Estimating Long-term Trends in the Incidence and Prevalence of Opiate Use/Injecting Drug Use and the Number of Former Users: Back-Calculation Methods and Opiate Overdose Deaths

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The authors explored an age-specific back-calculation approach to estimating long-term trends in the incidence and prevalence of opiate use/injecting drug use (IDU) in England for 1968–2000. The incidence of opiate use/IDU was estimated by combining information on the observed opiate overdose deaths of persons aged 15–44 years with knowledge on the distribution of the time between starting opiate use/IDU and death by overdose (incubation time distribution). The resulting incidence, together with the incubation time distribution, other drug-related mortality, and the general age-specific mortality rate, was then used to estimate the prevalence of current and former users. Provisional estimates suggested two major increases in incidence in the late 1970s and early 1990s, with models including information on age at death suggesting a recent decline since 1997 and that prevalence of opiate use/IDU increased substantially in the 1990s. Results were crucially dependent on assumptions about key parameters of the back-calculation framework. In theory, the approach is a valuable addition to the portfolio of indirect methods for estimating incidence and prevalence of dependent opiate use/IDU. In practice, its full potential will be realized only once better information on the process of stopping opiate use/IDU becomes available and more precise estimates of current and historical overdose mortality are obtained.

epidemiologic methods; incidence; overdose; prevalence; substance abuse, intravenous

Abbreviations: EM, expectation-maximization; HIV, human immunodeficiency virus; IDU, injecting drug use.

The lack of evidence on trends in the prevalence and incidence of opiate use/injecting drug use (IDU) and IDU behaviors in the population is an ongoing problem that hinders effective drug policy and public health action (1). Opiate use/IDU poses significant public health problems. Epidemics of human immunodeficiency virus (HIV) can be mediated through IDU; in many countries, hepatitis C virus morbidity is associated with the size of the current and former injecting population, and mortality due to opiate use/IDU is approximately 1 percent per year, 10–20 times higher than in the general population (1–3).

Heroin use and IDU are chronic, relapsing conditions. Some persons manage to stop using drugs relatively quickly, while others may experience multiple episodes of treatment and imprisonment before ceasing use (4, 5). Interventions such as setting up specialist drug treatment centers and needle exchange services can minimize the harm associated with IDU. Strategies to prevent such use and accelerate transitions away from injecting are being encouraged (6). However, without evidence on the prevalence and incidence of IDU in the population, policy makers and public health advocates are unable to estimate the likely coverage of interventions and are therefore unable to evaluate the magnitude of the unmet need. Equally, without information on long-term trends in incidence and prevalence, the effectiveness of policy and strategies to prevent IDU and its associated harms cannot be judged, nor can services be effectively planned to

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deal with its long-term consequences (e.g., treatment of hepatitis C virus infection) (7).

Unfortunately, assessment of the likely magnitude of opiate use/IDU, especially long-term trends, is not straightforward partly because opiate users and injecting drug users represent an elusive and marginalized population (8). Traditional general-population survey methods do not work because they lack power and are subject to substantial response biases (9). Routine monitoring of the number of opiate users (e.g., with statistics from drug treatment, syringe exchange programs, or criminal justice) not only produces underestimates but also is subject to the usual limitations of many disease surveillance systems (10). Reported trends typically will be affected by factors such as underreporting and changes in policy that, unrelated to the underlying phenomenon of interest, make interpretation difficult. Extensive progress has been made on using routine data, especially through capture-recapture techniques, to generate prevalence estimates (11–13). However, these estimates are snapshots and do not give information on the direction of the underlying incidence. The likely high cost and complexity of following up a cohort of susceptible persons make direct estimation of the current incidence of IDU impractical. Little attention has been given to indirect methods for estimating long-term trends in incidence and prevalence, which also are important in the context of monitoring a chronic problem and are the subject of this paper (1, 14).

We have already pointed out parallels between the problem of estimating the incidence of HIV and that of estimating the incidence of opiate use/IDU. In a previous paper, we adapted a lag correction method to estimate the "relative incidence" of opiate use from trends in drug treatment data (15). However, we were unable to estimate the absolute incidence, or prevalence, because information on the proportion of heroin users entering treatment was unavailable. In the present paper, we consider the use of back-calculation in drug misuse epidemiology.

Back-calculation works on the basis that the incidence of a relevant disease endpoint a and the incidence of the infection resulting in the endpoint b are related through the incubation time c between the infection and development of the endpoint (16). Knowledge of any two of the three components—a, b, and c—allows estimation of the third. Typically, the distribution of the incubation time and the incidence of the endpoint are assumed known, and the incidence of the infection leading to trends in the endpoint is estimated. This method has been applied to HIV and other diseases with a long incubation time, such as Creutzfeldt-Jakob disease, and it can be adopted for the current problem of estimating the incidence of opiate use (17, 18). In the context of opiate use/IDU, a natural choice for the observed endpoint in a back-calculation setup would be the incidence of deaths due to opiate overdose. Therefore, the incubation distribution is the distribution of the time between starting opiate use/IDU and death from such use, without having stopped.

We can approximate the complexity of the natural history of injecting sufficiently to model its evolution, as if it were a chronic disease. Doing so is not new, as others have observed the typical pattern of injecting spreading among young people and have described it in terms of an epidemic (14, 19). In particular, Law et al. (18) introduced the use of back-calculation to estimate the number of injecting drug users in Australia. In the present paper, we extend the method to allow greater variation in key parameters, including age-specific overdose mortality, cessation rate, and age at first injection (20, 21). We illustrate the method by using trends in overdose mortality in England from 1968 to 2000 to obtain a range of incidence and prevalence estimates of opiate use/IDU over time and the number of current and former users.

MATERIALS AND METHODS

The statistical methods are given in more detail in the Appendix. Briefly, trends in opiate overdose deaths and estimates of the opiate overdose mortality rate and opiate use/IDU cessation rate are used in a back-calculation framework to estimate the number of new opiate users over time. The resulting estimates of incidence, the same information on the cessation rate and drug-related mortality (from opiate overdose and from other causes), are then combined to estimate the prevalence of "current" drug use. We also estimate the number of former users in the population. In total, 12 back-calculation models were specified (refer to the information below).

Epidemiologic studies suggest that the majority of adult opiate overdose deaths are attributable to dependent heroin users who inject (22). However, throughout this paper, we refer to the target population as opiate users/injecting drug users rather than heroin users or injecting drug users because routine mortality statistics refer to opiates and do not record route of administration.

Overdose deaths

The number of deaths by underlying cause of death, 5-year age group, and calendar year from 1968 to 2000 was provided by the Office for National Statistics. These data were coded by using two versions of the *International Classification of Diseases*: the Eighth Revision (1968–1978) and the Ninth Revision (1979–2000). Table 1 shows the selected underlying causes of death.

Deaths coded as drug dependence and abuse were included because, in 99 percent of cases when a drug was specified on the death certificate, it was an opiate (Clare Griffiths, Office for National Statistics, personal communication, 2002) (23). Deaths classified as "open verdicts" or "suicide" had to be excluded because the underlying *International Classification of Diseases* codes do not distinguish opiates from other analgesics, such as paracetamol. The age range was restricted to 15–44 years to reduce the chance of including children and older adults who may not be dependent opiate users.

Incubation time distribution parameters

Cessation rate. The cessation rate is a measure of the average length of time between starting and stopping opiate use/IDU expressed as the proportion of persons ceasing

TABLE 1. Opiate overdose deaths in England, 1968–2000: causes of death extracted from routine mortality data

ICD version*	Code	Definition	Proportion in data set (%)
ICD-8	3040	Drug dependence—opium alkaloids and their derivatives	1
ICD-8	3041	Drug dependence—synthetic analgesics with morphine-like effects	1
ICD-8	E8530	Accidental poisoning—opiates and synthetic analogues	2
ICD-9	3040	Drug dependence—morphine	27
ICD-9	3047	Drug dependence—combinations of morphine and any other drug	6
ICD-9	3055	Nondependent abuse of drugs—morphine	20
ICD-9	E8500	Accidental poisoning—opiates and related narcotics	44

* ICD-8, *International Classification of Diseases*, Eighth Revision; ICD-9, *International Classification of Diseases*, Ninth Revision.

such use per year. In three recent modeling exercises, different rates were used. Law et al. (18) assumed a constant yearly cessation rate of 0.05, suggesting an average length of injecting of 20 years and a median of about 13 years; Kaplan (24) estimated the cessation rate to be substantially higher at approximately 0.12 per year, giving an average injecting career of 8 years and a median of just over 5; and Pollack (25) assumed that the true cessation rate lay somewhere in between and adopted a rate of 0.09, giving an average injecting career of 11 years and a median of about 8. Given this uncertainty, in this paper we used these three estimates of the cessation rate: 0.05, 0.09, and 0.12.

Mortality rate. In the original Australian study, a constant yearly overdose mortality rate of 0.8 percent was assumed (2, 18), whereas most cohort studies show that the risk of overdose mortality increases with age (22, 26). In this paper, estimates of mortality rates were derived from a published study on a cohort of about 93,000 opiate addicts notified to the United Kingdom Home Office from 1968 to 1993; drug-related deaths were reported by calendar period and age group (table 2) (27). Opiate mortality rates were imputed from information given in the published study, assuming that 1) 80 percent of the drug-related mortality in the cohort was due to an accidental overdose; 2) before 1976, deaths recorded as accidental poisoning were due in equal proportion to barbiturates and opiate use; 3) after 1976, the proportion of such deaths related to opiate use increased to 90 percent; and 4) given the lack of information after 1993, rates from 1994 to 2000 remained at the same level as in 1993.

The overall opiate overdose mortality rate, independent of calendar year or age, was estimated to be 0.75 percent per year. We assumed that once opiate users cease use, they experience the age-specific mortality rate of the general population.

Age at first injection. It has long been recognized that young people are more susceptible to opiate use/IDU and that the average age at initiation may be stable over a specific geographic area and time period (14). Recent surveys of IDU in England (28) have suggested a mean age at starting of 22 years (median, 20; mode, 17). This information is used, for example, to fix age susceptibility in the fourth set of models, whereas, in the first three models, the age susceptibility parameter is estimated.

Models. The following models, each with three annual cessation rates (0.05, 0.09, 0.12), were investigated:

TABLE 2. Estimates (%) of drug-related and opiate overdose mortality in England by calendar period and age group

Calendar period	Age-group (years)					
	15–24		25–34		35–44	
	Overall drug-related mortality	Opiate overdose	Overall drug-related mortality	Opiate overdose	Overall drug-related mortality	Opiate overdose
1968–1976	1.43	0.72	1.68	0.67	1.68	0.67
1977–1983	0.56	0.50	1.60	1.15	1.60	1.15
1984–2000	0.32	0.29	0.83	0.60	1.39	1.00

* Adapted from Ghodse et al. (27).
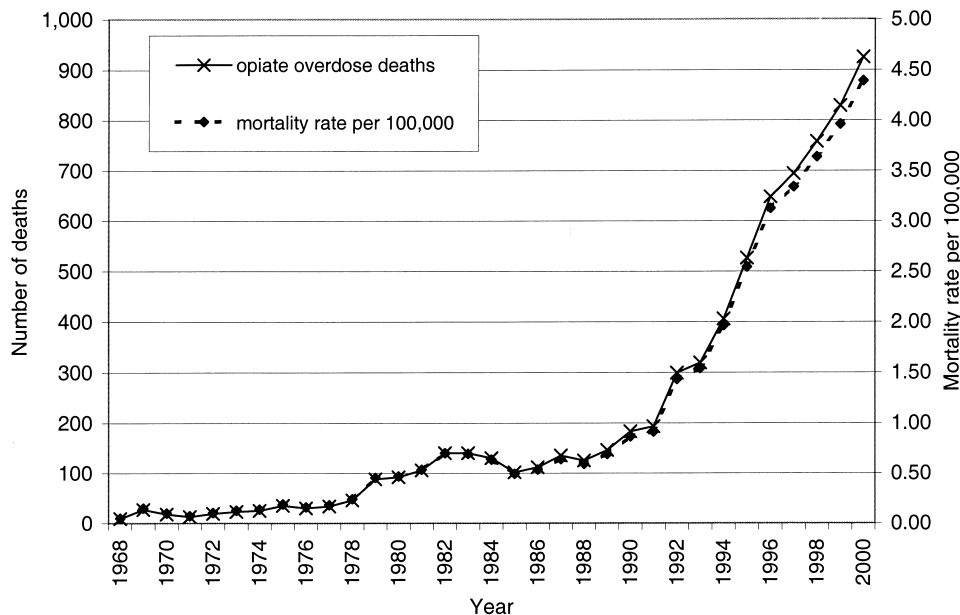
FIGURE 1.   Number of deaths and mortality rate due to opiate overdose in persons aged 15–44 years, England, 1968–2000.

- Model 1 uses the total number of overdose deaths by year and a single, overall opiate overdose mortality rate (independent of calendar year).
- Model 2 uses age-specific mortality data (annual number of overdose deaths by age group) and a single, overall opiate overdose mortality rate.
- Model 3 uses age-specific mortality data and allows the opiate overdose mortality rate to vary by calendar period.
- Model 4 uses age-specific mortality data and allows the opiate overdose mortality rate to vary by calendar period and age group; it also fixes the distribution of age at first use.

Ninety-five percent confidence intervals for the unknown quantities were generated by bootstrap methods (29) (refer to the Appendix). These confidence intervals are shown for one model only because the main source of uncertainty in the results is model uncertainty rather than statistical uncertainty.

RESULTS

In total, 7,375 deaths of persons aged 15–44 years were coded as drug misuse or as accidental opiate overdose in the period 1968–2000. Figure 1 shows that the number of opiate overdose deaths increased 100-fold over time from nine in 1968 to more than 900 in 2000, with the mortality rate in the general population aged 15–44 years increasing more than 80-fold from 0.05 per 100,000 in 1968 to 4.4 per 100,000 in 2000. Age at death also increased over time: before 1980, 80 percent of opiate overdose deaths were in those less than 30 years of age; from 1990 to 2000, 52 percent were associated with persons less than 30 years of age.

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Incidence

Figures 2, 3, and 4 show back-calculation estimates of the trends in incidence of opiate use/IDU. These estimates illustrate a number of points. First, statistical uncertainty (expressed by the 95 percent confidence intervals shown in figure 2) is far smaller than model uncertainty except for the most recent year, as shown by the difference between the estimates from one model in which different cessation rates were used (figure 2) and by the difference in the magnitude of the estimates between four models when the same single-cessation rate was adopted (figure 3). Second, by increasing the cessation rate from 0.05 per year to 0.09 and 0.12, the size of the incidence estimates increases by approximately 25 percent and 45 percent, respectively, as shown in figures 2 and 4. Third, in general, until 1995, the shape of the incidence curves in figures 2, 3, and 4 looks similar: two epidemic periods sandwiching an endemic period, with the results suggesting a threefold increase in incidence between 1975 and 1979 and a five- to sixfold increase between 1987 and 1995. Fourth, the interplay between the age-specific mortality rates and the distribution of the number of deaths within each age group is potentially important (figures 3 and 4). Estimates obtained by introducing period- and age-specific mortality rates applied to age-specific deaths (model 4) were generally larger than those derived from model 1, where a constant mortality rate is applied to the total number of deaths. Also note that results from models including the extra information provided by age-specific deaths (models 2–4) suggest a potential recent decline in the incidence of opiate use/IDU, which is not particularly supported by model 1. However, it needs to be emphasized that incidence in the recent past cannot be estimated very well by using this
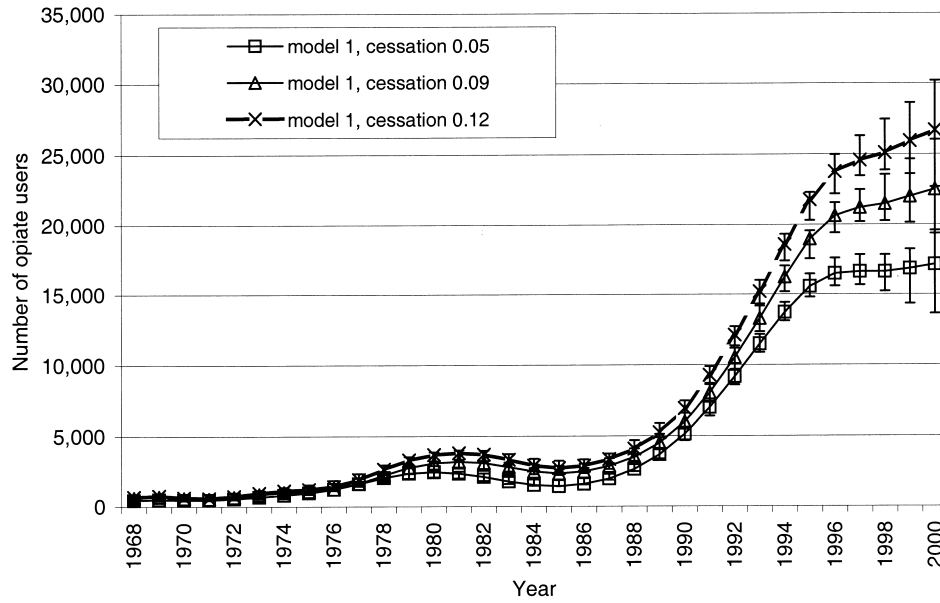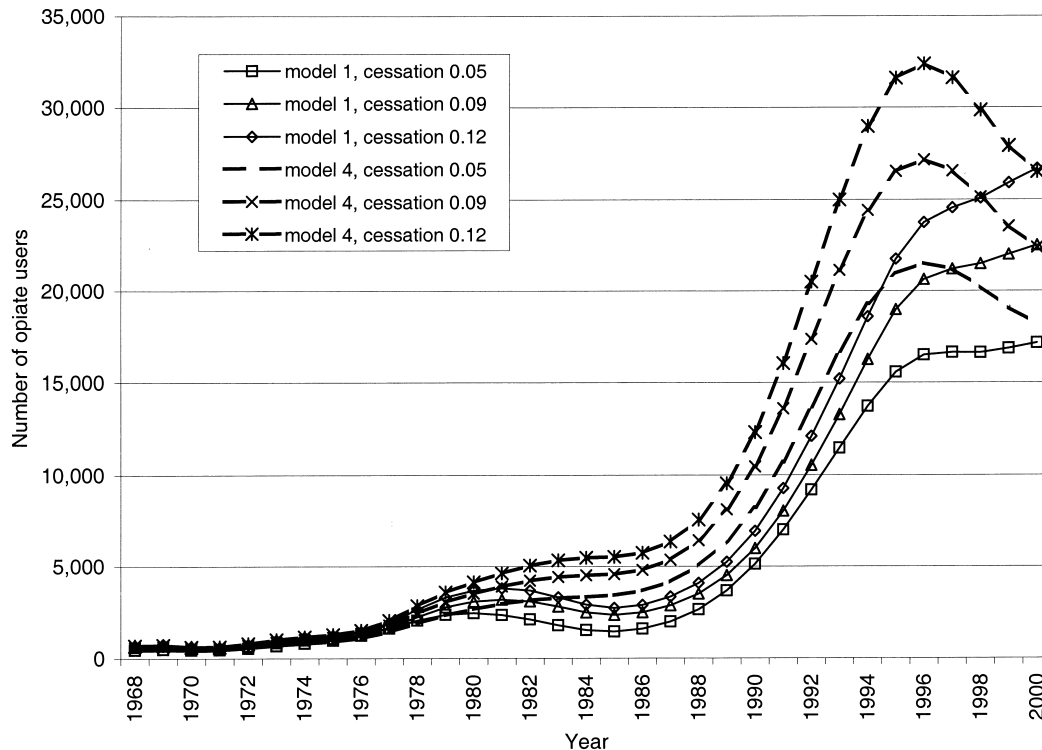
FIGURE 2. Back-calculation estimates of the incidence of opiate use/injecting drug use, England, 1968–2000: model using the total number of opiate overdose deaths by year, a constant mortality rate, and three cessation rates. Model 1 uses the total number of overdose deaths by year and a single overall opiate overdose mortality rate (independent of calendar year).
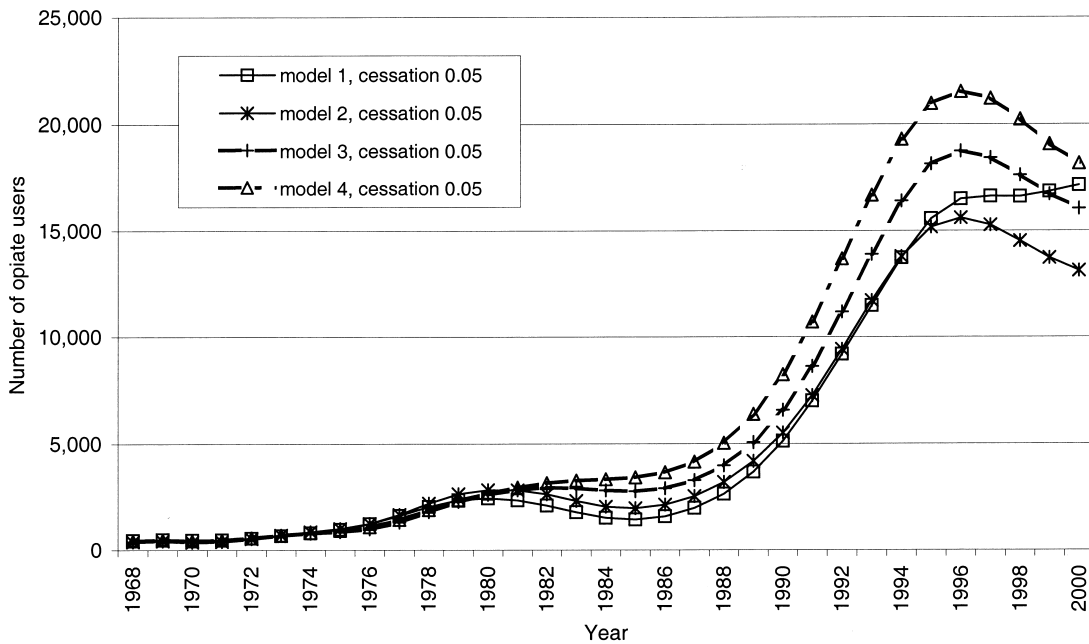
FIGURE 3. Back-calculation estimates of the incidence of opiate use/injecting drug use, England, 1968–2000: four models and a single cessation rate of 0.05 per year. Model 1 uses the total number of overdose deaths by year and a single overall opiate overdose mortality rate (independent of calendar year); model 2 uses age-specific mortality data (annual number of overdose deaths by age group) and a single overall opiate overdose mortality rate; model 3 uses age-specific mortality data and allows the opiate overdose mortality rate to vary by calendar period; and model 4 uses age-specific mortality data, allows the opiate overdose mortality rate to vary by calendar period and age group, and fixes the distribution of age at first use.

FIGURE 4. Back-calculation estimates of the incidence of opiate use/injecting drug use, England, 1968–2000: two models, each with three cessation rates. Model 1 uses the total number of overdose deaths by year and a single overall opiate overdose mortality rate (independent of calendar year); and model 4 uses age-specific mortality data, allows the opiate overdose mortality rate to vary by calendar period and age group, and fixes the distribution of age at first use.

method (refer to the Appendix), so results need to be interpreted with caution.

Prevalence

Estimates of the current prevalence of opiate use, derived from the estimated incidence, and assumed cessation rates and mortality rates are shown in figure 5. Only four of the models specified are shown because current prevalence is unaffected by variation in cessation rates. The results suggest that the prevalence of opiate use has continued to rise since the early 1970s, doubling between 1977 and 1982 and rising more than fourfold from 1987 to 1996. The models that include information on age at death (models 2–4) suggest that prevalence, although still increasing, may have slowed from 1996 onward, whereas model 1 suggests that prevalence rose linearly throughout the 1990s.

Mortality and former use

In addition to opiate overdose deaths, we estimated that more than 10,000 opiate users/injecting drug users would have died in 1968–2000 from other drug-related causes or

general mortality. England has a population of approximately 21 million aged 15–44 years. Table 3 summarizes the back-calculation estimates of the incidence, prevalence, number of former users (ceased injecting/opiate use and still alive), and ever users (current and former) per 100 population for 2000. The estimate of former opiate use/IDU is higher from models that include time- and age-specific mortality data, and the ratio of current to former users depends on the assumed cessation rate; for example, the proportion of current to former users ranges from more than 2:1 (70 percent:30 percent) to about 50:50 for cessation rates of 0.05 and 0.12, respectively. For 2000, estimates of the incidence of opiate use/IDU in England ranged from 13,100 (0.06 per 100 persons aged 15–44 years) to 26,800 (0.13 per 100 persons aged 15–44 years), prevalence ranged from 105,400 (0.5 percent) to 154,200 (0.73 percent), and ever use ranged from 154,100 (0.73 percent) to 323,300 (1.5 percent).

DISCUSSION

We have explored a back-calculation method, building on work initiated in Australia, that proposes using opiate overdose deaths over time and the probability of an opiate user
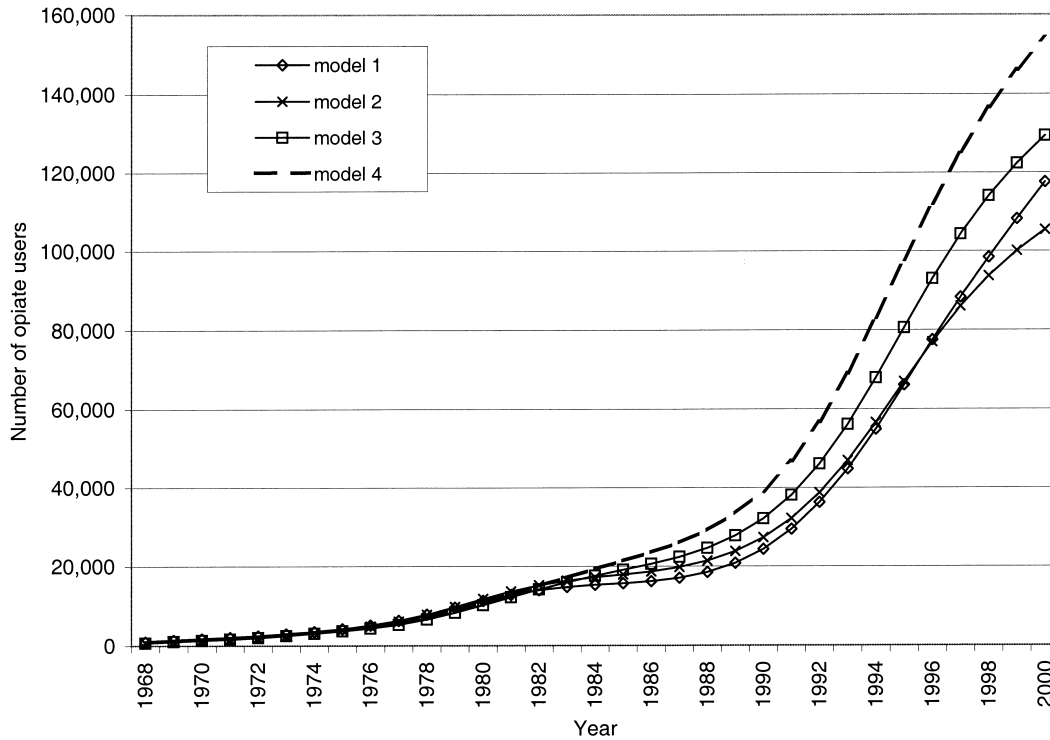
FIGURE 5. Back-calculation estimates of prevalence of opiate use/injecting drug use, England, 1968–2000: four models. Model 1 uses the total number of overdose deaths by year and a single overall opiate overdose mortality rate (independent of calendar year); model 2 uses age-specific mortality data (annual number of overdose deaths by age group) and a single overall opiate overdose mortality rate; model 3 uses age-specific mortality data and allows the opiate overdose mortality rate to vary by calendar period; and model 4 uses age-specific mortality data, allows the opiate overdose mortality rate to vary by calendar period and age group, and fixes the distribution of age at first use.

dying from overdose to estimate the underlying historical incidence and prevalence of opiate use/IDU (18). In this section of the paper, we first discuss issues related to the applicability of back-calculation methods, data availability, and quality; finally, we briefly address the credibility of these estimates for England.

TABLE 3. Summary back-calculation estimates of the incidence, prevalence, and number of former and ever opiate users alive in England, 2000*

Estimate	Cessation rate	Model 1		Model 2		Model 3		Model 4	
		No.	Rate/prevalence (%)	No.	Rate/prevalence (%)	No.	Rate/prevalence (%)	No.	Rate/prevalence (%)
Incidence	0.05	17,100	0.08	13,100	0.06	16,000	0.08	18,200	0.09
	0.09	22,500	0.11	18,100	0.09	21,800	0.10	22,400	0.11
	0.12	26,700	0.13	22,300	0.11	26,800	0.13	26,500	0.13
Prevalence		117,600	0.56	105,400	0.50	129,300	0.61	154,200	0.73
Former use	0.05	47,300	0.22	48,700	0.23	56,800	0.27	66,900	0.32
	0.09	85,400	0.41	87,500	0.42	101,900	0.48	124,000	0.59
	0.12	114,200	0.54	116,500	0.55	135,600	0.64	169,100	0.80
Ever use	0.05	164,900	0.78	154,100	0.73	186,100	0.88	221,100	1.05
	0.09	203,000	0.96	192,900	0.92	231,200	1.10	278,200	1.32
	0.12	231,800	1.10	221,900	1.05	264,900	1.26	323,300	1.53

* Model 1 uses the total number of overdose deaths by year and a single overall opiate overdose mortality rate (independent of calendar year); model 2 uses age-specific mortality data (annual number of overdose deaths by age group) and a single overall opiate overdose mortality rate; model 3 uses age-specific mortality data and allows the opiate overdose mortality rate to vary by calendar period; and model 4 uses age-specific mortality data, allows the opiate overdose mortality rate to vary by calendar period and age group, and fixes the distribution of age at first use.

Back-calculation: assumptions, applicability, and utility

A number of conceptual and empirical limitations of the approach need to be considered critically. For example, does the method estimate an important population in public health terms? The endpoint is opiate overdose deaths (as recorded in England by the Office for National Statistics); therefore, incidence will refer to opiate users at risk of death, that is, dependent opiate users. It will exclude cocaine users and "recreational" opiate users who have a low probability of overdose death.

Does information on the "incubation distribution" relate sufficiently to the observed endpoint? The relevant incubation period distribution for an endpoint such as opiate overdose deaths is given by the probability of death from an opiate overdose within a given period after starting opiate use. This probability is conditional on the subject not dying of another drug-related cause or an overdose being misclassified (30, 31). Clearly, HIV-positive opiate users may have a higher death rate than HIV-negative opiate users, and other subgroups of injecting drug users, such as those experiencing higher rates of imprisonment, also may have raised mortality rates compared with other groups (22, 32). The implication is that information on the mortality rate (opiate and nonopiate) needs to be derived from contemporaneous representative cohort studies of opiate users/injecting drug users to allow for any misclassification and differential mortality rates among subgroups of the population. The need for unbiased estimates of the incubation distribution applies to all examples of back-calculation, and any potential bias in the estimation of the mortality rate certainly will have to be explored further in sensitivity analyses. In addition, our estimates of the overdose mortality rates were based on an interpretation of published data, so the findings should be treated with caution pending further analysis of the original historical data set and recruitment of new mortality cohort studies (27).

Is the incubation distribution oversimplified? In common with many models of IDU, the cessation rate was expressed as a continuous function, which is a simplification of the pattern of opiate use/IDU over time (18, 24, 25). In truth, as several cohort studies have shown, a proportion of opiate users/injecting drug users will have repeated periods of recovery and relapse before death or cessation of use (33–36). This problem needs further investigation to test whether the assumption of uninterrupted drug use until complete cessation is adequate or whether the back-calculation formulation should be complicated further to take account of multiple periods of IDU over time. This problem is not unique to drug use because chronic diseases and infections also can have variable periods of pathogenesis.

In the epidemiology of acquired immunodeficiency syndrome, knowledge of the incubation distribution is based on strong evidence derived from a number of cohort studies. Unfortunately, the same wealth of evidence does not exist to estimate the cessation rate, the choice of which has a significant impact on the estimation of incidence and the number of former opiate users. Regrettably, very few countries have active cohorts of opiate users (37) (e.g., one cohort in the United Kingdom was last followed up 10 years ago), and

cohorts often recruit people with extensive injecting careers (e.g., at the start of the study, the ALIVE cohort had injected for an average of 10 years) (38). Pooling data from multiple cohorts would enable investigation of more realistic models for the cessation process. In one of the models, we included information on age at first use rather than allowing it to be estimated. However, we need to consider the possibility that the distribution of age at first use might have changed over time and seek data from earlier time periods.

Finally, is the method worthwhile? Undoubtedly, the back-calculation model could be improved and made more realistic given better information on the overdose mortality rate and cessation rate. In common with other applications of back-calculation, the most recent estimates will be the most uncertain because they are based on the smallest amount of information. However, the findings are and could be of value given our lack of knowledge of long-term trends in the incidence and prevalence of opiate use/IDU. First, there are no known estimates of the absolute incidence of injecting/opiate use over time, which could raise questions and inform policy makers on how effective long-term strategies have been in preventing injecting/opiate use and the likely direction in incidence and prevalence. Second, the method provides estimates of the number of former injecting drug users, which are critical for estimating hepatitis C virus morbidity and planning hepatitis C virus treatment (7). Third, the estimated trends can be used in other models, such as system dynamic models of the transmission of blood-borne viruses among injecting drug users and the general population and of econometric models of the criminal and social consequences of opiate use/IDU (39).

The findings

Our findings have implications for the original work conducted in Australia, based on a model in which the total number of overdose deaths and a constant mortality rate were used (18). In our example, introducing time- and age-specific mortality data in combination with the age-specific overdose deaths changed the shape of the incidence curves for most recent years and substantially increased the size of the estimates of incidence and prevalence. This situation may not apply in Australia but merits investigation.

The estimates must be treated with great caution because they are pilot results deriving from an illustration of the method. Nonetheless, they point to a number of issues that highlight the importance of developing the method further.

Is it true that opiate use/IDU rose so substantially in the 1990s, and is incidence decreasing? The prevalence of opiate use/IDU in 2000 ranged from over 100,000 to 150,000 (0.5–0.7 percent) when the epidemic curve was reconstructed, suggesting that prevalence has increased threefold in England since 1990. The estimated incidence in 2000 ranged from over 13,000 (0.06 per 100 adults aged 15–44 years) to over 26,000 (0.13 per 100 adults aged 15–44 years). The public health implications could be stark, starting from the need to expand treatment and harm-minimization interventions simply to maintain the same level of coverage to avoid increasing the problems associated with opiate/IDU; however, policy makers might take some encouragement

from model estimates suggesting that, since 1996, incidence has decreased by over 10 percent. Nevertheless, supporting evidence is sketchy. Experts from the Royal Colleges suggested that the United Kingdom was experiencing another heroin epidemic in the 1990s (40). Other data do point to substantial rises in the number of injecting drug users in the population. For instance, new notifications by physicians of opiate addicts to the Addicts Index (a register held by the Home Office) increased over 30-fold from approximately 600 in 1966 to more than 18,000 in 1996 and nearly threefold during the 1990s (41). Drug seizures and arrests also increased three- to fivefold in the 1990s. Unfortunately, none of these indicators provides direct evidence of the number of new opiate users.

Few existing prevalence estimates are based on strong evidence, and most are equally inaccurate. The United Kingdom drug strategy reported in the mid-1990s that there were 100,000–200,000 problem drug users (42). A pilot study of national estimation methods suggested that there were 143,000–266,000 problem drug users, with perhaps 75,000–150,000 opiate users in England and Wales in 1996 (43).

How many people have ever injected? How many former users are there—less than 50,000 or more than 100,000, and are there proportionally more current users than former users? Assuming a cessation rate of 0.05 per year given the trends in opiate overdose deaths implies that 70 percent of the population of opiate users/injecting drug users have not ceased drug use. A better understanding of the cessation rate would reduce uncertainty over the ratio of former to current users. The National Survey of Sexual Attitudes and Lifestyle reported that the prevalence of persons aged 15–44 years who have ever injected was 0.8 percent in 1990 and 1.3 percent in 2000 (44, 45).

Lastly, the historical trends are at odds with earlier estimates. The Advisory Council on the Misuse of Drugs estimated that there were 75,000–150,000 opiate addicts and 37,000–75,000 injecting drug users in 1985 (46). Our estimates based on trends in overdose deaths propose a much lower number of opiate users/injecting drug users in 1985: from 18,000 to 24,000, once again suggesting interesting questions worthy of further investigation.

Conclusions

There are good reasons to establish ongoing surveillance of opiate-drug-related deaths and improve our knowledge of the natural history of opiate use/IDU, including the cessation rate. The reliability of the results and the opportunity to explore the conceptual problems raised in this paper depend on improving the quality of available data. However, this paper clearly shows that back-calculation methods could provide considerable added value by estimating long-term trends of the incidence and prevalence of opiate use/IDU.

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APPENDIX

As outlined at the beginning of this paper, the back-calculation method relates the incidence of a given disease endpoint and the number of infections generating the endpoint through the distribution of the incubation time between the infection and development of the endpoint. Thus, if a time series of the endpoint of interest is available and the distribution of the incubation time is assumed to be known, the incidence of infection giving rise to the endpoint can be estimated. A number of forms of the back-calculation method have been proposed in the literature (16). In what follows, we have used a nonparametric version, where the incidence of infection is assumed to have a nonparametric form rather than a prespecified, functional expression. This nonparametric back-calculation was originally developed by Becker et al. (20) and was later extended by Becker and Marschner (21) to estimate simultaneously the time-dependent HIV incidence trends and the relative risk of infection for persons of different ages.

The latter approach has been adopted in this paper to estimate the incidence of opiate use/IDU in England: deaths from overdose represent the endpoint of interest, and death rates from overdose, combined with rates of cessation of IDU, provide the distribution of the incubation time. More formally, the back-calculation model can be described as follows.

Consider a discrete timescale (e.g., a year) and indicate by Y_{at} the number of persons aged a ($a = 1, 2, 3, \ldots, A$) who die of overdose in year t ($t = 1, 2, 3, \ldots, T$). Let f_{sd} be the probability that a person starting opiate use/IDU in year s will die of overdose in year $s + d$. Denote by N_{at} the unobserved number of persons aged a who start drug use in year t. Then, under the assumption that each person starting use in year t is given an incubation time independently, we have

$$E(Y_{at}|\{N_{at}\}) = \sum_{x=1}^{t} N_{a-t+x,\,x} f_{x,\,t-x}$$

and

$$E(Y_{at}) = \sum_{x=1}^{t} \nu_{a-t+x, x} f_{x, t-x}, \quad (1)$$

where $\nu_{a-t} = E(N_{a-t})$. Convolution equation 1 states that the expected number of overdose deaths occurring at age a in year t is the result of those persons who started at age $a - t + x$ in year x ($x = 1, 2, 3, \ldots, t$) and have been using drugs (without stopping) for a duration of $t - x$ years before overdose death. Assuming that both probability of overdose death and incidence of overdose deaths are known, the unknown expected number of starters of age a in year t can then be estimated. Note that those who have started using drugs recently will have little probability of death by time T. Therefore, the number of deaths up to time T will not contain much information on those persons. As a consequence, the method will not provide accurate estimates of the number starting use in the recent past.

Estimation of the ν_{at} is carried out as follows. Assume that N_{at} are independent Poisson variables and that their dependence on age and time is expressed via the multiplicative model:

$$E(N_{at}) = \nu_{at} = \pi_a \beta_a \lambda_t, \quad (2)$$

where λ_t represents the time component and π_a is the proportion of persons in the population of age a. With such a definition for π_a, the parameter β_a reflects the relative susceptibility of persons of age a. To avoid identifiability problems in equation 2,

$$\sum_{a=1}^{A} \pi_a \beta_a = 1, \quad (3)$$

which gives to λ_t the meaning of rate of starting drug use regardless of age. Given the overdose deaths y_{at} observed up to time T, from equation 1, equation 2, and the Poisson assumption on the Y_{at} a likelihood function $L(\beta, \lambda \,|\, y)$ can be constructed and maximum likelihood estimates of β_a and λ_t derived through the EM (expectation-maximization) algorithm (47). The EM algorithm is an iterative procedure used to obtain maximum likelihood estimates of parameters in an incomplete data problem (i.e., when data are incomplete). In the current estimation problem, it is also possible to derive explicit expressions for updating the parameters' values at each step of the iteration process (refer to Becker and Marschner for details (21)). However, since the problem is one of nonparametric estimation, the EM algorithm produces unstable estimates. This shortcoming, in conjunction with the expectation that estimates of β_a and λ_t would be smooth, induced Becker and Marschner to use a smoothed EM algorithm (EMS). The smoothed EM algorithm follows the same philosophy as the EM algorithm, except that it involves an extra step, the S step, where the values of the parameters obtained in the current iteration are replaced by smoothed values. In our case,

$$\beta_a^{new} = \sum_{i=1}^{k_1} w_{1i} \beta^*_{a+i-\frac{k_1}{2}}$$

and

$$\lambda_t^{new} = \sum_{i=1}^{k_2} w_{2i} \lambda^*_{t+i-\frac{k_2}{2}}$$

represent the smoothed updated estimates of β_a and λ_t at the current iteration (β^* and λ^* are the unsmoothed values at the same iteration), where k_i ($i = 1, 2$) is the (integer value) bandwidth and the w_{ij} are symmetric weights such that $\Sigma_j w_{ij} = 1$. Here, $k_1 = 5$ and $k_2 = 2$ and $w_{1j} = 1/k_1$ ($j = 0, 1, 2$) and

$$w_{2j} = \binom{k_2}{j} 2^{-2}$$

($j = 0, 1, 2, 3, 4, 5$). Thus, for example, $\lambda_t^{new} = w_{20}\lambda^*_{t-1} + w_{21}\lambda^*_t + w_{22}\lambda^*_{t+1}$; that is, the value of the parameter λ_t^{new} at the current iteration of the algorithm is a weighted average of the values provided by the EM algorithm at times $t - 1$, t, and $t + 1$.

Usually, in the standard EM algorithm, convergence of the procedure is reached if the difference in likelihood at two consecutive updates of the parameter estimates is smaller than a given threshold. The smoothed EM procedure, with the added after smoothing step, is no longer a standard maximum likelihood method; therefore, convergence is now based on the difference between values of the parameters. As proposed by Becker and Marschner (21), small positive values for ε_1 and ε_2 are chosen, and the iteration is stopped when both $\|\beta^{new} - \beta^{old}\|/\|\beta^{old}\| < \varepsilon_1$ and $\|\lambda^{new} - \lambda^{old}\|/\|\lambda^{old}\| < \varepsilon_2$ are satisfied, where β^{old} represent the value of the estimate of β at the iteration previous to the current one and

$$\|\mathbf{X}\| = \sqrt{\sum_i (x_i)^2}.$$

Here, $\varepsilon_1 = \varepsilon_2 = 0.0001$.

The above can be extended to the case in which the probability of overdose death depends on the age at which the person starts drug use; that is, f_{sd} becomes f_{asd}. Equation 1 now becomes

$$E(Y_{at}) = \sum_{x=1}^{t} \nu_{a-t+x, x} f_{a-t+x, x, t-x},$$

where $f_{a-t+x, x, t-x}$ is the probability that a person starting opiate use/IDU at age $a - t + x$ in year x dies at age a in year t. This situation is more complex, particularly if both β_a and λ_t are to be inferred. In this work, however, no attempt is made to estimate β_a, which is, in this case, derived from external information (29). Note that, in this setting, an estimate of the underlying incidence of opiate use is given by $\hat{\lambda} \sum_a \pi_a \beta_a$ rather than $\hat{\lambda}$.

The bootstrap can be used to provide a measure of the uncertainty surrounding these estimates, because asymptotic theory does not apply to estimates obtained from the EM smoothing algorithm (refer to Becker and Marschner for details (21)).