais et al., 1996 New York City, USA; prospective cohort study using pooled data from three studies in a high-prevalence area	601 IDUs at several exchange sites	HIV incidence among continuing NSP users compared with nonusers	Multivariate proportional-hazards analysis, not using an NSP was associated with a hazard ratio of 3.35 (95% CI, 1.29, 8.65) for incident HIV compared with using an NSP
Hurley et al., 1997 Ecological study of 81 cities between 1988 and 1993	Data from reports on HIV seroprevalence linked with details of NSP implementation in 81 cities worldwide	HIV seroprevalence among IDU in 52 cities with NSP compared with that in 29 cities without NSPs	On average HIV seroprevalence increased by 5.9% per year in cities without NSPs and declined by 5.8% per year in cities with NSPs. Average annual change in seroprevalence was 11% lower in cities with NSPs (95% CI, -17.6 to -3.9, $p = .004$)
Monteroso et al., 2000 Five US cities; observational study	Some 2,306 street IDUs recruited from 5 U.S. cities and a State Women's prison and followed up 8 months later	HIV incidence among NSP participants compared with nonparticipants	Participation in NSPs associated with substantially reduced risk of HIV acquisition, but not statistically so
Health Outcomes International (HOI), 2002 Ecological study of 778 calendar years of data from 103 cities worldwide	Details of NSP implementation and HIV seroprevalence measurements for 67 cities without NSP, 36 cities with NSP	HIV seroprevalence compared in cities with and without NSPs	HIV seroprevalence in cities with NSPs declined by a mean annual 18.6% compared with an 8.1% increase in cities without NSPs

Table 3b
Efficacy of needle syringe programs. NSP use and HIV seroprevalence or seroconversion as outcomes: studies with negative findings

Study	Respondents	Outcome variables	Results
Bruneau et al., 1997 Montreal, Canada; nested case-control study	408 treated and untreated IDU; any vs. no NSP use, last 6 months	HIV seroconversion	Exclusive NSP users four times more likely to seroconvert than never-users (OR, 4.2; 95% CI, 1.5–11.5) Nonexclusive NSP users three times more likely to seroconvert than never-users (OR, 3.3; 95% CI, 1.6–6.7)
Bruneau et al., 1997 Montreal, Canada; prospective cohort study	1,599 treated, untreated IDU; NSP users compared with nonusers; mean follow-up period 21.7 months	HIV seroconversion	Consistent NSP use strongly associated with seroconversion (OR, 10.5; 95% CI, 2.7–41.0)
Strathdee et al., 1997 Vancouver, Canada; observational study	1,006 untreated IDU; frequent NSP attenders compared with nonattenders	HIV seroprevalence	Substantially increased risk of HIV seroconversion associated with NSP use (adjusted OR, 2.2; 95% CI, 1.5–3.2) Frequent NSP attenders more likely to be HIV positive than nonattenders

Table 3c

Efficacy of needle syringe programs. NSP use and HIV seroprevalence or seroconversion as outcomes: studies with indeterminate findings

Study	Respondents	Outcome variables	Results
Patrick et al., 1997 Vancouver, Canada; case-control study	281 untreated IDU; ever-users of NSP compared with never-users	HIV seropositivity	No association between ever using an NSP and HIV seropositivity
Schechter et al., 1999 Vancouver, Canada; prospective cohort study	694 treated and untreated IDU followed for 15 months; frequent attenders vs. infrequent NSP attenders	HIV incidence	No differences in HIV incidence between frequent attenders and infrequent attenders

Interpretation in this review has been conservative. There is also no recognized acceptable method for deciding whether sufficient Bradford Hill criteria have been fulfilled to justify the conclusion that the intervention has been demonstrated to be effective. Again, interpretation in this review has been conservative. The full report of this project was published by the World Health Organization as part of their Evidence for Action series (Wodak and Cooney, 2004). The definitions used for the criteria in this review follows.

Bradford Hill Causal Criteria

Strength of Association. The strength of a supposed association between an exposure factor and an outcome is gauged by the appropriate statistic used to measure the protective effect of an intervention. The preferred statistic, where available, is relative risk or odds ratio (OR) with associated confidence intervals.

Replication of Findings. Also referred to as “Consistency,” this criterion examines whether different studies conducted in different locations by different investigators have reported similar findings.

Specificity of Association. Specificity is said to be present when the alleged exposure factor (or intervention) is exclusive to the outcome and when the outcome has no other known cause or associated risk factors. This criterion is easy to explain by use of examples: Apart from lung cancer, cigarette smoking is causally associated with numerous other serious health consequences such as coronary artery disease, peripheral vascular disease, and emphysema. The association between smoking and lung cancer is therefore not specific. Car safety belts, on the other hand, reduce deaths and serious injury but have no other major benefits or costs.

Temporal Sequence. For a cause-and-effect relationship to be supported, was the introduction of an intervention followed by a reduction in the outcome factor? Did the

Table 4a

Efficacy of needle syringe programs. NSP use and HIV risk behavior outcomes: studies with positive findings

Study	Respondents	Outcome variables	Results
Hartgers et al., 1989 Amsterdam, the Netherlands; observational study	145 untreated IDU in community sample. NSP users vs. nonusers.	Syringe borrowing	NSP users less likely to borrow than nonusers in previous month (10% compared with 23%) and also in previous 2 years (33% compared with 57%)
Donoghoe et al., 1989 Scotland and England; prospective cohort study, pre-post (2 months) comparison	282 NSP users and non-NSP control group	Syringe sharing	Significant decline in syringe sharing among NSP users in previous month compared with no change in control group
Kaplan et al., 1991, 1994, 1995 New Haven, USA; syringe tracking and modeling studies		Syringe exchange rate, syringe return rate, syringe circulation time	The syringe exchange rate per IDU and the return rate of program syringes both increased, implying a decreased mean circulation time for each syringe.
Frisher and Elliott, 1993 Glasgow, Scotland; observational study	503 IDU community sample. NSP users in last 6 months vs. nonusers.	Syringe borrowing or lending	NSP attenders less likely (mean 4.5 times a month) than nonattenders (mean 9.2 times a month) to borrow used syringes, despite legal pharmacy sale of syringes.
Keene et al., 1993 Wales, UK; observational study	328 mostly untreated IDU. NSP attenders vs. nonattenders	Syringe sharing in last year and last 4 months	NSP attenders less likely to share syringes in last year and last 4 months
Watters et al., 1994 San Francisco, USA; observational study	752 treated, untreated IDU. NSP users vs. nonusers.	Syringe sharing	NSP use was strong independent predictor of not sharing syringes (OR, 0.71; 95% CI, 0.59–0.87)
		Injection frequency	Median number of injections declined following NSP attendance, from 1.9 injections/day to 0.7 injections/day

Des Jarlais et al., 1995 New York City; multiple cross-sectional study	1,115 IDU entering methadone treatment	Syringe borrowing, lending	Quarterly level of NSP use correlated negatively with proportion of IDU reporting borrowing and lending of syringes ($X^2 = -0.67, p < .02$ and $X^2 = -0.44, p < .13$, respectively).
Oliver et al., 1994 Portland, USA; prospective pre-post NSP evaluation study	115 NSP clients, pre- and post-NSP attendance. No comparison group	Syringe sharing, renting and borrowing	Substantial decline in sharing (20% to 7%), renting (9% to 3%) and also borrowing of syringes
Oliver et al., 1994 Portland, USA; prospective cohort study	412 untreated IDU followed for 6 months. NSP users compared with outreach IDU	Syringe borrowing	NSP users borrowed less and outreach clients (who bleached more)
Paone et al., 1994 New York City; retrospective pre-post comparison study	1269 NSP clients	Syringe borrowing	Substantial decline in borrowing used syringes (from 29% to 12%) and in renting or buying a used syringe (from 22% to 6%)
Peak et al., 1995 Kathmandu, Nepal; multiple cross-sectional study	586 NSP clients	Number of sharing partners and sharing occasions	Median number of sharing partners declined from 2 to 1 and median number of sharing occasions declined from 14 to 2 following NSP attendance
Guydish et al., 1995 San Francisco, USA; observational study	50 NSP clients; compared number of months since first used NSP	Number of sharing partners	Recent NSP users had fewer sharing partners and number of sharing partners was negatively correlated with number of NSP visits in past 30 days

(Continued on next page)

Table 4aEfficacy of needle syringe programs. NSP use and HIV risk behavior outcomes: studies with positive findings (*Continued*)

Study	Respondents	Outcome variables	Results
Schoenbaum et al., 1996 New York City; prospective cohort study	329 treated IDU, NSP users compared with nonusers	Syringe sharing	NSP users significantly less likely than non-users to report syringe sharing 4 years after the NSP was introduced
Vlahov et al., 1997 Baltimore, USA; prospective cohort study	221 NSP clients pre-NSP, 2 week, 6 month, follow-ups. No comparison group.	Syringe borrowing, lending, and indirect sharing	Substantial declines in syringe borrowing (22% to 8%) and syringe lending (27% to 12%).
Singer et al., 1997 Hartford, USA; multiple cross-sectional study	710 untreated IDU; pre-post comparison	Syringe reuse (a proxy for syringe sharing)	Respondents significantly reduced their "reuse" of syringes following introduction of NSP and legalisation of pharmacy sale of syringes
Guydish et al., 1998 San Francisco, USA; observational study	114 NSP clients; Compared on basis of proportion of syringes obtained from NSP	Syringe sharing	Those who obtained a higher proportion of syringes from the NSP (92% vs. 81% were less likely to report the sharing of syringes)
Heimer et al., 1998 New Haven, San Francisco, Baltimore and Chicago; retrospective analysis of data	Large sample of NSP attenders; first visit data compared with later visits	Syringe reuse	Self-reported reuse of injection equipment declined by at least half in three of the four cities. In the fourth city different methods of data collection (including syringe tracking) corroborated these findings
Gleghorn et al., 1998 Seven metropolitan centers, USA; observational study	Broad sample of IDUs	Source of most recent syringe (reliable/unreliable)	IDUs were most likely to have used a reliable source to obtain their most recent syringe in cities with an NSP (OR, 5.3; 95% CI, 3.3–8.5).

Bluthenthal et al., 1998 Oakland, USA; observational study	1,304 untreated IDU in community sample. Compared NSP users with nonusers	Syringe sharing	NSP use conferred a greater than 40% protective effect on syringe sharing adjusted (adjusted OR, 0.57; 95% CI, 0.46–0.72).
Bluthenthal et al., 2000 Oakland, USA; controlled cohort study	340 high-risk IDU. NSP users compared with nonusers	Syringe sharing cessation	IDU who began using the NSP were more likely to stop sharing than nonusers (adjusted OR, 2.68; 95% CI, 1.35–5.33), as were IDU who continued using the NSP (adjusted OR, 1.98; 95% CI, 1.05–3.75).
Cox et al., 2000 Dublin, Ireland; evaluation study of NSP	IDU who attended the NSP; compared data at first visit and 3 months later	Sharing of injection paraphernalia	Significant reductions in borrowing and lending of syringes
Monterroso et al., 2000 Five U.S. cities and a State Women’s prison; prospective study	2,306 street IDUs; NSP participants compared with nonparticipants. 8 months follow-up	Syringe reuse	Reported use of NSP was significantly associated with not using previously used needles. (adjusted OR, 2.08; 95% CI, 1.15–3.85; $p = .015$)
Power et al., 2002 Sverdlovsk Oblast, Russia; short-term process evaluation of three NSPs	IDU attenders compared with nonattenders 6 months after NSP opened	HIV risk behaviors	NSP attenders reported less HIV risk behavior than nonattenders. The following risk behaviors were statistically significant at $p < .0005$: only use own syringe; only use own needle; only use own filter; only use own drug solution; use another’s syringe for measuring drug dose
Gibson et al., in press San Francisco; prospective cohort study	259 IDU followed for mean period of 10.7 months. NSP users compared with nonusers	HIV risk behavior	NSP use had a substantial protective effect against HIV risk behavior (a two-fold decreased odds of HIV risk behavior), compared with non-use. Controlled for baseline risk behavior and exchange use as markers of risk-taking tendency, and other potential confounders

Table 4b

Efficacy of needle syringe programs. NSP use and HIV risk behavior outcomes: study with negative findings

Study	Respondents	Outcome variables	Results
Klee et al., 1991 Northwest England, UK; observational study	217 treated, untreated IDU; regular NSP users compared with rare or never users	Syringe lending	Regular use of NSP associated with passing of syringes

introduction of NSPs precede a reduction in needle sharing, other risk behaviors, or HIV incidence? Conversely, in locations where NSPs were closed, did risk behavior and HIV incidence increase subsequently?

Biological Plausibility. This criterion refers to the presence or absence of a likely biological mechanism linking the risk exposure or intervention to the observed findings.

Biological Gradient. Evidence that increasing exposure to an intervention or risk factor results in a commensurate positive or negative change in an outcome is indicative of a biological gradient.

Experimental Evidence. This criterion often provides the strongest support for causation and examines whether preventive action, in this case increased availability and utilization of sterile injecting equipment, actually reduces needle sharing, which in turn reduces HIV incidence and/or prevalence.

Reasoning by Analogy. Causality is supported by analogy if there are similar associations or causal relationships in other clinical or epidemiological areas of relevance. This may involve “apposite” studies where, say, NSP use leads to lower hepatitis C (HCV) or B virus incidence compared with non-NSP use.

Coherence. When the evidence from different disciplines and different sources “hangs well together,” this criterion is considered to be fulfilled. For example, lack of supportive laboratory findings would count against coherence. Are there documented examples of HIV incidence declining without NSPs? Does the apparently lower impact of NSPs on HCV incidence damage the evidence for effective HIV prevention?

Additional Feasibility and Implementation Criteria

Cost-Effectiveness. Although estimated in a number of different ways, authorities pay increasing attention these days to the magnitude of benefit achieved from allocation of scarce public resources. Is the introduction of NSPs and other interventions cost-effective in all parts of the world and at different stages of an HIV epidemic?

Absence of Negative Consequences. Consideration of possible inadvertent adverse consequences is an important part of evaluating clinical and public health interventions. The

Table 4c

Efficacy of needle syringe programs. NSP use and HIV risk behavior outcomes: studies with indeterminate findings

Study	Respondents	Outcome variables	Results
Donoghoe et al., 1992 London, UK; observational study	207 untreated IDU; NSP users compared with nonusers	Syringe sharing	NSP users and nonusers equally likely to share used injection equipment
Hartgers et al., 1992 Amsterdam, the Netherlands; observational study	131 HIV-seronegative IDU; mostly NSP users	Syringe borrowing	Regular NSP use not associated with increased or decreased borrowing
Van Ameijden et al., 1992 Amsterdam, the Netherlands; case-control study	232 untreated IDU; NSP users compared with nonusers	Proportion of syringes exchanged	No protective effect associated with proportion of syringes exchanged at the NSP
Van Ameijden et al., 1994 Amsterdam, the Netherlands; observational study	Community sample of 616 treated, untreated IDU; NSP users compared with nonusers, previous year	Syringe borrowing and lending	Bivariate negative association with borrowing and lending of syringes. Later multivariate analysis (1998) adjusted for possible confounders discounted these negative findings
Klee et al., 1995 Northwest England, UK; observational study	Community sample of 663 treated, untreated, opiate, nonopiate IDU in three studies; regular NSP users compared with rare or never users	HIV risk behavior	Mixed pattern of NSP use and HIV risk behavior in three studies
Van Haastrecht et al., 1996 Amsterdam, the Netherlands; prospective cohort study	632 treated, untreated IDU followed over 8 years; NSP users compared with nonusers	Predictors of mortality among HIV-positive and HIV-negative IDUs	Mortality rate of NSP attenders about the same as that for nonattenders
Van Ameijden <i>et al.</i> , 1998 Amsterdam, the Netherlands; observational study	Community sample of 879 treated, untreated IDU seen at 6,645 visits; NSP users compared with nonusers, previous year	Syringe borrowing and lending	Irregular NSP users at statistically greater risk of borrowing and lending of syringes than regular users or nonusers

Table 4d

Tally of studies finding positive vs. negative or null effects of syringe exchange broken down by presence or absence of legal access to pharmacy syringes^a (Gibson and Flyun, 2001)

		Positive	Negative/null	Total
Legal pharmacy access?	Yes	5	13	18
	No	7	0	7
Total		12	13	25

^aRelationship between positive vs. negative or null findings and legal pharmacy access significant by Fisher's exact test at $p < .002$.

presence of unintended negative consequences has a major impact on adoption or expansion of interventions. Fear that increased availability of sterile NSPs might exacerbate illicit drug use has been a major factor delaying adoption and expansion of these programs.

Feasibility of Implementation, Expansion, and Coverage. Is it feasible to implement NSPs in diverse settings, including resource-poor settings, and to expand these to a scale commensurate with public health need?

Unanticipated Benefits. Does the introduction of NSPs lead to other unintended and welcome benefits (such as increased referral to drug user treatment)?

Special Populations. How successful are NSPs in reaching special populations that have been identified as particularly "at risk" (such as young IDUs) or of considerable public health significance (such as bridge populations like homosexual male IDUs or commercial sex workers who also inject drugs)?

Results

The published evidence for NSPs conservatively fulfills six (strength of association; replication of findings; temporal sequence, biological plausibility, coherence of the evidence, and argument by analogy) of the nine Bradford Hill criteria. Three criteria (specificity of association, biological gradient, and experimental evidence) were not satisfied. All extended criteria were satisfied (Table 2).

Effectiveness of NSPs

Strength of Association. Forty-five studies dating from 1989 to 2002 were identified with NSP implementation as an intervention and HIV seroconversion, HIV seroprevalence, or HIV risk behaviors among IDUs examined as outcome variables. Some studies assessed multiple outcomes. Six of ten studies that evaluated HIV seroconversion or seropositivity as outcomes found that NSP use was protective (Table 3a), (Ljungberg et al., 1991; Heimer et al., 1993; Des Jarlais et al., 1996; Hurley et al., 1997; Monterroso et al., 2000; Health Outcomes International (HOI), NDARC, and Drummond, 2002), outcomes in two studies were negatively associated with NSP use (Table 3b), (Bruneau et al., 1997; Strathdee et al., 1997) and two studies showed no effect (Table 3c) (Patrick et al., 1997; Schechter et al., 1999).

HIV risk behavior outcomes were examined in 33 studies (with some authors reporting on more than one study or outcome). Most focused on syringe sharing, borrowing, lending, or reuse (23 positive (Table 4a), (Donoghoe et al., 1989; Hartgers et al., 1989 Frischer and Elliot, 1993; Keene et al., 1993; Des Jarlais et al., 1994; Oliver et al., 1994; Paone et al., 1994; Watters et al., 1994; Guydish et al., 1995; Peak et al., 1995; Schoenbaum et al., 1996; Singer et al., 1997; Vlahov et al., 1997; Bluthenthal et al., 1998, 2000; Gleghorn et al., 1998; Guydish et al., 1998; Heimer et al., 1998; Monterroso et al., 2000; Cox et al., 2000; Gibson and Flynn, 2001; Gibson et al., 2002; Power and Nozhkina, 2002) 1 negative (Table 4b) (Klee et al., 1991), and 7 indeterminate (Table 4c) (Donoghoe et al., 1992; Hartgers et al., 1992; van Ameijden, 1992; van Ameijden et al., 1994; Klee and Morris, 1995; van Haastrecht et al., 1996; van Ameijden and Coutinho, 1998), whereas 6 studies examined diverse outcomes, including injection frequency (1 positive (Watters et al., 1994)), proportion of syringes exchanged (1 indeterminate (van Ameijden et al., 1992)), syringe return rate or exchange rate (3 positive (Kaplan, 1991; Kaplan et al., 1994; Kaplan and Heimer, 1995)), and mortality among NSP users versus nonusers (1 indeterminate (van Haastrecht et al., 1996)). Overall, these studies provide strong evidence to reject the null hypothesis that attendance at NSP does not confer protection against HIV. However, it is not possible to exclude the possibility that selection bias may account for the findings in studies comparing IDUs who attend NSPs with those who do not.

Several authors have offered explanations for the counterintuitive finding of some studies that HIV was more prevalent in attendees compared with nonattendees (Lurie and Drucker, 1997; Schechter et al., 1999; Bastos and Strathdee, 2000; Coutinho, 2000; Strathdee and Vlahov, 2001). It is well known that NSPs in many settings attract high-risk IDUs who may therefore have a higher risk of HIV seroconversion before ever attending the program. This self-selection factor may help explain why cities such as Montreal and Vancouver have observed higher HIV seroconversion rates among NSP attendees compared with nonattendees (Lowndes and Alary, 1998; Schechter et al., 1999). As pointed out by Bastos and Strathdee (2000), evaluations of NSPs typically used dichotomous categorizations (such as NSP attendees vs. nonattendees, frequent vs. infrequent attendees). This simplistic approach overlooks the fact that nonattendees may have only used sterile injecting equipment, obtaining these from sources other than NSPs. For example, in an analysis of NSP attendees in Amsterdam, a city where sterile syringes are readily available through pharmacies, irregular NSP attendees but not non or frequent attendees were at highest risk of HIV seroconversion (van Ameijden and Coutinho, 1998). The authors concluded that irregular NSP attendees had the least exposure to sterile injection equipment and consistent prevention messages, which placed them at highest risk of infection.

Studies examining NSP effectiveness have generally relied on self-reported outcome measures. At least one study compared self-reported risk behavior with actual program data and concluded that self-reported risk data underestimated the protective association of NSP attendance by 18% (Safaeian et al., 2002).

Strong as the evidence is for NSP effectiveness, these data are confounded by the presence or absence of alternative availability of sterile injecting equipment through pharmacies. A systematic review (Gibson et al., 2001) identified 42 published studies evaluating NSP effectiveness. The potential confounding of pharmacy access to syringes for these studies (Gibson and Flynn, 2001) was examined. Twenty-eight studies concluded that NSP use had positive effects (reduced risk-behavior or seroconversion), 12 showed no effectiveness, and 2 found negative effects. Thirteen (Table 4d) of the 14 studies with no effect or negative effects compared clients with nonclients of NSPs. When these 13 studies were examined carefully and an additional 12 studies that compared users with nonusers

of NSPs were considered, all 13 studies with negative or null findings were found to have been conducted in settings where IDUs had legal access to syringes from pharmacies as well as NSPs. By way of contrast, in settings with NSPs but without additional legal access to sterile injecting equipment, there were no negative or null findings. Five studies found positive effects (reduced risk behavior and/or seroconversion) despite legal access through NSPs and pharmacies. Nevertheless, the relationship between pharmacy access (yes/no) and positive versus negative findings was significant ($p = .002$). Finally, when studies in settings where legal pharmacy access was available were excluded, 23 of the remaining 24 studies showed positive effects for NSP use.

There is sufficient evidence to consider that the criterion of “Strength of Association” has been fulfilled.

Replication of Findings. The above findings strongly support the effectiveness of NSPs as interventions that reduce risk behavior such as syringe sharing among IDUs and HIV infection. The number of studies showing protective effects far outweighs those with ambiguous or negative effects. The preponderance of positive findings is strengthened by their replication by different authors, at different stages of the HIV epidemic, at different times and geographical locations, and with diverse study designs. Furthermore, in instances where NSP use has been statistically associated with increased HIV incidence or higher risk behaviors, convincing arguments for possible sources of confounding have been presented.

The efficacy of individual NSPs has been reported in at least 10 different countries (Australia, Bangladesh, Brazil, Canada, England, Nepal, the Netherlands, Scotland, Sweden, and the United States), including several resource-poor countries. In addition, ecological studies have found strong associations between NSP implementation and lower HIV incidence and prevalence in comparisons involving diverse countries. Most notably, the Return on Investment study (HOINDARC and Dummond, 2002) compared HIV prevalence in 103 cities in 24 countries and 16 of these countries had NSPs. HIV seroprevalence was found to have declined by a mean annual 18.6% for 36 cities with NSPs compared with an 8.1% increase in 67 cities without NSPs. Hurley et al. (1997) compared HIV seroprevalence among IDUs in 52 cities without NSPs and 29 cities with NSPs in North America, South America, Europe, Asia, and the South Pacific. On average, seroprevalence increased by 5.9% per year in the 52 cities without NSPs and decreased by 5.8% per year in the 29 cities with NSPs. In a systematic review, results favoring the efficacy of NSP use were recorded from six studies with longitudinal/prospective designs, four studies with multiple cross-sectional designs, eight observational studies, five ecological studies, and several modeling studies (Gibson et al., 2001).

There is sufficient evidence to consider that the criterion of “Replication of Findings” has been fulfilled.

Specificity of Association. Many studies have demonstrated multiple other health benefits of NSPs apart from a reduction in HIV infection. These additional benefits include improved entry to primary health care and drug user treatment, prevention of other bloodborne viral infections, reduced proximal bacterial infection (e.g., abscess and cellulitis), and reduced distal bacterial infection (e.g., subacute bacterial endocarditis, brain abscess). NSPs offer a “package” of different services, including education about protection against other bloodborne viruses and sexually acquired HIV, education about cleaning injection equipment, and information about drug user treatment. Reductions in risk behavior and HIV seroconversion could be the result of these other services (such as acquiring clean syringes from pharmacies, using condoms and other safer sexual practices) rather than the needle

and syringe exchange, distribution, or sale. Although reduced HIV infection is not the only benefit of NSPs, the other benefits are less well documented and do not seem to be as powerful as the impact on HIV infection. There do not appear to be any well-documented accounts of declining HIV incidence in a population with high prevalence levels in the absence of NSPs. Although the existence of these additional benefits is attractive from a public health and policy perspective, the effect of NSPs does not appear to be specific to HIV prevention.

There is sufficient evidence to consider that the criterion of “Specificity of Association” has not been fulfilled.

Temporal Sequence. Although NSPs are not the only intervention credited with achieving reduced risk behavior, in most settings where an NSP was introduced, a subsequent reduction in risk behavior and, where measured, HIV seroconversion were reported. As discussed above (see Strength of Association), in settings where NSP implementation has been followed by increased risk behavior and/or seroconversion among actual NSP users, the availability of pharmacy access to clean syringes has been shown to confound study results (Gibson and Flynn, 2001). NSP clients have also been shown at baseline in two studies to be at greater risk of HIV seroconversion than nonclients (Lowndes and Alary, 1998; Schechter et al., 1999). It is now thought that the findings in these studies resulted from selection bias and other factors. A unique study in Windham, Connecticut observed “reversal” effects on risk behavior among IDUs when an NSP was closed down. Significant increases in syringe reuse and syringe sharing occurred postclosure compared with preclosure (Broadhead et al., 1999). Any resulting change in HIV infection rates was not measured. These observations are consistent with the expected direction of temporal sequence.

A number of studies measured behavior at multiple points over time, and all supported an appropriate temporal sequence. In New York City, 584 IDUs attending NSPs were interviewed on three occasions and HIV drug use risk-related behavior was found to decline with the continuing use of NSPs (Paone et al., 1998). Heimer and colleagues, in their evaluation of the New Haven needle exchange, demonstrated that the prevalence of HIV in syringes decreased after an increase in the exchange rate (Heimer et al., 1993). In a large multiple cross-sectional study of 1,304 untreated IDUs in Oakland, USA, needle and syringe sharing declined over time concurrent with an increase in NSP use and distribution of supplies (Bluthenthal et al., 1998).

Analysis of trends in HIV risk behaviors among over 5,000 IDUs in New York City from 1990 to 1997 led to the conclusion that all three injection risk behaviors studied declined significantly (all $p < .01$) accompanied by a substantial increase in syringe exchange participation. Seroprevalence among IDUs also declined from approximately 45% in 1991 to approximately 30% in 1996 (Des Jarlais et al., 2000). There do not appear to be any published studies reporting an unexpected temporal sequence.

There is sufficient evidence to consider that the criterion of “Temporal Sequence” has been fulfilled.

Biological Plausibility. Although the minimum quantity (infectious dose) of HIV necessary to result in infection is not known, viable HIV has been detected in syringes stored at room temperature for up to 4 weeks (Abdala et al., 1999). Field studies confirm that HIV can be detected in blood-contaminated syringes for some weeks. The presence of HIV-1 RNA in needles and syringes indicates the risk associated with sharing of needles and syringes, and presumably also paraphernalia and wash waters by IDUs. A study of needles and

syringes obtained from shooting galleries in Miami found that 39% of rinses from 36 needles and syringes containing visible blood had detectable amounts of HIV-1 RNA when quantified and analyzed for the presence of antibodies for viral proteins. Antibodies to HIV-1 polypeptides were detected in 94% of the same sample (Shapshak et al., 2000). Earlier studies found HIV-1 in 3% of blood-contaminated needle and syringes collected from exchange programs in Sydney (Wodak et al., 1987), 10% of needle and syringes from shooting galleries in South Florida (Chitwood et al., 1990), 50% of used needles and syringes obtained from shooting galleries in Miami (McCoy et al., 1995a, 1995b; Shah et al., 1996), and in New Haven, Connecticut HIV-1 was detected in 67.5% of used "street" syringes and in 91.7% of needles from a shooting gallery (Heimer et al., 1993).

Further evidence of a biologically plausible link between the use of shared injecting equipment and HIV seroconversion among IDUs is provided by field studies of the biological mechanisms of HIV transmission among IDUs. Practices such as "booting" (a process performed after administering the drug solution with the needle still in the vein whereby the injector draws back on the plunger of the syringe to fill the barrel with blood and then reinjects the blood, sometimes repeating this practice several times) and "backloading" (transferring the drug from one syringe to another by removing the plunger from the receiving syringes) have been shown to increase the risk of HIV-1 transmission by directly placing blood within the needle and syringe (Page et al., 1990; Samuels et al., 1991; Inciardi et al., 1994). Chitwood et al. (1995) used logistic regression analysis that adjusted for age, gender, and race to determine risk factors associated with HIV-1 seroconversion among IDUs and found that sharing needles and syringes in the year before conversion was the primary independent risk factor, much stronger than sexual factors. Other studies have broadened the definition of sharing to shared injection paraphernalia such as cookers, cottons, and rinse water and to the practice of "frontloading."

IDUs with a history of diabetes have a significantly lower HIV seroprevalence rate (9.8%) compared with nondiabetic IDUs (24.3%) ($p = .03$). This result highlighted that increased access to sterile syringes and less use of contaminated equipment were important factors contributing to lower HIV infection rates (Nelson et al., 1991).

One study investigated where IDUs obtain needles and syringes from before the implementation of NSPs. A cross-sectional study of 741 current IDUs in Baltimore found that most participants (85%) obtained at least some needles from street needle sellers (Latkin and Forman, 2001). Participants who sold needles reported that it was easy to make used needles appear to be unused, and some admitted to selling used syringes as new. The authors concluded that street needle sellers were an important source of needles for drug injectors, and few injectors were able to determine whether these needles were actually sterile.

There is sufficient evidence to consider that the criterion of "Biological Plausibility" has been fulfilled.

Biological Gradient. Heimer and associates (Heimer et al., 1993) found in their syringe tracking study in New Haven that HIV prevalence in syringes decreased as the exchange rate increased. Few studies have investigated a possible relationship between increased implementation of NSPs and reduced HIV infections.

There is insufficient evidence to consider that the criterion of "Biological Gradient" has been fulfilled.

Coherence of the Evidence. The arguments for coherence of the evidence span several of the Bradford Hill criteria, including biological plausibility, strength of association, and

replication. To minimize repetition, material which has already been presented is not repeated here.

There is strong evidence that HIV can be transmitted when contaminated injection equipment is shared and such sharing is the strongest risk factor predicting HIV seroconversion among IDUs. Studies of IDU risk behavior in settings without NSPs show that most engaged in needle sharing and other unsafe injecting practices. For example, in a cross-sectional survey of active IDUs in Baltimore, Maryland, almost 50% of respondents said their usual source for needles and syringes was street dealers and a further 4.1% said their usual source was “friends/neighbors” or “shooting galleries” (Gleghorn et al., 1995). A number of studies investigating the main risk factors for HIV seroconversion found syringe borrowing to be an independent determinant, (van Ameijden et al., 1999), whereas some studies also found that backloading and frontloading were independent predictors.

Modeling studies have demonstrated that obtaining clean needles from NSPs reduces the circulation time of each syringe, whether for reuse by the same IDU or for sharing with other IDUs. Evaluations of numerous NSPs in many countries have concluded that IDUs who attend NSPs reduce their HIV risk behaviors compared with those who do not attend and that the evidence is particularly consistent in areas where nonattendees cannot obtain clean needles from any other sources (such as pharmacies or vending machines). Even in areas where pharmacy and other access to sterile syringes is available, most studies show that NSP use is significantly associated with a decline in risk behavior (Gibson and Flynn, 2001).

Evidence that a reversal to the status quo occurs after an intervention is withdrawn adds further to the coherence of arguments for causality. The positive effects of NSPs were observed when a needle exchange in Windham, Connecticut was closed. A significantly higher percentage of former exchange users reported obtaining syringes from an unreliable source and syringe sharing more than doubled, compared with preclosure (Broadhead et al., 1999). Some large ecological studies show a clear association with NSP implementation and declining HIV incidence and prevalence over time.

Evidence for the efficacy of NSPs in stemming the spread of HIV has been questioned because of an apparent lack of effect for HCV. HIV entered drug injecting populations in New York during the mid-1970s and Australia in the early 1980s, whereas prevention measures such as NSPs only began to be established in the early 1980s. In contrast, HCV first spread among IDUs in the 1960s and therefore had a comparatively higher baseline prevalence by the time NSPs were instigated (Crofts et al., 1999). HCV is about an order of magnitude more infectious by blood–blood contact than HIV (Coutinho, 1998; Crofts et al., 1999). Despite some reported disparities, there is increasing evidence that use of syringe exchanges have led to significant reductions in both hepatitis B and HCV (Hagan et al., 1995).

There is sufficient evidence to consider that the criterion of “Coherence of the Evidence” has been fulfilled.

Experimental Evidence. An appropriate experiment could theoretically be provided by a randomized clinical trial whereby IDUs were randomly allocated to an experimental group who would be issued with an adequate supply of sterile syringes at an exchange and a control group who would not be provided with sterile syringes. The experiment would need to take place in a setting isolated from potential access (by controls) to pharmacy or vending machine syringe acquisition. Other possible confounding factors would need to be measured and controlled for such issues as rate of incarceration, availability, accessibility, opportunity, appropriateness, and quality of drug user treatment (especially methadone treatment for heroin dependence); utilization of strategies to reduce sexual transmission

(such as condoms and treatment of sexually transmitted infections); and overlap with “bridge” populations (men who have sex with men and commercial sex workers). As discussed already, there are strong logistical and ethical arguments against conducting such experiments.

There is insufficient evidence to consider that the criterion of “Experimental Evidence” has been fulfilled.

Reasoning by Analogy. The provision of sterile injecting equipment to reduce HIV infection among IDUs has many similarities with condom provision to reduce sexual transmission of HIV. These interventions both have high biological plausibility. Condom provision is well accepted to have strong support from empirical evidence of effectiveness (Weaver et al., 2005). It could be argued that both are implemented less vigorously than would be justified by the evidence of effectiveness, safety, and cost-effectiveness. Concern has often been expressed that condom provision might inadvertently increase unsanctioned sexual activity such as reducing the age of initiation and increasing the frequency of sexual activity, especially among unmarried partners. There is no convincing evidence to support these concerns despite numerous and diligent attempts to detect these or other unintended negative consequences (Weaver et al., 2005). Drug use and sexual activity are sensitive issues in virtually all countries, especially when these occur among teenagers. Like NSPs, condom provision has considerable benefits apart from reduction of HIV infection, such as reducing the incidence of sexually transmitted infections and unwanted pregnancies. Condom provision and NSPs are both cost-effective interventions.

There is sufficient evidence to consider that the criterion of “Reasoning by Analogy” has been fulfilled.

Cost-Effectiveness. Many studies have demonstrated that the implementation of NSP is cost-effective and cost-saving. In a retrospective analysis, Lurie and Drucker (1997) estimated that the number of HIV infections that could have been prevented in the United States had NSPs been implemented during the early stages of the HIV/AIDS epidemic was between 4,394 (with a 15% incidence reduction due to NSPs) and 9,666 (with a 33% incidence reduction). The cost to the U.S. health care system of treating these HIV infections was calculated at between U.S.\$244 million and U.S.\$538 million, respectively (Lurie and Drucker, 1997). Furthermore, Lurie and colleagues (1998) also estimated the cost per syringe distributed for five syringe distribution strategies (an NSP, a pharmacy-based NSP, free pharmacy distribution of pharmacy kits, sale of such pharmacy kits to IDUs, and sale of syringes in pharmacies). All five strategies could distribute syringes at relatively low unit cost, with NSPs being the most expensive and syringe sales the cheapest. At an annual seroincidence exceeding 2.1%, all strategies were estimated to be cost saving.

Others have used mathematical modeling to estimate the cost per HIV infection averted by NSPs. Holtgrave and associates (Holtgrave et al., 1998) estimated that 100% coverage of a previously unmet need for sterile syringes for IDUs in the United States would require 954.8 million syringes at a cost of U.S.\$423 million. This would prevent 12,350 cases of HIV, with subsequent HIV treatment costing approximately U.S.\$1.3 billion. Total societal expenditure of U.S.\$277 million was estimated for NSP costs with U.S.\$145.8 million for pharmacy-based sales. It was estimated that approximately one third of the cost would comprise out-of-pocket payments by IDUs purchasing syringes from pharmacies. This amounts to a cost saving of U.S.\$34,278 per HIV-infection averted, well under the estimated lifetime medical costs of treating an HIV-infected individual (U.S.\$108,469).

Using conservative estimates, it was predicted that the Hamilton NSP in Canada (Gold et al., 1997) would prevent 24 cases of HIV infection over 5 years, thereby providing cost savings of U.S.\$1.3 million after the program expenses were taken into account. This translates into a savings-to-cost ratio of 4:1. The cost-effectiveness of the Edmonton Streetworks NSP in Canada was estimated at C\$9,500 per HIV infection delayed for 1 year (Jacobs et al., 1999). The discounted cost per case averted was less than the cost of a case of AIDS.

A variety of HIV prevention strategies was compared for cost-effectiveness in an East Coast city of the United States. Cost per HIV infection prevented was equal lowest for needle exchange and counselling/education (about U.S.\$4,000) (Kahn et al., 1992). The cost per HIV infection averted for an year by a NSP in New York City was estimated to be U.S.\$2,667. This is far below the estimated cost of lifetime medical treatment for one HIV-infected individual (before protease inhibitors)—U.S.\$56,000 to U.S.\$80,000. Thus the net cost savings per HIV infection averted for an NSP in New York City could be estimated to be U.S.\$53,000 to U.S.\$77,000 (Kahn and Haynes Sanstad, 1997). Another analysis of New York State-approved NSPs concluded that syringe exchange is a cost-effective and cost-saving strategy for reducing HIV transmission (Laufer, 2001), with an estimated 87 HIV infections averted across seven programs at a total cost of US\$1.8 million, resulting in a cost-effectiveness ratio of almost U.S.\$20,947 per HIV infection averted.

A cost-effectiveness study of NSPs in Svetlogorsk, Belarus evaluated a comprehensive strategy that included NSPs, safe sex counseling, condom promotion, bleach distribution, and referral for sexual transmitted disease services. The average cost per HIV infection averted was estimated at only about U.S.\$68 (estimated range, U.S.\$54 to U.S.\$100) (Kumaranayake et al., 2004). If the cost of the associated mass-media campaign was included, the cost per HIV infection averted rises to a range of U.S.\$240 to U.S.\$442, still notably cost-effective. This is a very significant study because it confirms that the cost-effectiveness of NSPs as an HIV prevention measure also applies in a resource-poor setting.

A cost-effectiveness study assessed whether prevention interventions targeted at high-risk populations have a greater effect on the number of HIV infections prevented than if they are targeted to low-risk populations. Assuming that the program reduces risk behaviors by a modest 10%, the study showed that one million dollars (U.S.) in annual prevention spending over 5 years could prevent about 100 HIV infections in high-risk populations with HIV prevalences of 10–15% (such as IDUs) (Kahn and DeCarlo, (1996). Kahn and DeCarlo (1996) also highlight the fact that there are certain cases where a simple cost-effectiveness analysis does not reflect the value of a program. For example, some programs benefit more risk groups than just their audience.

A cost-effectiveness analysis applied a simplified Yale Needle Circulation Model to four hypothetical NSPs in four U.S. cities with differing HIV prevalence and incidence rates. Reductions in HIV incidence rates varied across cities from 17% to 70% across the four hypothetical settings. Higher reductions were associated with more needles per client-year and greater efficiency was associated with low cost per needle exchanged. The estimated cost savings per HIV infection averted ranged from U.S.\$12,000 to U.S.\$99,000 (Kahn, 1998). Most cost-effectiveness studies have been conducted in developed countries with far fewer conducted in resource-poor settings.

There is sufficient evidence to consider that the criterion of “Cost-Effectiveness” has been fulfilled.

Absence of Negative Consequences. Studies have searched for and found no convincing evidence of the following unintended complications associated with NSPs: greater injection frequency, (Hartgers et al., 1989; Watters et al., 1994) increased illicit drug use, (Wolk et al.,

1990; Guydish et al., 1993) a rise in syringe lending to other IDUs, (Hartgers et al., 1989; Schechter et al., 1999) recruitment of new IDUs, (Heimer et al., 1993; Watters et al., 1994; van Ameijden and Coutinho, 2001) social network formation (Junge et al., 2000), greater numbers of discarded used needles (Oliver et al., 1992; Broadhead et al., 1999; Doherty et al., 2000), less motivation to change (i.e., reduce) drug use (Bluthenthal et al., 2001), and increased transition from noninjecting drug use to IDU (Guydish et al., 1993).

There is sufficient evidence to consider that the criterion of “Absence of Negative Consequences” has been fulfilled.

Feasibility of Implementation, Expansion, and Coverage. The implementation of NSPs has been shown to be successful in a variety of settings. The historical development of NSPs in Germany has been described, concluding that establishing programs in larger cities were easier than meeting the demand for them in smaller cities and more conservative states. Establishing NSPs in German prisons was considered desirable but only possible as pilot projects on a limited basis (Weber and Schneider, 1998). An ecological study of IDUs in seven U.S. metropolitan areas demonstrated that the IDUs were more likely to have used a reliable source for obtaining their most recent syringe in cities with an NSP (OR, 5.3; 95% confidence interval [CI] 3.3–8.5) (Gleghorn et al., 1998). NSPs have been successfully established in a few resource-poor settings, such as Hanoi in Vietnam (Quan et al., 1998), Kathmandu in Nepal (Peak et al., 1995), and northern Thailand (Gray, 1995). A report on NSPs in northern Thailand mentioned cooperation from government agencies and nongovernment agencies in addition to the local communities as key factors for successful implementation (Gray, 1995). The Hanoi NSP gained local acceptance by holding workshops with key community people, including the local police, using outreach services to distribute needles and syringes rather than at established exchange sites, using appropriate methods to collect used injection equipment, and by training and recruitment of ex-user outreach workers (Quan et al., 1998).

Successful implementation has also been achieved in some transitional countries, such as Svetlogorsk, Belarus (Eastern Europe) (Kumaranayake and Watts, 2000; Vickerman and Watts, 2002) and Sverdlovsk Oblast, Russia (Power and Nozhkina, 2002). The latter was achieved through a process of “many months of negotiation and discussion with all relevant agencies” including the Ministry for Internal Affairs (which is responsible for law enforcement). These processes also included educating officials at seminars at which international research evidence of best practice was presented, a study tour to visit harm reduction programs in Britain, and a series of training workshops for workers at the pilot sites. It was necessary to provide an early evaluation report to satisfy politicians and health care providers so that the project could continue. A number of international organizations were also involved to encourage policy-makers and health practitioners to implement harm-reduction strategies, and in particular to champion NSPs (Power and Nozhkina, 2002).

An evaluation of a Hawaiian NSP showed that the following characteristics were required to achieve sustainable high coverage: broad-based political support; allocation of public funds; progressive expansion and removal of counterproductive aspects; peer educators; links to other services for drug users, especially drug user treatment; and periodic formal evaluation (Vogt et al., 1998). It is noteworthy that implementation of NSPs in the early stages of an HIV epidemic (when seroprevalence is still low) combined with multiple prevention initiatives, including community outreach, have been shown to have maximum impact (Des Jarlais et al., 1995).

Early and vigorous implementation has been demonstrated in a number of countries. The first NSP was established in Sydney, Australia in 1986 and within a couple of years,

a national network of programs had been implemented with a throughput of 30 million needles and syringes in 2000 for a population of less than 20 million (HOI, NDARC, and Drummond, 2002). However, in many countries implementation has been delayed and the scale has been inadequate. This is especially true in developing and transitional countries or in countries that respond to illicit drugs with a predominantly supply control perspective (Bastos and Strathdee, 2000).

There is sufficient evidence to consider that the criterion of 'Feasibility of Implementation, Expansion, and Coverage' has been fulfilled.

Unanticipated Benefits. A number of studies have demonstrated additional benefits resulting from NSP use, apart from a reduction in injecting risk behavior and HIV infection. At the New Haven and Seattle exchanges, increased enrollment into drug user treatment was reported as well as higher treatment retention rates compared with nonusers of NSPs (Heimer, 1998; Gibson, 2000; Hagan et al., 2000). An evaluation study in Baltimore found that NSP attendance was independently associated with entry into drug user treatment for HIV-infected IDUs (Strathdee et al., 1999). In San Francisco, Bluthenthal et al. (2001) found that NSP clients' attitudes and motivation to change their drug-using patterns was positive and concluded that NSP is a possible link to drug user treatment. Gibson (2000) found NSP use to be associated with substantially reduced injecting or cessation of injecting compared with IDUs who had never attended an NSP. During a pilot NSP conducted in a Swiss women's prison for a year, accommodating up to 110 women, no injection abscesses were observed and there were no instances of aggressive or threatening behavior among inmates using syringes (Nelles and Harding, 1995).

There is sufficient evidence to consider that the criterion of "Unanticipated Benefits" has been fulfilled.

Special Populations.

Prisons. A pilot intervention project was carried out in a Bern prison accommodating up to 110 women, of whom a high (but unspecified) proportion injected drugs while imprisoned. Sterile injection equipment was made available from a one-to-one automatic dispenser. Before distribution of injection material, nearly half of the prisoners who injected drugs reported sharing injecting material regularly, whereas sharing virtually ceased during the experiment. A total of 5,335 syringes was exchanged during the project (0.2 syringes a day per inmate) (Nelles and Harding, 1995).

Mathematical modeling has been proposed as a useful technique for estimating HIV transmission in prisons (Dolan et al., 1998). Using conservative assumptions where measurement of relevant variables for the model were unavailable, a relatively large number of HIV infections were estimated to occur in prisons through sharing of injection equipment. Importantly, these observations were made even in a country where HIV prevalence among IDUs is low.

By December 2000, 19 prisons in three countries—Spain, Germany, and Switzerland—had syringe exchange programs (Dolan et al., 2003). All evaluations of these programs have been favorable and without any reported unintended negative consequences (Dolan et al., 2003).

Young IDUs. Young IDUs have been found to be at higher risk of acquiring HIV. Multivariate analysis in one study showed recent onset injecting to be an independent predictor for seroconversion (Fennema et al., 1997). A study of IDUs in Rio de Janeiro, Brazil found that younger age was the principal factor associated with high-risk injecting behavior (Telles et al., 1997). In most countries, young people appear to be

under-represented among IDUs attending NSPs. This may be because attendance at an NSP amounts to a relatively public identification as an IDU.

A study that investigated an HIV prevention program for homeless young adult IDUs in San Francisco found significant differences between IDUs who frequented a secondary NSP intervention site and a comparison group who did not (Sears et al., 2001). The comparison group was more at risk of sharing syringes (adjusted OR, 3.748; 95% CI, 1.406–9.988) and reusing syringes (adjusted OR, 2.769; 95% CI, 1.120–6.847).

“Bridge” populations. Several studies have observed that women who attend NSPs and engage in sex work typically report greater HIV risk than women non-sex workers attending NSPs. A study comparing sex workers with non-sex workers in five U.S. cities found that sex workers were significantly more likely to inject more frequently ($p < .0005$), to reuse syringes more than twice ($p < .005$), to engage in backloading syringes ($p < .005$), and to obtain syringes from non-NSP sources ($p < .05$) (Paone et al., 1999). Current sex workers in a Vancouver study engaged in “heavier drug use,” reported a greater variety of injection and noninjection drugs, and injected substantially more frequently than both sexually active and nonsexually active women (Schechter et al., 1999). They also engaged more frequently in risky injection practices, such as renting, buying, or borrowing used syringes and using “shooting galleries,” than other women. Extensive HIV infection has occurred among commercial sex workers in some countries before a generalized epidemic (e.g., Thailand, Nelson et al., 1996; Ungchusak et al., 1989).

IDU men who have sex with men constitute another bridge population. A Brazilian study that aimed to determine risk factors for HIV-1 among IDUs ($n = 123$) in Rio de Janeiro found that being a male who has had sex with men in the previous 5 years was a significant independent risk factor for HIV infection. The authors concluded that homosexual/bisexual male drug injectors may have been a bridge group through which HIV entered drug-injecting networks in that city (Lima et al., 1994).

Successful NSP interventions have been set up either as pilot programs or ongoing services in a number of developing countries, including three remote villages in northern Thailand (Gray, 1995) Hanoi, Vietnam, and Dhaka and Rajshahi, Bangladesh (Jenkins et al., 2001). Evaluation results for these studies were reported above under Strength of Association and were further discussed under Feasibility of Implementation, Expansion, and Coverage.

There is sufficient evidence to consider that the criterion of “Special Populations” has been fulfilled.

Discussion

This study represents the first international review of NSPs. It is also the first systematic review to consider the extent to which evidence for NSPs fulfills the Bradford Hill criteria. These criteria, originally devised to assess inferences of causality drawn from observational studies, have been used increasingly in recent years to assess intervention studies. This review has attempted to rigorously and conservatively apply the Bradford Hill criteria but in so doing has often encountered the problem of “double negatives” in drawing conclusions. Accordingly, readers are encouraged to carefully review the wording of all conclusions relating to Bradford Hill criteria. Each of these refers specifically to a null hypothesis.

Although a wide variety of different activities and operational methods are now subsumed by the term “needle syringe programme,” there is sufficient commonality to

allow evaluation of this large and growing literature. Large numbers of research studies with widely differing designs in diverse countries have been reported. An increasing number of countries commenced NSPs and then began to expand them to scale. Although evidence supporting the effectiveness and safety of NSPs grew, HIV has continued to spread even more rapidly among and from IDUs than the adoption and later expansion of NSPs. Some excellent and comprehensive reviews of the evidence for NSPs have appeared (International Commission of AIDS, 1991; General Accounting Office, 1993; Lurie and Reingold, 1993; Office of Technology Assessment of the U.S. Congress, 1995; Normand et al., 1995; National Institutes of Health Consensus Panel, 1997; Satcher, 2000; Institute of Medicine of the National Academy of Science, 2001). All have confirmed the effectiveness of NSPs in reducing HIV spread. This conclusion was drawn with increasing confidence in more recent reviews as more and better quality data have become available.

The overwhelming majority of studies evaluating the effectiveness and safety of NSPs are highly supportive. But in spite of the impressive volume and quality of this supporting evidence, some still question the efficacy and safety of NSPs. A somewhat tendentious interpretation of a handful of negative studies from Montreal (Bruneau et al., 1997) and Vancouver (Strathdee et al., 1997) is relied on by critics of the proposition that NSPs are effective and safe, despite subsequent studies providing plausible alternative explanations for these negative findings (Lurie and Drucker, 1997; Schechter et al., 1999; Bastos and Strathdee, 2000; Coutinho, 2000; Strathdee and Vlahov, 2001). The benefits of NSPs are much easier to demonstrate when these are the *only outlets* for sterile injecting equipment. Another methodological issue is the tendency for studies to measure baseline and outcome variables dichotomously, substantially reducing the power of these studies.

The quantity and quality of the literature on pharmacy availability of sterile injecting equipment is not as impressive as the literature on NSPs. It is also more difficult to interpret because of the often confounding effect of NSPs and thus not easy to estimate the specific contribution of pharmacy availability. However, studies evaluating pharmacy availability in the absence of NSPs make it abundantly clear that pharmacies are also effective. The paucity of data for vending machines is even more marked than for pharmacies. However, there is a common finding that pharmacy and vending machine outlets often attract a somewhat different population from those attending NSPs. The attitude of pharmacists to IDUs is critical to the success or failure of pharmacy availability of sterile injecting equipment. There is a need to consider outlet density and type more as a system than in terms of its component parts.

This review should be considered in the light of several limitations. The only literature reviewed was in the English language. Most of this literature originated from developed countries, which although peer reviewed may still be subject to one or more forms of publication bias. The overwhelming majority of studies were quantitative, and there were very limited qualitative data to illuminate the findings of the quantitative studies. The literature regarding the second term of reference (NSP effectiveness) is so vast that there is little need to also review the relevant "gray literature." Any subsequent reviews of bleach and decontamination, pharmacy and vending machines, disposal and injecting paraphernalia legislation, should make greater use of gray literature. The "white literature" on these areas is small and often less than impressive in quality.

This review was also inevitably limited by inherent deficiencies in the quality of the existing literature. For example, much of the literature classifies IDUs as persons who either attend or do not attend NSPs, whereas in reality this phenomenon is dimensional rather than categorical. In addition, outcome measures are usually categorical, although again the phenomenon is usually dimensional. For example, sharing is usually measured as either

present or absent during a particular period rather than estimated on a continuum (Bastos and Strathdee, 2000).

Conclusions

1. *There is compelling evidence that increasing the availability, accessibility, and both the awareness of the imperative to avoid HIV and utilization of sterile injecting equipment by IDUs reduces HIV infection substantially.*

Overall, there is convincing evidence that NSPs, assessed conservatively, fulfill six of the nine Bradford Hill criteria and all of the five additional criteria. Measured against any objective standards, the evidence to support the effectiveness of NSPs in substantially reducing HIV must be regarded as overwhelming.

2. *There is no convincing evidence of any major unintended negative consequences.*

Specifically and after almost two decades of extensive research, there is still no persuasive evidence that NSPs increase the initiation, duration, or frequency of illicit drug use or drug injecting.

3. *NSPs are cost-effective.*

It is more difficult to generalize from studies of cost-effectiveness of NSPs in one country to other similar countries, let alone from developed countries to resource-poor settings. However, a number of careful studies in several developed countries and some transitional countries have demonstrated convincingly that NSPs are cost-effective.

4. *NSPs have additional and worthwhile benefits apart from reducing HIV infection among IDUs.*

There is reasonable evidence that NSPs can increase recruitment into drug user treatment and possibly also into primary health care.

5. *NSPs on their own are not enough to control HIV infection among IDUs.*

There is no evidence of a protective effect for single interventions strong enough to guarantee HIV control, but the aggregate effect of several harm reduction interventions appears to be generally successful in maintaining HIV control. Sterile needle and syringe availability needs to be considered as a system and has to be supported by a range of complementary measures if communities wish to control HIV infection among and from IDUs.

Recommendations

1. Authorities responsible for areas threatened by or experiencing an epidemic of HIV infection among IDUs should urgently adopt measures to increase the availability, access, and utilization of sterile injecting equipment and expand implementation to scale as soon as possible. As an approximation it is reasonable to assume that providing 200 sterile needles and syringes per drug injector per year is a figure that is achievable and likely to control HIV infection in this population. It may take several years, starting from scratch, to reach this figure. Higher targets may be needed where seroprevalence has already reached unacceptable levels. The precise quantity of injecting equipment required is not known. Cocaine injectors, for example, require more needles and syringes than heroin injectors.
2. The higher the seroprevalence of HIV among IDUs, the more HIV sexual transmission becomes an important factor. HIV sexual transmission is more difficult to control than HIV spread through sharing of injection equipment.

3. Carefully evaluated pilot programs of NSPs have their place in allowing the introduction of this invaluable protection of public health, but they also have some risks. First, the case for NSPs is already so compelling and the international experience so impressive that there is no longer any real justification for pilot programs. Pilot programs may further delay the much needed expansion phase. If the program remains frozen at the pilot phase level of implementation, then there is a risk that the program will remain chronically underfunded with attendant inadequate coverage.
4. NSPs are only one way of increasing the availability of sterile injection equipment, and these exist in many forms around the world with some cities requiring “one-for-one” exchange, others attempting to achieve high levels of exchange but accepting less than 100%, whereas authorities in other jurisdiction provide sale or free distribution without attempting to remove used injection equipment from circulation. There is no evidence that any one method is notably more efficacious or cost-effective. Many jurisdictions have found that a diversity of approaches is optimal with some methods working best in certain locations and conditions and other approaches better suited in other places and conditions. The paramount aim is to reduce the circulation time of needles and syringes.
5. Attempts to increase the availability of sterile injecting equipment should be accompanied by endeavors to increase the use of sterile injection equipment, reduce the use and availability of unsterile injection equipment, and improve the appropriateness of discarding of used injecting equipment. These objectives are best met through education of IDUs where peer-based explicit campaigns have generally been found to be highly effective.
6. However worthwhile it may be to increase the availability and use of sterile injecting equipment with the aim of controlling HIV infection among IDUs, this appears to be a necessary rather than a sufficient intervention. Other activities that complement the benefits of sterile injecting equipment programs include education of IDUs; increasing the capacity, accessibility range, appropriateness; (“matching”), and quality of drug user treatment (especially substitution treatment); and making available daily life resources (hot showers, a meal, a “time out” supportive environment, etc.) and community development of drug users.
7. Pharmacy-based NSPs appear to complement community-based schemes and may provide access to a somewhat different population of IDUs. Vending machines increase coverage geographically and across time zones but have the disadvantage of not providing information, counseling, or referral.
8. Special populations of IDUs are of great public health significance in HIV control, especially bridge populations (such as IDUs who are also men who have sex with men or male or female commercial sex workers). In most countries, a large proportion of IDUs spend a considerable proportion of their drug-injecting careers behind bars, whereas a large proportion of prison inmates have a history of drug injecting. Many inmates of correctional facilities continue to inject while they are incarcerated. The limited evidence available from evaluation of the few existing prison NSPs suggests that their benefits are similar to community programs, whereas there is no evidence to date that these programs are inherently unsafe or counterproductive. On the available evidence, there is a strong case for establishing and expanding NSPs in correctional facilities in many countries.
9. Disinfection and decontamination schemes are not supported by evidence of effectiveness and should only be advocated as a *temporary measure* where there

is implacable opposition to NSPs in certain communities or situations (e.g., correctional facilities).

10. This review has demonstrated significant gaps in research. The quantity and quality of research needs to be improved in bleach and disinfection field studies, pharmacy and vending machine evaluation, measures to reduce inappropriate disposal, and injecting paraphernalia legislation in countries other than the United States. More and better qualitative research would illuminate the findings of the numerous quantitative studies. Researches should make more use of continuous measures of baseline characteristics, interventions, and outcome variables. However, it is important to recognize that the limited implementation of NSPs is not fundamentally due to a lack of adequate research data. Therefore, it is unlikely that increasing the quantity of the same kind of research as exists already is unlikely to increase the implementation of NSPs. These findings are consistent with seven previous reviews conducted by or on behalf of U.S. government agencies. This is the first international review and also the first to use the Bradford Hill framework. Only a handful of negative studies have been published, and alternative explanations for the findings in these studies are readily available. Dichotomous measurement at baseline and outcome of NSPs evaluation studies reduces the power of these articles.

Glossary

Backloading: Injecting drug users use their syringes to give drugs to other drug users by squirting measured quantities of drug solution into the back of the syringes of other drug users after removing the plunger.

Booting: Drawing the plunger of the syringe backward and forward after the drugs have been injected while the tip of the needle is still inserted into the vein to rinse out the last remaining small quantities of residual drugs.

Bradford Hill Criteria: A set of criteria (strength of association, replication of findings, specificity of association, temporal sequence, biological plausibility, biological gradient, experimental evidence, reasoning by analogy, and coherence) devised by the noted English epidemiologist, Bradford Hill, are used to assess inferences of causality from epidemiological studies of association; now also widely used as a standard framework to assess the strength of evidence for public health interventions.

“Bridge” Populations: Populations of considerable public health significance as they overlap other populations enabling HIV to be transmitted very quickly throughout the general population. For example, homosexually active male injecting drug users are a bridge between men who have sex with men and injecting drug users.

Frontloading: Same as backloading except the drug solution is inserted into the front of the syringe after removing the needle.

Gray Literature: Produced by all levels of government, academia, business, and industry in print and electronic formats but which is not controlled by commercial publishers and is not peer reviewed.

HIV Epidemic: HIV is a retrovirus responsible for the frequently fatal AIDS. AIDS was first officially recognized on June 5, 1981 and somewhat later was found to be caused by HIV infection. HIV/AIDS is now a pandemic that has claimed the lives of over 20 million people worldwide.

Street Needle Sellers: Private dealers of syringes encouraged by a market that requires convenient, all-hour access to injecting equipment in neighborhoods where drugs are frequently purchased.

White literature: Conventional publications by international organizations, governments, nongovernmental organizations, peer-reviewed articles published in journals, and academic books.

Zero Tolerance: The absence of leniency, exception, or flexibility in the enforcement of a law, rule, or regulation, especially a law against what is deemed to be antisocial behavior. Zero tolerance against drugs is part of this phenomenon.

RÉSUMÉ

Cette première revue internationale de l'évidence dans laquelle les programmes de seringue d'aiguille réduisent la contamination par HIV parmi les utilisateurs de drogues d'injection a constaté que la traditionnelle interprétation des données publiées accomplit six critères parmi neuf nommées, "Bradford Hill" (force d'association, dédoublement de résultats, séquence temporaire, plausibilité biologique, cohérence de l'évident et raisonnement par analogie) et tous parmi les cinq critères additionnelles (rentabilité, absence des conséquences négatives, possibilité d'installation, expansion et couverture, avantages imprévus et application aux populations spécifiques). Les critères de Bradford Hill sont souvent utilisées pour évaluer les interventions de santé publique. La principale découverte de cette revue était le fait qu'il existe l'évidence considérable de l'effectivité, la sécurité et la rentabilité conforme aux sept revues précédentes réalisées par, ou représentées par des agences de gouvernement des Etats-Unis. Les autorités dans les pays affectés ou menacés par la contamination du virus du SIDA parmi les utilisateurs de drogues d'injection devraient soigneusement examiner cette évidence convaincante disponible, à présent, pour les programmes de seringue d'aiguille avec l'intention d'établir ou d'agrandir les programmes de seringue d'aiguille à balance.

RESUMEN

Esta primera revisión internacional de la evidencia que el programa de agujas y jeringas reduce el contagio del VIH entre los usuarios de drogas, se encontró que la información publicada satisface seis de los nueve criterios de Bradford Hill (ventajas de la asociación, resultados repetitivos, secuencia temporal, plausibilidad biológica, evidencia coherente y razonamiento por analogía) y todos los cinco criterios adicionales (costos efectivos, ausencia de consecuencias negativas, factible implementación, expansión de la cobertura; beneficios inesperados y la aplicación a una población especial). Los criterios Bradford Hill son utilizados comunmente para evaluar las intervenciones de salud pública. Lo que se encontró principalmente en esta revisión fue la evidencia de costos reducidos y seguridad; comparada con las siete anteriores revisiones realizadas o conducidas por las agencias del gobierno de los Estados Unidos de América. Autoridades dentro de los países afectados o amenazados por la infección del VIH entre los usuarios de drogas inyectables debe considerarse cuidadosamente las evidencias convincentes ahora disponibles para los programas de agujas y jeringas, con una vista hacia el establecimiento o expansión de los programas de agujas y jeringas a gran escala.

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References

- Abdala, N., Stephens, P. C., Griffith, B. P., Heimer, R. (1999). Survival of HIV-1 in syringes. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 20:73–80.
- Bastos, F. I., Strathdee, S. A. (2000). Evaluating effectiveness of syringe exchange programmes: current issues and future prospects. *Social Science & Medicine* 51:1771–1782.
- Bluthenthal, R. N., Gogineni, A., Longshore, D., Stein, M. (2001). Factors associated with readiness to change drug use among needle-exchange users. *Drug & Alcohol Dependence* 62:225–230.
- Bluthenthal, R. N., Kral, A. H., Erringer, E. A., Edlin, B. R. (1998). Use of an illegal syringe exchange and injection-related risk behaviors among street-recruited drug users in Oakland, California, 1992 to 1995. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 18:505–511.
- Bluthenthal, R. N., Kral, A. H., Gee, L., Erringer, E. A., Edlin, B. R. (2000). The effect of syringe exchange use on high-risk injection drug users: a cohort study. *AIDS* 14:605–611.
- Bradford Hill, A. (1965). The environment and disease: association or causation. *Proceedures of the Royal Society of Medicine* 58:295–300.
- Broadhead, R. S., van Hulst, Y., Heckathorn, D. D. (1999). The impact of a needle exchange's closure. *Public Health Reports* 114:439–447.

- Bruneau, J., Lamothe, F., Franco, E., Lachance, N., Désy, M., Soto, J., Vinclette, J. (1997). High rates of HIV infection among injection drug users participating in needle exchange programs in Montreal: results of a cohort study. *American Journal of Epidemiology* 146:994–1002.
- Buchanan, D., Shaw, S., Ford, A., Singer, M. (2003). Empirical science meets moral panic: an analysis of the politics of needle exchange. *Journal of Public Health Policy* 24:427–444.
- Burns, S. M., Brettell, R. P., Gore, S. M., Peutherer, J. F., Robertson, J. R. (1996). The epidemiology of HIV infection in Edinburgh related to the injecting of drugs: an historical perspective and new insight regarding the past incidence of HIV infection derived from retrospective HIV antibody testing of stored samples of serum. *Journal of Infection* 32:53–62.
- Chitwood, D. D., McCoy, C. B., Inciardi, J. A., McBride, D. C., Comerford, M., Trapido, E., McCoy, H. V., Page, J. B., Griffin, J., Fletcher, M. A., Ashman, M. A. (1990). HIV seropositivity of needles from shooting galleries in South Florida. *American Journal of Public Health* 80:150–152.
- Chitwood, D. D., Griffin, D. K., Comerford, M., Page, J. B., Trapido, E. J., Lai, S., McCoy, C. B. (1995). Risk factors for HIV-1 seroconversion among injection drug users: a case-control study. *American Journal of Public Health* 85:1538–1542.
- Coutinho, R. A. (1998). HIV and hepatitis C among injecting drug users: success in preventing HIV has not been mirrored for hepatitis C. *British Medical Journal* 317:424–425.
- Coutinho, R. A. (2000). Needle exchange, pragmatism, and moralism [letter;comment]. *American Journal of Public Health* 90:1385–1387.
- Cox, G. M., Lawless, M. C., Cassin, S. P., Geoghegan, T. W. (2000). Syringe exchanges: a public health response to problem drug use. *Irish Medical Journal* 93:143–146.
- Crofts, N., Aitken, C. K., Kaldor, M. J. (1999). The force of numbers: why hepatitis C is spreading among Australian injecting drug users while HIV is not. *Medical Journal of Australia* 170:220–221.
- Des Jarlais, D. C., Friedman, S. R., Sotharan, J. L., Wenston, J., Marmor, M., Yancovitz, S. R., Frank, B., Beatrice, S., Mildvan, D. (1994). Continuity and change within an HIV epidemic. Injecting drug users in New York City, 1984 through 1992. *JAMA* 271:121–127.
- Des Jarlais, D. C., Hagan, H., Friedman, S. R., Friedmann, P., Goldberg, D., Frischer, M., Green, S., Tunving, K., Ljungberg, B., Wodak, A. (1995). Maintaining low HIV seroprevalence in populations of injecting drug users. *JAMA* 274:1226–1231.
- Des Jarlais, D. C., Marmor, M., Paone, D., Titus, S., Shi, Q., Perlis, T., Jose, B., Friedman, S. R. (1996). HIV incidence among injecting drug users in New York City syringe-exchange programmes. *The Lancet* 348:987–991.
- Des Jarlais, D. C., Perlis, T., Friedman, S., Chapman, T., Kwok, J., Rockwell, R., Paone, D., Milliken, J., Monterroso, E. (2000). Behavioral risk reduction in a declining HIV epidemic: injection drug users in New York City, 1990–1997. *American Journal of Public Health* 90:1112–1116.
- Doherty, M. C., Junge, B., Rathouz, P., Garfein, R. S., Riley, E., Vlahov, D. (2002). The effect of needle exchange program on numbers of discarded needles: a 2-year follow-up. *American Journal of Public Health* 90:936–939.
- Dolan, K., Rutter, S., Wodak, A. D. (2003). Prison-based syringe exchange programmes: a review of international research and development. *Addiction* 98:153–158.
- Dolan, K., Wodak, A., Hall, W., Kaplan, E. (1998). A mathematical model of HIV transmission in NSW prisons. *Drug & Alcohol Dependence* 50:197–202.
- Donoghoe, M. C., Dolan, K., Stimdon, G. V. (1992). Life-style factors and social circumstances of syringe sharing in injecting drug users. *British Journal of Addiction* 87:993–1003.
- Donoghoe, M. C., Stimson, G. V., Dolan, K., Alldritt, L. (1989). Changes in HIV risk behaviour in clients of syringe-exchanges schemes in England and Scotland. *AIDS* 15:267–272.
- Fennema, J. S. A., van Ameijden, E. J. C., van den Hoek, A., Coutinho, R. A. (1997). Young and recent-onset injecting drug users are at higher risk for HIV. *Addiction* 92:1457–1466.
- Frischer, M., Elliot, L. (1993). Discriminating needle exchange attender from non-attenders. *Addiction* 88:681–687.

- General Accounting Office. (1993). *Needle Exchange Programs: Research Suggests Promise as an AIDS Prevention Strategy*. Washington, DC: U.S. Government Printing Office.
- Gibson, D. R. (2000). Two- to sevenfold decreased risk associated with use of needle exchange. Paper presented at University of California 3rd annual Conference on AIDS Research in California, 17th Annual AIDS investigators' Meeting, University of California, South San Francisco, California.
- Gibson, D. R., Brand, R., Anderson, K., Kahn, J. G., Perales, D., Gyuish, J. (2002). Two- to sixfold decreased odds of HIV risk behavior associated with use of syringe exchange. *Journal of Acquired Immune Deficiency Syndromes* 31:237–242.
- Gibson, D. R., Flynn, N. M. (2001). *Some Observations Concerning the Contrary Evidence of Syringe Exchange Effectiveness*. University of California, San Francisco: AIDS Research Institute.
- Gibson, D. R., Flynn, N. M. (2001). *Some Observations Concerning the Contrary Evidence of Syringe Exchange Effectiveness*. Barcelona: AIDS Research Institute, University of California, San Francisco.
- Gibson, D. R., Flynn, N. M., Perales, D. (2001). Effectiveness of syringe exchange programs in reducing HIV risk behavior and HIV seroconversion among injecting drug users. *AIDS* 15:1329–1341.
- Gleghorn, A. A., Jones, T. S., Doherty, M. C., Celentano, D. D., Vlahov, D. (1995). Acquisition and use of needles and syringes by injecting drug users in Baltimore, Maryland. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 10:97–103.
- Gleghorn, A. A., Wright-De Aguerro, L., Flynn, C. (1998). Feasibility of one-time use of sterile syringes: a study of active injection drug users in seven United States Metropolitan areas. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 18:S30–S36.
- Gold, M., Gafni, A., Nelligan, P., Millson, P. (1997). Needle exchange programs: an economic evaluation of a local experience. *Canadian Medical Association Journal* 157:255–262.
- Gray, J. (1995). Operating needle exchange programmes in the hills of Thailand. *AIDS Care* 7:489–499.
- Gyuish, J., Bucardo, J., Clark, G., Bernheim, S. (1998). Evaluating needle exchange: a description of client characteristics, health status, program utilization, and HIV risk behavior. *Substance Use & Misuse* 33:1173–1196.
- Gyuish, J., Bucardo, J., Young, M., Woods, W., Grinstead, O. (1993). Evaluating needle exchange: are there negative effects? *AIDS* 7:871–876.
- Gyuish, J., Clark, G., Garcia, D., Bucardo, J. (1995). Evaluation of needle exchange using street-based survey methods. *Journal of Drug Issues* 25:33–41.
- Hagan, H., Des Jarlais, D. C., Friedman, S. R., Purchase, D., Alter, M. J. (1995). Reduced risk of hepatitis B and hepatitis C among injection drug users in the Tacoma syringe exchange program. *American Journal of Public Health* 85:531–537.
- Hagan, H., McGough, J. P., Thiede, H., Hopkins, S., Duchin, J., Alexander, E. R. (2000). Reduced injection frequency and increased entry and retention in drug treatment associated with needle-exchange participation in Seattle drug injectors. *Journal of Substance Abuse Treatment* 19:247–252.
- Hartgers, C., Buning, E. C., van Santen, G. W., Verster, A. D., Coutinho, R. A. (1989). The impact of the needle and syringe-exchange programme in Amsterdam on injecting risk behaviour. *AIDS* 3:571–576.
- Hartgers, C., van Ameijden, E. J., van den Hoek, J. A., Coutinho, R. A. (1992). Needle sharing and participation in the Amsterdam Syringe Exchange program among HIV-seronegative injecting users. *Public Health Reports* 107:675–681.
- Health Outcomes International (HOI), NDARC, Drummond M. (2002). *Return on Investment in Needle and Syringe Programs in Australia*. Canberra: Commonwealth Department of Health and Ageing.
- Heimer, R. (1998). Can syringe exchange serve as a conduit to substance abuse treatment? *Journal of Substance Abuse Treatment* 15:183–191.

- Heimer, R., Kaplan, E. H., Khoshnood, K., Jariwala, B., Cadman, E. C. (1993). Needle exchange decreases the prevalence of HIV-1 Proviral DNA in returned syringes in New Haven, Connecticut. *The American Journal of Medicine* 95:214–220.
- Heimer, R., Khoshnood, K., Bigg, D., Guydish, J., Junge, B. (1998). Syringe use and reuse: effects of syringe exchange programs in four cities. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 18:S37–S44.
- Holtgrave, D. R., Pinkerton, S. D., Jones, T. S., Lurie, P., Vlahov, D. (1998). Cost and cost-effectiveness of increasing access to sterile syringes and needles as an HIV prevention intervention in the United States. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 18:S133–S138.
- Hurley, S. F., Jolley, D. J., Kaldor, J. M. (1997). Effectiveness of needle-exchange programmes for prevention of HIV infection. *The Lancet* 349:1797–1800.
- Inciardi, J. A., Page, J. B., McBride, D. C., Chitwood, D. D., McCoy, C. B., McCoy, H. V., Trapedo, E. J. (1994). The risk of exposure to HIV-contaminated needles in shooting galleries. In: Inciardi, J. A., McElrath, K., eds. *The American Drug Scene*. Los Angeles: Roxbury Press.
- Institute of Medicine of the National Academy of Science. (2001). *No Time to Lose: Getting More from HIV Prevention*. Washington, DC: National Academies Press.
- International Narcotics Control Board. (2004). *Report of the International Narcotics Control Board for 2003*. Vienna: International Narcotics Control Board.
- Jacobs, P., Calder, P., Taylor, M., Houston, S., Saunders, L. D., Albert, T. (1999). Cost effectiveness of Streetworks' needle exchange program of Edmonton. *Canadian Medical Association Journal* 90:168–171.
- Jenkins, C., Rahman, H., Saidel, T., Jana, S., Hussain, A. M. Z. (2001). Measuring the impact of needle exchange programs among injecting drug users through the National Behavioural Surveillance in Bangladesh. *AIDS Education & Prevention* 13:452–461.
- Junge, B., Valente, T., Latkin, C., Riley, E., Vlahov, D. (2000). Syringe exchange not associated with social network formation: results from Baltimore. *AIDS* 14:423–426.
- Kahn, J., Haynes Sanstad, K. C. (1997). The role of cost-effectiveness analysis in assessing HIV-prevention interventions. *AIDS & Public Policy Journal* 12:21–30.
- Kahn, J. G. (1998). Economic evaluation of primary HIV prevention in injection drug users. *Handbook of Economic Evaluation HIV Prevention Programs*. New York: Plenum Press.
- Kahn, J. G., Washington, A. E., Showstack, J. A. (1992). *Updated Estimates of the Impact and Cost of HIV Prevention in Injection Drug Users*. Prepared for the Centers for Disease Control. San Francisco: Institute for Health Policy Studies, School of Medicine, University of California, San Francisco.
- Kahn, J. G., DeCarlo, P. (1995). *Is HIV Prevention a Good Investment?* Infact sheet San Francisco CA: Center for AIDS Prevention Studies (CAPS), University of California, San Francisco.
- Kaplan, E. H., Heimer, R. (1995). HIV incidence among New Haven needle exchange participants: updated estimates from syringe tracking and testing data. *Journal of Acquired Immune Deficiency Syndromes* 10:175–176.
- Kaplan, E. H., Khoshnood, K., Heimer, R. (1994). A decline in HIV-infected needles returned to New Haven's needle exchange program: client shift or needle exchange? *American Journal of Public Health* 84:1991–1994.
- Kaplan, E. H. (1991). Evaluating needle exchange programs via syringe tracking and testing. *AIDS and Public Policy* 6:109–115.
- Keene, J., Stimson, G. V., Jones, S., Parry-Langdon, N. (1993). Evaluation of syringe-exchange for HIV prevention among injecting drug users in rural and urban areas of Wales. *Addiction* 88:1063–1070.
- Klee, H., Faugier, J., Hayes, C., Morris, J. (1991). The sharing of injection equipment among drug users attending prescribing clinics and those using needle exchange. *British Journal of Addiction* 86:217–223.
- Klee, H., Morris, J. (1995). The role of needle exchanges in modifying sharing behaviour: cross-study comparisons 1989–1993. *Addiction* 90:1635–1645.

- Kumaranayake, L., Vickerman, P., Walker, D., Samoshkin, S., Romantsov, V., Emelyanova, Z., Zviagin, V., Watts, C. (2004). The cost-effectiveness of HIV preventive measures among injecting drug users in Svetlogorsk, Belarus. *Addiction* 99:1565–1576.
- Kumaranayake, L. V., Walker, P., Samoshkin, D., Romantsov, V., Emelyanova, Z., Zviagin, V., Watts, C. (2004). *The Cost-Effectiveness of HIV Preventive Measures Among Injecting Drug Users in Svetlogorsk, Belarus: Addiction* 99:1565–1571.
- Latkin, C. A., Forman, V. L. (2001). Patterns of needle acquisition and sociobehavioral correlates of needle exchange program attendance in Baltimore, Maryland, U.S.A. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 27:398–404.
- Laufer, F. N. (2001). Cost-effectiveness of syringe exchange as an HIV prevention strategy. *Journal of Acquired Immune Deficiency Syndromes* 28:273–278.
- Lima, E. S., Friedman, S. R., Bastos, F. I., Telles, P. R., Friedmann, P., Ward, T. P., des Jarlais, D. C. (1994). Risk factors for HIV-1 seroprevalence among drug injectors in the cocaine-using environment in Rio de Janeiro. *Addiction* 89:689–698.
- Ljungberg, B., Christensson, B., Tunving, K., Andersson, B., Landvall, B., Lundberg, M., Zall-Friberg, A. C. (1991). HIV prevention among injecting drug users: three years of experience from a syringe exchange program in Sweden. *Journal of Acquired Immune Deficiency Syndromes* 4:890–895.
- Lowndes, C. M., Alary, M. (1998). Re: High rates of HIV infection among injection drug users participating in needle exchange programs in Montreal: results of a cohort study [letter]. *American Journal of Epidemiology* 148:713–714.
- Lurie, P., Drucker, E. (1997). An opportunity lost: HIV infections associated with lack of a national needle-exchange programme in the USA. *The Lancet* 349:604–608.
- Lurie, P., Drucker, E. (1997). An opportunity lost: HIV infections associated with lack of a national needle-exchange programme in the USA. *The Lancet* 349:604–608.
- Lurie, P., Gorsky, R., Jones, S. T., Shomphe, L. (1998). An economic analysis of needle exchange and pharmacy-based programs to increase sterile syringe availability for injection drug users. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 18:S126–S132.
- Lurie, P., Reingold, A. L., eds. (1993). *The Public Health Impact of Needle Exchange Programs in the United States and Abroad.*, Vol. 1. Atlanta, GA: Centers for Disease Control and Prevention.
- MacCoun, R. J., Reuter, P. (2001). *Drug War Heresies: Learning from Other Vices, Times, and Places.* London: Cambridge University Press.
- McAllister, W. B. (2000). *Drug Diplomacy in the Twentieth Century: An International History.* London: Routledge.
- McCoy, C. B., Shapshak, P., Metsch, L. R., Rivers, J. E., McCoy, H. V., Weatherby, N. L., Shah, S. M., Chitwood, D. D. (1995b). HIV-1 prevention: interdisciplinary studies on the efficacy of bleach and development of prevention protocols. *Arch Immunol Ther Exp* 43:1–9.
- McCoy, C. B., Shapshak, P., Shah, S. M., McCoy, H. V., Rivers, J. E., Page, J. B., Chitwood, D. D., Weatherby, N., Inciardi, J. A., McBride, D. C., Mash, D. C., Watters, J. K. (1995a). HIV-1 prevention: interdisciplinary studies and reviews on efficacy of bleach and compliance to bleach prevention protocols. Paper presented at Workshop on Needle Exchange and Bleach Distribution Programs, Washington, DC.
- McCoy, A. W. (2003). *The Politics of Heroin: CIA Complicity in the Global Drug Trade.* Chicago, IL: Lawrence Hill Books.
- Monterroso, E. R., Hamburger, M. E., Vlahov, D., Des Jarlais, D. C., Ouellet, L. J., Altice, F. L., Byers, R. H., Kerndt, P. R., Watters, J. K., Bowser, B. P., Fernando, M. D., Holmberg, S. D. (2000). Prevention of HIV infection in street-recruited injection drug users. The Collaborative Injection Drug User Study (CIDUS). *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 25:63–70.
- National Commission on AIDS. (1991). *The Twin Epidemics of Substance Use and HIV.* Washington, DC.
- National Institutes of Health Consensus Panel. (1997). *Interventions to Prevent HIV Risk Behaviors.* Bethesda, MD: NIH.

- Nelles, J., Harding, T. (1995). Preventing HIV transmission in prison: a tale of medical disobedience and Swiss pragmatism. *The Lancet* 346:1507–1508.
- Nelson, K. E., Celentano, D. D., Eiumtrakol, S., Hoover, D. R., Beyrer, C., Suprasert, S., Kuntolbutra, S., Khamboonruang, C. (1996). Changes in sexual behaviour and a decline in HIV infection among young men in Thailand. *The New England Journal of Medicine* 335:297–303.
- Nelson, K. E., Vlahov, D., Cohn, S., Lindsay, A., Solomon, L., Anthony, J. C. (1991). Human immunodeficiency virus infection in diabetic intravenous drug users. *JAMA* 266:2259–2261.
- Normand, J., Valhov, D., Moses, L. E., eds. (1995). *Preventing HIV Transmission The Role of Sterile Needles and Bleach*. Washington, DC: National Academy Press.
- Oliver, K. J., Friedman, S. R., Maynard, H., Magnuson, L., Des Jarlais, D. C. (1992). Impact of a needle exchange program on potentially infectious syringes in public places. *Journal of Acquired Immune Deficiency Syndromes* 5:534–535.
- Oliver, K. J., Maynard, H., Friedman, S. R., Des Jarlais, D. C. (1994). Behavioral and community impact of the Portland syringe exchange program. In: Normand, J., Vlahov, D., Moses, L. E., eds. *Proceedings: Workshop on Needle Exchange and Bleach Distribution Programs*. Washington, DC: National Academy Press, pp. 35–46.
- Page, J. B., Chitwood, D. D., Smith, P. C., Kane, N., McBride, D. C. (1990). Intravenous drug use and HIV infection in Miami. *Medical Anthropology* 4:56–71.
- Paone, D., Cooper, H., Alperen, J., Shi, Q., Des Jarlais, D. C. (1999). HIV risk behaviors of current sex workers attending syringe exchange: The experiences of women in five US cities. *AIDS Care* 11:269–280.
- Paone, D., Des Jarlais, D. C., Caloir, S., Friedman, P. B., Ness, I., Friedman, S. R. (1994). New York City syringe exchange: an overview. Paper presented at Workshop on Needle Exchange and Bleach Distribution Programs, September 27–28, 1993. Washington, D.C.: National Academy Press.
- Paone, D., Des Jarlais, D. C., Shi, Q. (1998). Syringe exchange use and HIV risk reduction over time. *AIDS* 12:121–123.
- Patrick, D. M., Strathdee, S. A., Archibald, C. P., Ofner, M., Craib, K. J., Cornelisse, P. G. (1997). Determinants of HIV seroconversion in injection drug users during a period of rising prevalence in Vancouver. *International Journal of STD & AIDS* 8:437–445.
- Peak, A., Rana, S., Maharjan, S. H., Jolley, D., Crofts, N. (1995). Declining risk for HIV among injecting drug users in Kathmandu, Nepal: the impact of a harm-reduction programme. *AIDS* 9:1067–1070.
- Power, R., Nozhkina, N. (2002). The value of process evaluation in sustaining HIV harm reduction in the Russian Federation. *AIDS* 16:303–304.
- Quan, V. M., Chung, A., Abdul-Quader, A. S. (1998). The feasibility of a syringe-needle-exchange program in Vietnam. *Substance Use & Misuse* 33:1055–1067.
- Safaeian, M., Brookmayer, R., Vlahov, D., Latkin, C., Harx, M., Strathdee, S. A. (2002). Validity of self-reported needle exchange attendance among injection drug users: implications for program evaluation. *American Journal of Epidemiology* 155:169–175.
- Samuels, J. S., Vlahov, D., Anthony, J. C., Solomon, L., Celentano, D. D. (1991). The practice of “frontloading” among intravenous drug users: association with antibody. *AIDS* 5:343–345.
- Satcher, D. (2000). *Evidence-Based Findings on the Efficacy of Syringe Exchange Programs: An Analysis of the Scientific Research Completed Since April 1998*. Washington, DC: Department of Health and Human Services.
- Schechter, M. T. S., Cornelisse, Peter, G. A., Currie, S., Patrick, D. M., Rekart, M. L., O’Shaughnessy, Michael, V. (1999). Do needle exchange programs increase the spread of HIV among injection drug users: an investigation of the Vancouver outbreak. *AIDS* 13:F45–F51.
- Schoenbaum, E. E., Hartel, D. M., Gourevitch, M. N. (1996). Needle exchange use among a cohort of injecting drug users. *AIDS* 10:1729–1734.
- Sears, C., Guydish, J. R., Weltzien, E. K., Lum, P. J. (2001). Investigation of a secondary syringe exchange program for homeless young adult injection drug users in San Francisco, California, U.S.A. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 27:193–201.

- Shah, S. M., Shapshak, P., Rivers, J. E., Stewart, R. V., Weatherby, N. L., Xin, K. Q., Page, J. B., Chitwood, D. D., Mash, D. V., Vlahov, D., McCoy, C. B. (1996). Detection of HIV-1 DNA in needle/syringes, paraphernalia, and washes from shooting galleries in Miami: a preliminary laboratory report. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 11:301–306.
- Shapshak, P., Fujimura, R. K., Page, J. B., Segal, D., Rivers, J. E., Yang, J., Shah, S. M., Graham, G., Metsch, L., Weatherby, N., Chitwood, D. D., McCoy, C. B. (2000). HIV-1. RNA load in needles/syringes from shooting galleries in Miami: a preliminary laboratory report. *Drug & Alcohol Dependence* 58:153–157.
- Singer, M., Himmelgreen, D., Weeks, M. R., Radda, K. E., Martinez, R. (1997). Changing the environment of AIDS risk: findings on syringe exchange and pharmacy sales of syringes in Hartford, CT. *Medical Anthropology* 18:107–130.
- Strathdee, S. A., Celentano, D. D., Shah, N., Lyles, C., Stambolis, V. A., Macal, G., Nelson, K., Vlahov, D. (1999). Needle-exchange attendance and health care utilization promote entry into detoxification. *Journal of Urban Health* 76:448–460.
- Strathdee, S. A., Patrick, D. M., Currie, S. L., Cornelisse, P. G., Rekart, M. L., Montaner, J. S., Schechter, M. T., O’Shaughnessy, M. V. (1997). Needle exchange is not enough: lessons from the Vancouver injecting drug use study. *AIDS* 11:F59–F65.
- Strathdee, S. A., Vlahov, D. (2001). The effectiveness of needle exchange programs: a review of the science and policy. *AIDS Science* 1:1–33.
- Telles, P. R., Bastos, F. I., Guydish, J., Inciardi, J. A., Surratt, H. L., Pearl, M., Hearst, N. (1997). Risk behavior and HIV seroprevalence among injecting drug users in Rio de Janeiro, Brazil. *AIDS* 11(Suppl 1):S35–S42.
- UNAIDS. (2002). *Report on the Global HIV/AIDS Epidemic 2002*. Geneva: United Nations.
- UNAIDS. (2004). *United States of America: Country HIV and AIDS Estimates, end 2003*. (Accessed on 27 June 2005) <http://www.unaids.org/EN/geographical+area/by+country/united+states+of+america.asp>
- UNDCP. (2002). *Flexibility of Treaty Provisions as Regards Harm Reduction Approaches Legal Affairs Section*. Vienna: United Nations International Drug Control Programme (UNDCP).
- Ungchusak, K., Sriprapandh, S., Pinichpongse, S., Kunasol, P., Thanprasertsuk, S. (1989). First national sentinel seroprevalence survey of HIV-1 infection in Thailand, June 1989. *Thai AIDS Journal* 1:57–74.
- van Ameijden, E. J., Coutinho, R. A. (2001). Large decline in injecting drug use in Amsterdam, 1986–1998: explanatory mechanisms and determinants of injecting transitions. *Journal of Epidemiology & Community Health* 55:356–363.
- van Ameijden, E. J., Coutinho, R. A. (1998). Maximum impact of HIV prevention measures targeted at injecting drug users. *AIDS* 12:625–633.
- van Ameijden, E. J., Langendam, M. W., Notenboom, J., Coutinho, R. A. (1999). Continuing injecting risk behaviour: results from the Amsterdam Cohort Study of drug users. *Addiction* 94:1051–1061.
- van Ameijden, E. J., van den Hoek, A. R., Coutinho, R. A. (1994). Injecting risk behavior among drug users in Amsterdam, 1986 to 1992, and its relationship to AIDS prevention programs. *American Journal of Public Health* 84:275–281.
- van Ameijden, E. J., van den Hoek, J. A. R., van Haastrecht, H. J. A., Coutinho, R. A. (1992). The harm reduction approach and risk factors for human immunodeficiency virus seroconversion in injecting drug users, Amsterdam. *Am. J. Epidemiol* 136:236–243.
- van Haastrecht, H. J., van Ameijden, E. J., van den Hoek, J. A., Mientjes, G. H., Bax, J. S., Coutinho, R. A. (1996). Predictors of mortality in the Amsterdam cohort of human immunodeficiency virus (HIV)-positive and HIV-negative drug users. *Am J Epidemiol* 143:380–391.
- Vickerman, P., Watts, C. (2002). The impact of an HIV prevention intervention for injecting drug users in Svetlogorsk, Belarus: model predictions. *International Journal of Drug Policy* 13:149–164.

- Vlahov, D., Junge, B., Brookmeyer, R., Cohn, S., Riky, E., Armenian, H., Beilenson, P. (1997). Reductions in high-risk drug use behaviors among participants in the Baltimore needle exchange program. *Journal of Acquired Immune Deficiency Syndromes* 16:400–406.
- Vogt, R. L., Breda, M. C., Des Jarlais, D. C., Gates, S., Whitticar, P. (1998). Hawaii's statewide syringe exchange program. *American Journal of Public Health* 88:1403–1404.
- Watters, J. K., Estilo, M. J., Clark, G. L., Lorvick, J. (1994). Syringe and needle exchange as HIV/AIDS prevention for injection drug users. *JAMA* 271:115–120.
- Weaver, H., Smith, G., Kippax, S. (2005). School-based sex education policies and indicators of sexual health among young people: a comparison of the Netherlands, France, Australia and the United States. *Computer Science Education* 5:171–188.
- Weber, U., Schneider, W. (1998). Syringe exchange in Germany. *Substance Use & Misuse* 33:1093–1112.
- Wodak, A., Cooney, A. (2004). *Effectiveness of Sterile Needle and Syringe Programming in Reducing HIV/AIDS among Injecting Drug Users*. Geneva: World Health Organization.
- Wodak, A., Dolan, K., Imrie, A. A., Gold, J., Wolk, J., Whyte, B. M., Cooper, D. A. (1987). Antibodies to the HIV virus in needles and syringes used by intravenous drug abusers. *Medical Journal of Australia* 147:275–276.
- Wolk, J., Wodak, A., Guinan, J. J., Macaskill, P., Simpson, J. M. (1990). The effect of a needle and syringe exchange on a methadone maintenance unit. *British Journal of Addiction* 85:1445–1450.

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