Bird, S.M. and Hutchinson, S.J. (2010) Over 1200 drugs-related deaths and 190,000 opiate-user-years of follow-up: relative risks by sex and age-group. Addiction Research and Theory . ISSN 1606-6359

Over 1200 drugs-related deaths and 190,000 opiate-user-years of follow-up: relative risks by sex and age-group.

Sheila M. Bird*, MRC Biostatistics Unit, Cambridge CB2 0SR

(email: sheila.bird@mrc-bsu.cam.ac.uk) on behalf of European COSMO

*(**CO**hort **S**tudies on **M**ortality of **O**piate-users) Workshop*

*corresponding author (phone: 44 1223 330368; fax: 44 1223 330388)

Short title: COSMO drugs-related deaths

Word count: 3,701

ABSTRACT

Heroin users/injectors' risk of drugs-related death by sex and current age is weakly estimated both in individual cohorts of under 1000 clients, 5000 person-years or 50 drugs-related deaths and when using cross-sectional data.

A workshop in Cambridge analysed six cohorts who were recruited according to a common European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) protocol from drug treatment agencies in Barcelona, Denmark, Dublin, Lisbon, Rome and Vienna in the 1990s; and, as external reference, opiate-user arrestees in France and hepatitis C diagnosed ever-injectors in Scotland in 1993-2001, both followed by database linkage to December 2001.

EMCDDA cohorts recorded approximately equal numbers of drugs-related deaths (864) and deaths from other non-HIV causes (865) during 106,152 person-years of follow-up. External cohorts contributed 376 drugs-related deaths (Scotland 195, France 181) and 418 deaths from non-HIV causes (Scotland 221, France 197) during 86,417 person-years of follow-up (Scotland 22,670, France 63,747).

EMCDDA cohorts reported 707 drugs-related deaths in 81,367 man-years {8.7 per 1000 person-years, 95% CI: 8.1 to 9.4} but only 157 in 24,785 person-years for females {6.3 per 1000 person-years, 95% CI: 5.4 to 7.4}.

Except in external cohorts, relative risks by current age-group were not particularly strong, and more modest in Poisson regression than in cross-sectional analyses: relative risk was 1.2 (95% CI: 1.0-1.4) for 35-44 year olds compared to 15-24 year

olds, but 1.4 for males (95%CI: 1.2-1.6), and dramatically lower at 0.44 after the first year of follow-up (95% CI: 0.37-0.52). [242 words]

Key words: drugs-related deaths, heroin users, injectors, sex, age-group, non-HIV mortality.

Key-points: Back-calculating past injector incidence and projecting late sequelae of Hepatitis C should take into account that male injectors' risk of drugs related death is 1.4 times higher than for females. Drugs-related deaths account for half of all non-HIV deaths among heroin users/injectors. Hazard of drugs-related death may be only moderately affected by current age.

INTRODUCTION

Most European countries have national or regional registers which identify the deceased by name, postal address, sex and date of birth. Registers record date of death and code for cause of death according to the International Classification of Diseases (ICD). Heterogeneity in ICD codes used to classify 'drugs-related deaths' (Advisory Council on the Misuse of Drugs, 2000) has led the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2000) to implement a standard classification to improve comparability. We adopt EMCDDA's classification.

Standardized in this way, routine mortality data give total numbers of drugs-related deaths by region, sex and age-group (Jackson, 2003; Jossels and Sartor, 2006), which can be related to a suitable reference population, either general (Uren et al., 2001; Quaglio et al., 2001; Jossels and Sartor, 2006) or, preferably, problem or injection drug users (see Hay et al., 2001; EMCDDA, 2003; Bird et al., 2003; Hickman et al., 2004; King et al., 2005; King et al., 2008). Mortality studies in cohorts of problem drug users or injectors are arguably a better approach still (see Wahren et al., 1997; Versino et al., 2000; Langendam et al., 2001; Bargagli et al., 2001; Risser et al., 2001; Gossop et al., 2002; Hickman et al., 2003; Galai et al., 2003; Copeland et al., 2004; Bargagli et al., 2005; Bloor et al., 2008) because: a) they document not only drugs-related but also HIV-related and other-cause mortality (see Darke and Ross, 2002 and Bloor et al., 2008), b) the covariate influences of sex and current age on the risk of drugs-related death can be estimated for individuals whose drugs history, including treatment referral (Buster et al., 2002 and Fugelstad et al., 2007), route of administration of primary drug and initiation age, was documented in a standardized manner at enrolment to the cohort (Hickman et al., 2003 and Copeland et al., 2004),

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and c) with shared protocol for enrolment, comparably-estimated risks can be compared across cohorts.

Bird et al. (2003), for example, applied evidence-synthesis techniques to published data from Scotland to deduce that the relative risk of drugs-related death per 100 injectors could be 1.8 times as high for males (95% CI: 1.3 to 2.3) and two to six times higher for older injectors. Later, by accessing primary, but still cross-sectional, data King et al. (2005; 2008) revised these estimates down; and allowed for a sex by age-group interaction, as did Copeland et al.(2004) in their Edinburgh cohort. In this paper, we study the relative risk of drugs-related death by sex and older age in major cohorts, rather than by synthesis of cross-sectional data. We also take epoch of follow-up into account since a client's pattern of opiate use may change – without its having been necessarily documented - in the elapsed time since recruitment.

A week-long analysis workshop was convened in Cambridge for representatives of eight major cohorts of European heroin users or injectors, see also Bargagli et al. (2005) and Bird and Hutchinson (2003). For drugs-related deaths, we used limited demographic data for individual patients and Poisson (or Cox) regression to assess the influence of sex, current age, epoch of follow-up, injector status at enrolment and time since start of heroin use. Six of the eight cohorts shared a common EMCDDA protocol (see also Bargagli et al., 2005) to recruit heroin users (among others) who presented at drug treatment agencies in Barcelona, Lisbon, Rome, Vienna, Dublin and throughout Denmark. For external reference, two other large cohorts, respectively of 1992-93 and 1996-97 arrests in France for heroin use (or heroin use and trafficking)

and injection-related Hepatitis C diagnoses in Scotland in 1993-2001, were included as a check on generalising from cohorts recruited only at drug treatment agencies.

Because large cohorts of heroin users or injectors - whether recruited at drug treatment agencies, as arrestees, or at the time of Hepatitis C diagnosis – are costly to maintain in individual follow-up (see Hickman et al., 2003 and Galai et al., 2003), the alternative of database linkage of client identifiers to the national (or regional) register of deaths can be used (see Bird and Hutchinson, 2003; Singleton et al., 2003; McDonald et al., 2008), as here, to establish clients' date and cause of death. Unlike more intensively followed-up cohorts, which ascertain when clients subsequently become abstinent, were off-injecting, or dropped out of drugs rehabilitation (see Darke et al., 1996; Dettmer et al., 2000; Gossop et al., 2002; Preti et al., 2002; Buster et al., 2002; and Mattick and Degenhardt, 2003), or were incarcerated (see Bird and Hutchinson, 2003; Singleton et al., 2003; Seaman et al., 1998), these later events cannot be taken into account directly when follow-up is by database linkage. Instead, we checked indirectly on the persistence of enrolment characteristics by limiting follow-up to the first two years after enrolment in a sensitivity analysis.

The workshop was convened because understanding how the risk of drugs-related death in heroin users or injectors depends on sex and current age is critically important both for back-calculation of the past incidence of injecting and for projecting the late sequelae of injection-related hepatitis C infection (Bird et al., 2001; Law et al., 2001; Law et al, 2003; De Angelis et al., 2004; Hutchinson et al., 2005). Our focus is on drugs-related and all non-HIV deaths because HIV prevalence in heroin users/injectors is highly variable between countries, but well studied - as is

HIV progression itself. We therefore provide precisely-estimated sex and age-appropriate hazards of drugs-related death from EMCDDA and external reference cohorts.

METHODS

COSMO Workshop cohorts

To enhance comparability across cohorts, eligibility was limited to enrolments in 1990 or later of heroin users or injectors, and information was required on cause as well as date of death. Six EMCDDA cohorts were represented: see Bargagli et al. (2005) for additional background on individual EMCDDA cohorts. How representative of eligible clients at drug treatment centres the EMCDDA cohorts are is not reportable, because the proportion of invitees who declined to provide sufficient identifying information for follow-up by database linkage was never recorded.

Confidential linkage of Scotland's register of Hepatitis C diagnosed ever-injectors to its deaths register was based on master index (initial of first name, soundex of surname, gender and date of birth) because patient names are not recorded on Scotland's Hepatitis C register (Surveillance, 2003). Enrolment date was set at 28 days after the date of Hepatitis C diagnosis to exclude diagnoses made either post-mortem or proximal to death. See McDonald et al. (2008) for cause-specific mortality follow-up on all Scotland's Hepatitis C diagnoses.

The eighth cohort was individuals arrested in France for heroin use (or heroin use and trafficking) in 1992, 1993, 1996 and 1997. Because only year of arrest was recorded

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on the research database, enrolment date was forwarded to 1 January of the calendar year following the arrest year.

COSMO Workshop classification of causes of death

Underlying cause of death was classified as drugs-related or HIV-related by grouping ICD9 (or ICD10) codes as follows:

Drugs-related

Drug abuse (more precisely: mental and behavioural disorders due to use of . . .):

ICD9: 292; 304.0 to 304.9; 305.2 to 305.9. **ICD10:** F11 to F16, F18 & F19.

Accidental poisoning by drugs, medicaments and biological substances:

ICD9*: E850-E858. **ICD10:** X40 to X44 & X49.

* In combination with N-codes (N965.0 to 965.9 & N969.0 to 969.9) which specify the nature of the injury.

Intentional self-poisoning by drugs, medicaments and biological substances:

ICD9*: E950.0 to E950.5 & E950.9. **ICD10:** X60 to X64.

Poisoning of undetermined intent by drugs, medicaments and biological substances:

ICD9*: E980.0 to E980.5 & E980.9. **ICD10:** Y10 to Y14 & Y19.

Assault by drugs, medicaments and biological substances:

ICD9*: E962.0. **ICD10:** X85.

<u>HIV-related</u>

ICD9:   042.0 to 044.9 & 279.1.   **ICD10:**   B20 to B24.

Exceptionally, deaths which remained unclassified as to drugs-related, HIV-related or other causes are shown in **Table 1** as 'cause of death not known'. Sub-classifications of drugs-related deaths were not analysed.

How COSMO Workshop operated

Key data for analysis at COSMO Workshop were determined in advance so that analysis files could be brought in common format. In practice, the data management step, and associated checks, was not fully operational until the workshop's third day, which encroached on analysis time and limited the scope for further data correction due to anomalies at analyses. Only one important data anomaly came to light after the COSMO Workshop, which had to be rectified at a later date. The workshop was organised into three writing-analysis teams with intended feedback between teams at the end of each working day, particularly to share data-management decisions. Even so, some residual disparities in coding conventions between teams have resulted in minor differences between papers in person-years of follow-up, different decisions on eligibility (for example, because this paper focuses on drugs-related mortality, the Danish cohort was limited to1997-99 recruits with follow-up to 31 December 1999 to minimise missing causes of death, see Bargagli et al. (2005)), and even some differences in classification of deaths. With one exception, see above, these have not been revisited because their impact is likely to be minor, and to do so would – in effect - require another workshop, but also because they reflect the reality that

common enrolment protocols need to be matched in future also by a common database with initially programmed data-checks.

Statistical methods

The time-scale most relevant for public health projections and back-calculation is the risk of drugs-related death (or all non-HIV deaths) according to current age of the heroin user/injector. Poisson regression was used to estimate drugs-related death risks according to sex, current-age band (under 25, 25-34, 35-44 years, with an imposed upper age-limit of 45 years) and follow-up epoch **(half-year)**. Pooling of covariate influences across cohorts is reported for the two external cohorts [1], for clients enrolled at drug treatment agencies [2], and for all eight cohorts combined [3]. Results of a sensitivity analysis, in which the frailty of enrolment characteristics was checked by restricting follow-up to within two years, were qualitatively similar and are available from the authors.

A second important time-scale is time since start of heroin/injector career, to understand whether any apparent increase in the risk of drugs-related death for older heroin users/injectors is genuinely an aging effect, or due to partial confounding of duration of heroin user/injector career with current age. Age at initiation to heroin use was available from four cohorts only (Barcelona, Lisbon, Rome and Denmark), and enabled proportional hazards regression modelling of whether the career-specific risk of drugs-related death increases when current age is over 34 years.

RESULTS

Table 1 shows that the six 1990s-recruited EMCDDA cohorts from drug treatment agencies had effective last follow-up dates between end of May 1997 (Rome) and end of December 2001 (Barcelona and Lisbon), and accounted for approximately equal numbers of drugs related deaths (864) and deaths from specified other non-HIV causes (865) during 106,152 person-years of follow-up. There was, however, marked heterogeneity in the number of HIV-related deaths, which nearly equalled - or exceeded - drugs-related deaths in Rome, Lisbon and Barcelona, but were otherwise mostly less than half the cohort's number of drugs-related deaths, see also France's heroin-user arrestees and Scotland's hepatitis C diagnosed ever-injectors. These two external reference cohorts together contributed a further 376 drugs-related deaths (Scotland 195, France 181) and 418 deaths from specified other non-HIV causes (Scotland 221, France 197) during 86,417 person-years of follow-up (Scotland 22,670, France 63,747). **Table 1** shows that each cohort contributed at least 5,000 person-years of follow-up within two years of enrolment, and the minimum number of drugs-related deaths was 34 (Dublin), 26 of which occurred in the first two years after enrolment.

In all eight cohorts, 70% or more of clients (heroin users or ever-injectors) were male. Denmark's heroin user cohort (restriction: with knowable cause of death) was recruited wholly in 1997 to 1999. The external reference cohorts related predominantly to enrolments in 1997 or later – 71% of Scotland's hepatitis C diagnosed ever-injectors and 82% of France's heroin-user arrestees – whereas three (Lisbon, Rome, Barcelona) of the six 1990s-recruited EMCDDA cohorts from drug treatment agencies related essentially to clients who enrolled before 1997.

Table 1 shows also that the eight analysed cohorts differed in the percentage of clients aged under 20 years at enrolment, which exceeded 10% only for Lisbon and Dublin, whereas Denmark's heroin user cohort and Scotland's hepatitis C diagnosed ever-injectors had the greatest representation of clients over 39 years of age at enrolment, respectively 24% and 9%.

Because all cohorts were followed-up by database linkage, time-specific information about clients' drug-dependence and injecting after enrolment was lacking. For greater comparability between cohorts, **Table 1** therefore shows drugs-related deaths and person-years of follow-up within the first two years after enrolment, during which enrolment characteristics may be considered relatively apposite still.

During the first two years of follow-up, the 1990s-recruited EMCDDA cohorts accounted for 475 drugs-related deaths and 46,868 person-years of follow-up; Scotland's hepatitis C diagnosed ever-injectors for 109 drugs-related deaths and 11,297 person-years of follow-up; and France's heroin-user arrestees for only 125 drugs-related deaths despite 39,618 person-years of follow-up. In sum, there were 709 drugs-related deaths in 97,783 person-years during cohorts' first two years of follow-up. The much lower drugs-related death rate for France's heroin-user arrestees is striking – and applies to other causes also, which could suggest under-ascertainment of deaths.

Table 2 shows drugs-related deaths (also all non-HIV deaths), person-years of follow-up, and drugs-related death-rate for the six EMCDDA combined, and separately for the two external cohorts by current age-group (15-24 years, 25-34 years, 35-44 years,

45+ years old) and gender. Trends in drugs-related death rate by current age-group did not appear particularly strong, but drugs-related death rate was higher for males than females, France's heroin-user arrestees excepted. The combined non-HIV death-rate, on the other hand, shows consistent increase (over 60%) between current age-group of 15-24 years versus 25-34 years, whether one looks at the six EMCDDA cohorts combined, or external cohorts from Scotland and France.

Table 3 presents pooled Poisson regression analyses for the two external reference cohorts [1], for the six 1990s-recruited EMCDDA cohorts [2], and for all eight combined [3]. Drugs-related death rates were highest in Barcelona, followed by Denmark and Scotland, rates were comparable for Lisbon, Rome and Vienna, and lowest in Dublin and France (see **Table 3**: RR[3]). The six drug treatment cohorts and combined analysis confirmed a significantly higher risk of drugs-related deaths for males (see RR[3], 1.4 with 95% confidence interval from 1.2 to 1.6).

By contrast, the EMCDDA cohorts gave little support for there being an increased risk of drugs-related death at older current age for clients at drug treatment agencies (see **Table 3**: RR[2] results), whereas the two external cohorts signalled that the relative risk of drugs-related death was significantly higher for heroin-user arrestees or HCV-diagnosed ever-injectors aged 35-44 years compared to under 25 years of age (see RR[1], 1.7 with 95% confidence interval from 1.2 to 2.5). Irrespective of recruitment setting, drugs-related death-rates were lower by the third or later epoch of follow-up.

Age at heroin initiation was available for most, but not all, clients from four EMCDDA cohorts (Rome, Barcelona, Lisbon and Denmark). With time since start of heroin career as the time-scale for proportional hazards analysis, higher drugs-related death rate for males (RR = 1.2; 95% CI: 1.0 to 1.5) and by injecting as primary route (RR = 1.6; 95% CI: 1.4 to 1.9) were confirmed. Against a backdrop whereby the underlying time-specific hazard of drugs-related death increased markedly from the second decade of a heroin career, the data were neutral on whether older current age-group conferred a higher risk of drugs-related death (95% CI: 0.7 to 1.3).

DISCUSSION

As injectors increase their heroin consumption over time, the gap between tolerance of its euphoric effects and respiratory depression narrows (White and Irving, 1999), so that other tolerance-mediating factors (Warner-Smith et al., 2001; Best et al., 2000; Caplehorn et al., 1996; Preti et al., 2002; and Bird et al., 2001) - use of respiratory depressants, systemic disease, imprisonment, discharge from treatment, attempts to moderate use, unfamiliar environments or homelessness - may be more likely to precipitate an overdose. Indeed, the reported sex difference (Bird et al., 2003) in risk of drugs-related death may be related to cofactors that elevate the risk of overdose, for example the use of other respiratory depressants, alcohol, rate of imprisonment, or homelessness; or may be intrinsic.

Internationally, and confirmed in this analysis, the risk of drugs-related death is substantially higher for injecting drug users compared to non-injecting opiate users (Preti et al., 2002 and Darke, Degenhardt and Mattick, 2007); and substantially lower for opiates users receiving substitution treatment (Mattick and Degenhardt, 2003).

Differences in the proportion of current injectors by age, or of opiate users in treatment, may explain differences between countries, or account for cohorts' ranking in terms of drugs-related death rates. The main virtue of a combined analysis, as reported here, is therefore not international league tables, but to identify influences on drugs-related deaths which are broadly consistent across a range of regional and enrolment settings. When the label "injector" refers, as here, either to ever-injectors or to users who primarily injected, the associated relative risk (1.6; 95% CI 1.4 to 1.9) will tend to under-estimate the drugs-related death risk associated with current injecting.

Consistency has been borne out across the eight cohorts in respect of male heroin users' or injectors' 1.4 times higher age-specific risk of drugs-related death (95% CI: 1.2 to 1.6), see also cross-sectional synthesis of national data from member state in European Union (below). Back-calculation of past incidence for heroin use/injecting should take into account males' 1.4 times higher age-specific risk of drugs-related death (Bargagli et al., 2005); and a forteriori for all non-HIV deaths, see **Table 2**.

Synthesis of national data for 10 European countries (EMCDDA, 2003), in which the age distribution of two recent years' drugs-related deaths (mainly 2000+2001) was compared to the age-distribution of new clients at drug treatment agencies, found a median relative risk of drugs-related death of 2.4 for problem drug users aged 35+ years versus younger, see **Table 4**. This contrasts markedly with the influence of current age that emerges from our within-cohort analyses which failed strongly to convince that the drugs-related death-rate is higher for heroin users/ever-injectors aged 35-44 years versus under 25 years (RR: 1.2 with 95% CI from 0.95 to 1.42).

Different cohort-recruitment biases by sex and age or different physiological or pathological mechanisms (in, or out of treatment) may explain the better concordance for the influence of sex (versus current age) on the risk of drugs-related death between national data synthesis and cohorts' analyses. For example, greater alcohol consumption by males, and associated risk for overdose death, may be an enduring phenomenon in and out of treatment settings (White and Irving, 1999; Warner-Smith et al., 2001; Best et al., 2000; Caplehorn et al., 1996; and Darke, Degenhardt and Mattick, 2007).

Possible explanations with different practical, public health consequences are: a) older heroin users and injectors are relatively *under*-represented as new clients at drug treatment agencies compared to nationally, which inflates older users' apparent drugs-related death rate in synthesis of national data sources; or b) enrolment at a drug treatment (versus other) agency effectively mitigates an otherwise-high drugs-related death rate for heroin users or injectors aged 35 years or older in the outside community. If true, mitigation of age-related hazard of drugs-related death could be an additional benefit of recruitment into drugs treatment for older opiate users – but differential age effect was not substantiated by a data-inspired test for interaction by cohort (external versus EMCDDA).

Even the upper 95% confidence limit of 2.5 for relative risk (35-44 years versus under 25 years) in the two externally-recruited cohorts conveys a more moderate impression of the influence of current age than the national data syntheses in **Table 4**, and is sufficient to rule out an extreme influence of current age such as six times higher risk (Bird et al., 2003) for heroin users or *ever-injectors* aged 35+ years.

Our results mean that back-calculations which assume constant relative risk by age of drugs-related death (Law et al., 2003 and Hutchinson et al., 2005) cannot be gainsaid, but the external cohorts (and national data syntheses) admit of the possibility that the age-related risk could be 2.5 times higher for heroin users aged 35+ years. De Angelis et al. (2004) have shown that relative risks of even this magnitude have major consequences for back-calculated inferences about injector incidence in past decades. That males' risk of drugs-related death is 1.4 times higher than for females should be taken into account in back-calculations, even if the hazard of drugs-related death is unaffected by current age. Moreover, back-calculations need to take into account that opiate-users, like ex-prisoners (Bird and Hutchinson, 2003 and Singleton et al., 2003), have about five times their age-appropriate risk of dying from other causes than HIV and drugs-related (Bird and Hutchinson, 2003).

Although the purpose of the COSMO Workshop was not to create an international league-table of drugs-related death rates, we should be remiss if we did not remark upon the marked inter-cohort heterogeneity in **Table 3** – so much so that member states would do well to document the mortality by date and cause for all who are referred to their drug treatment agencies.

Recruitment of nearly 6000 clients is needed to observe around 100 drugs-related deaths in the first two years of follow-up. More extended follow-up risks that clients' enrolment characteristics no longer represent current drug-dependency or route of administration. Thus, database linkage studies which do not intend to follow-up individual clients should be powered on the number of drugs-related deaths expected within at most two years of enrolment; should establish age at first use of heroin, and

age at starting to inject; and should enter data immediately so that programmed logical checks can be made when the client is present which enables inconsistencies to be resolved immediately.

Across our eight cohorts, deaths from other causes (excluding HIV) approximately equalled the number of drugs-related deaths. Other papers in this series put the COSMO Workshop in wider context and report standardized mortality ratios by gender, and gauge the fraction of overall mortality at ages 15-49 years which is accountable to opiate users, see Bargagli et al., 2005.

COSMO WORKSHOP

Anna Maria Bargagli (Department of Epidemiology, ALS Roma E, Rome, Italy)

bargagli@asplazio.it

Joseph Barry (Trinity College, Dublin, Ireland). joebarry@tcd.ie

Valeria Belleudi (Department of Epidemiology, ALS Roma E, Rome, Italy)

belleudi@asplazio.it

Sheila Bird (MRC Biostatistics Unit, Cambridge, UK)

sheila.bird@mrc-bsu.cam.ac.uk

Teresa Brugal (Institut Municipal de Salut Pœblica, Barcelona, Spain)

tbrugal@aspb.es

Marcel Buster (Health Service of Amsterdam, Cluster Infectious Diseases,

Department of Research, Amsterdam, The Netherlands)

mbuster@ggd.amsterdam.nl

Marina Davoli (Department of Epidemiology, ALS Roma E, Rome, Italy)

davoli@asplazio.it

Daniela De Angelis (MRC Biostatistics Unit, Cambridge, UK)

daniela.deangelis@mrc-bsu.cam.ac.uk

Filipa Ferraz de Oliveira (Department of Public Health, Faculty of Medical Sciences,

Lisbon, Portugal). filipafo@mail.telepac.pt

David Goldberg (Health Protection Scotland, Glasgow, UK)

David.Goldberg@hps.scot.nhs.uk

Paul Griffith (European Monitoring Centre for Drugs and Drug Addiction, Portugal)

paul.griffith@emcdda.europa.eu

Lene Haastrup (National Board of Health, Copenhagen, Denmark)

LH22@bbh.hosp.dk

Eva Hammerby (National Board of Health, Copenhagen, Denmark). EHA@SST.DK

Gordon Hay (Centre for Drug Misuse Research, University of Glasgow, UK)

g.hay@socsci.gla.ac.uk

Axel Heinemann (Institut fur Rechtsmedizin, Hamburg, Germany)

heineman@uke.uni-hamburg.de

Matthew Hickman (Department of Social Medicine, University of Bristol, UK)

Matthew.Hickman@bristol.ac.uk

Sharon Hutchinson (Health Protection Scotland, Glasgow, UK)

Sharon.Hutchinson@hps.scot.nhs.uk

Dominique Lopez (formerly Observatoire Francais des Drogues et des Toxicomanies,

France; now European Monitoring Centre for Drugs and Drug Addiction, Portugal)

Dominique.Lopez@emcdda.europa.eu

Louise Mullen (Department of Public Health, Dublin, Ireland)

Louise.mullen@erha.ie

Carlo Perucci (Department of Epidemiology, ALS Roma E, Rome, Italy)

perucci@asplazio.it

Daniele Risser (Institute of Forensic Medicine, Vienna, Austria)

daniele.risser@univie.ac.at

Patrizia Schifano (Department of Epidemiology, ALS Roma E, Rome, Italy)

schifano@asplazio.it

Alessandra Sperati (Department of Epidemiology, ALS Roma E, Rome, Italy)

eurotos@asplazio.it

Colin Taylor (European Monitoring Centre for Drugs and Drug Addiction, Portugal)

Colin.Taylor@emcdda.europa.eu

Julian Vicente (European Monitoring Centre for Drugs and Drug Addiction,

Portugal). Julian.Vicente@emcdda.europa.eu

REFERENCES

Advisory Council on Misuse of Drugs. (2000). *Reducing drug related deaths*.
London: Home Office.

Bargagli, A.M., Sperati, A., Davoli, M., Forastiere, F., Perucci, C.A. (2001). Mortality
among problem drug users in Rome: an 18-year follow-up study, 1980-97. *Addiction,*
96, 1455 – 1463.

Bargagli, A.M., Hickman, M., Davoli, M., Perucci, C., Schifano, P., Buster, M.,
Brugal, T., Vicente, J., and COSMO European Group. (2005). Drug-related mortality
and its impact in eight European countries. *European Journal of Public Health*,
September, 1681-1685. (eurpub.oxfordjournals.org/cgi/rapidpdf/cki168v1.pdf).

Best, D., Man, L-H., Zador, D., Darke, S., Bird, S., Strang, J., Ashton, M. (2000). Thematic review: Overdosing on Opiates. Part 1: Causes. *Drug & Alcohol Findings* , 4, 4-7 and 16-20.

Bird, S.M., Goldberg, D.J., Hutchinson, S.J. (2001). Projecting severe sequelae of injection-related hepatitis C virus epidemic in the UK; part 1 – critical hepatitis C and injector data. *Journal of Epidemiology and Biostatistics*, 6, 243 – 265.

Bird, S.M., Hutchinson, S.J. (2003). Male drugs-related deaths in the fortnight after release from prison: Scotland, 1996-99. *Addiction,* 97, 185 – 190.

Bird, S.M., Hutchinson, S.J., Goldberg, D.J. (2003). Drug-related deaths by region, sex, and age-group per 100 injecting drug users in Scotland, 2000 – 01. *Lancet,* 362, 941 – 944.

Bloor, M., Gannon, M., Hay, G., Jackson, J., Leyland, A.H., McKeganey, N. (2008). Contribution of problem drug users' deaths to excess mortality in Scotland: secondary analysis of cohort study. *British Medical Journal*, 337, a478 (doi: 10.1136/bmj.a478. Accessed on 26 January 2009).

Buster, M.C.A., van Brussel, G.H.A., van den Brink, W. (2002). An increase in overdose mortality during the first 2 weeks after entering or re-entering methadone treatment in Amsterdam. *Addiction*, 97, 993 – 1001.

Caplehorn, J.R., Dalton, M.S., Haldar, F., Petrenas, A.M., Nisbet, J.G. (1996). Methadone maintenance and addicts' risk of fatal heroin overdose. *Substance Use and Misuse*, 31, 177-196.

Copeland, L., Budd, J., Robertson, J.R., Elton, R.A. (2004). Changing patterns in causes of death in a cohort of injecting drug users, 1980-2001. *Archives of Internal Medicine*, 164, 1214 – 1220.

Darke, S., Degenhardt, L., Mattick, R.P. (2007). *Mortality among illicit drug users: epidemiology, causes, and intervention.* Cambridge: Cambridge University Press.

Darke, S., Ross J. (2002). Suicide among heroin users: rates, risk factors and methods. *Addiction*, 97, 1383 – 1394.

Darke, S., Zador, D.A. (1996). Fatal heroin 'overdose': a review. *Addiction,* 12, 1765-1772.

De Angelis, D., Hickman, M., Yang, S. (2004). 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. *American Journal of Epidemiology*, 160, 994 - 1004.

Dettmer, K., Saunders, B., Strang, J. (2000). Take home naloxone and the prevention of deaths from opiate overdose: two pilot schemes. *British Medical Journal*, 322, 895-896.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). (2000). *Co-ordination of implementation of the EMCDDA standard guidelines on the Drugs-Related Deaths Indicator in the EU Member States, and collection of information on drug-related deaths* (EMCDDA Project CT.99.RTX.04). Lisbon: EMCDDA.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). (2003) *Annual Report 2003. The State of the Drugs Problem in the European Union and Norway.* Lisbon: EMCDDA, October.

Fugelstad, A., Stenbacka, M., Leifman, A., Nylander, M., Thiblin, I. (2007). Methadone maintenance treatment: the balance between life-saving treatment and fatal poisonings. *Addiction*, 102, 406 – 412.

Galai, N., Safaeian, M., Vlahov, D., Bolotin, A., Celentano, D.D. (2003). Longitudinal patterns of drug injection behavior in the ALIVE study cohort, 1988-2000: Description and determinants. *American Journal of Epidemiology*, 158, 695 – 704.

Gossop, M., Stewart, D., Treacy, S., Marsden, J. (2002). A prospective study of mortality among drug misusers during a 4-year period after seeking treatment. *Addiction*, 97, 39 – 47.

Hay, G., McKeganey, N., Hutchinson, S. on behalf of Project Team. (2001). *Executive report: estimating the national and local prevalence of problem drug use in*

Scotland. Glasgow: NHS Scotland, University of Glasgow and Scottish Centre for Infection and Environmental Health.

Hickman, M., Carnwath, Z., Madden, P., Farrell, M., Rooney, C., Ashcroft, R., Judd, A., Stimson G. (2003). Drug-related mortality and fatal overdose risk: Pilot study of heroin users recruited from specialist drug treatment sites in London. *Journal of Urban Health (Bulletin of the New York Academy of Medicine)*, 80, 274 – 287.

Hickman, M., Higgins, V., Hope, V., Bellis, M., Tilling, K., Walker, A., Henry, J. (2004). Injecting drug use in Brighton, Liverpool, and London: best estimates of prevalence and coverage of public health indicators. *Journal of Epidemiology and Community Health*, 58, 766 – 771.

Hutchinson, S.J., Bird, S.M., Goldberg, D.J. (2005). Modelling the current and future disease burden of Hepatitis C among injecting drug users in Scotland. *Hepatology,* 42, 994 – 1004.

Jackson, G.W.L. (2002). *Drug-related deaths in Scotland in 2001: occasional paper no 8.* Edinburgh: General Register Office for Scotland.

Jossels, G., Sartor, F. (2006). Drug-related deaths in Belgium, 1987-1997. *Archives of Public Health*, 64, 185 – 197.

King, R., Bird, S.M., Brooks, S.P., Hutchinson, S.J., Hay, G. (2005). Prior information in behavioural capture-recapture methods: demographic influences on

drug injectors' propensity to be listed in data sources and their drug-related mortality. *American Journal of Epidemiology*, 162, 1 – 10.

King, R., Bird, S.M., Hay, G., Hutchinson, S.J. (2008). Estimating current injectors in Scotland and their drug-related death rate by sex, region and age-group via Bayesian capture-recapture methods. *Statistical Methods in Medical Research OnlineFirst*, November 28, doi:10.1177/0962280208094701 (Accessed on 26 January 2009).

Langendam, M.W., van Brussel, G.H.A., Coutinho, R.A., van Ameijden, E.J.C. (2001). The impact of harm-reduction-based methadone treatment on mortality among heroin users. *American Journal of Public Health*, 91, 774 – 780.

Law, M.G., Lynskey, M., Ross, J., Hall, W. (2001). Back-projection estimates of the number of dependent heroin users in Australia. *Addiction,* 96, 433 – 443.

Law, M.G., Dore, G.J., Bath, N., Thompson, S., Crofts, N., Dolan, K., Giles, W., Gow, P., Kaldor, J., Loveday, S., Powell, E., Spencer, J., Wodak, A. (2003). Modelling hepatitis C virus incidence, prevalence and long-term sequelae in Australia, 2001. *International Journal of Epidemiology*, 32, 717 – 724.

McDonald, S.A., Hutchinson, S. J., Bird, S.M., Mills, P.R., Dillon, J., Bloor, M., Robertson, C., Donaghy, M., Hayes, P., Graham, L., Goldberg, D.J. (2008). A population-based record linkage study of mortality in hepatitis C diagnosed persons with or without HIV coinfection in Scotland. *Statistical Methods in Medical Research OnlineFirst*, November 28, doi:10.1177/0962280208094690 (Accessed on 26 January 2009).

Mattick, R.P., Degenhardt, L. (2003). Methadone-related and heroin-related deaths among opiate users: methadone helps save lives. *Addiction*, 98, 387 – 388.

Preti, A., Miotto, P., De Coppi, M. (2002). Deaths by unintentional illicit drug overdose in Italy, 1984 – 2000. *Drug and Alcohol Dependence*, 66, 275 – 282.

Quaglio, G., Talamini, G., Lechi, A., Venturini, L., Lugoboni, F., Gruppo Intersert di Collaborazione Scientifica (GICS), Mexxelani, P. (2001). Study of 2708 heroin-related deaths in North Eastern Italy 1985-98 to establish the main causes of death. *Addiction,* 96, 1127-37.

Risser, D., Honigschnabel, S., Stichenwirth, M., Pfudl, S., Sebald, D., Kaff, A., Bauer, G. (2001). Mortality of opiate users in Vienna, Austria. *Drug and Alcohol Dependence*, 64, 251 – 256.

Seaman, S.R., Brettle, R.P., Gore, S.M. (1998). Mortality from overdose among injecting drug users recently released from prison: database linkage study. *British Medical Journal,* 316, 426 – 428.

Singleton, N., Pendry, E., Taylor, C., Farrell, M., Marsden, J. (2003).*Drug-related mortality among newly-released offenders*. London: Home Office Online Report 16, Home Office Research Development and Statistical Directorate.

Surveillance of known Hepatitis C antibody positive cases in Scotland. Results to 30 June 2002. (2003). *Scottish Centre for Infection and Environmental (SCIEH) Weekly Report*, 15 April, 96 – 101.

Uren, Z., Baker, A., Majeed, A. (2001) Trends in deaths from drug overdose and poisoning in England and Wales 1993-1998. *Public Health Medicine*, 23, 242 – 246.

Versino, E., Faggiano, F. (2000). VEdeTTE A study of the efficacy of drug treatments in Italy. *Internet Journal of Public Health Education*, 2, B27 – 33.

Wahren, C.A., Brandt, L., Allbeck, P. (1997). Has mortality in drug addicts increased? A comparison between two hospitalized cohorts in Stockholm. *International Journal of Epidemiology,* 26, 1219-1226.

Warner-Smith, M., Darke, S., Lynskey, M., Hall, W. (2001). Heroin overdose: causes and consequences. *Addiction*, 96, 1113-1125.

White, J.M., Irvine, R.J. (1999). Mechanisms of fatal opioid overdose. *Addiction,* 94(7), 961-72.

Table 1: Cohorts at a glance

Cohort	All Clients; male clients (%)	Recruitment Period; & number of clients (%) enrolled in 1997+	Last follow-up date; & deaths by cause: DRDs, HIV, other, nk	Analysis horizon of 2 years: person-years & number of drugs-related deaths (DRDs)	Number of clients (%) with enrolment age under 20 years; over 39 years
France's heroin arrestees: enrolment date = 1 January in year after arrest	19976; 16432 (82.3%)	1992-1993 & 1996-1997; 16393 (82.1%)	31 Dec 1999; 181, 58, 197, 17	39618 pys & 125 DRDs	1251 (6.3%); 465 (2.3%)
Scotland's ever-IDUs, enrolled at HCV diagnosis* date + 28 days	6840; 4876 (71.3%)	1993-2001; 4869 (71.2%)	31 Dec 2001; 195, 115, 221, 0	11297 pys & 109 DRDs	319 (4.7%); 626 (9.2%)
Barcelona: [ever-IDU status - not currently available]	5039; 3853 (76.5%)	1992-1997; 480 (9.5%) {includes 25 enrolments in 1991}	31 Dec 2001; 395, 428, 271, 58	9409 pys & 207 DRDs	224 (4.4%); 293 (5.8%)
Lisbon's primary opiate users: known IDUs = 760	3266; 2606 (79.8%)	1992-1997; 158 (4.8%)	31 Dec 2001; 122, 178, 91, 48	6440 pys & 35 DRDs	408 (12.5%); 49 (1.5%)

Rome's heroin users: known IDUs = 4106	5924; 4876 (82.3%)	1992-1995; 0 (nil%)	31 May 1997; 141, 135, 142, 7	11489 pys & 94 DRDs	186 (3.1%); 269 (4.5%)
Vienna	4152; 2898 (69.8%)	1990-1998; 1251 (30.1%)	31 Dec 1998; 98, 37, 60, 1	6939 pys & 45 DRDs	373 (9.0%); 192 (4.6%)
Dublin	5287; 3769 (71.3%)	1993-1997; 1589 (30.1%)	31 Dec 1997; 34, 24, 52, 4	7461 pys & 26 DRDs	1024 (19.4%); 140 (2.6%)
Denmark: [ever-IDU status - not currently available]	3486; 2602 (74.6%)	1997-1999; 3486 (100%)	31 Dec 1999; 74, 3, 52, 6	5130 pys & 68 DRDs	115 (3.3%); 852 (24.4%)

Footnotes*

Scotland: recruitment was limited to 1993 onwards to minimise contamination by earlier HCV "diagnosis" dates which represented retrospective HCV testing of stored sera from later HCV-diagnosed individuals. France & Lisbon: based on local knowledge, ill-defined deaths were classified as drugs-related.

Table 2: Drugs-related deaths (DRDs) and all non-HIV deaths by current age*;

and drugs-related deaths by sex

Causes	Drugs-related				All non-HIV			
Current age	**15-24**	**25-34**	**35-44**	**45+**	**15-24**	**25-34**	**35-44**	**45+**
France								
Deaths	34	117	29	1	72	247	69	7
PY at risk	15602	39394	8048	700	15602	39394	8048	700
Rate per1000	2.2	3.0	3.6	1.4	4.6	6.3	8.6	10.0
(95% CI)	(1.4- 2.9)	(2.4- 3.5)	(2.3–4.9)	(0.2-10.1)	(1.8- 9.0)	(3.7- 5.9)	(6.6-10.6)	(4.8-21.0)
Scotland								
Deaths	27	108	54	6	42	196	131	40
PY at risk	3116	12399	6053	1026	3116	12399	6053	1026
Rate per1000	8.7	8.7	8.9	5.8	13.5	15.8	21.6	39.0
(95% CI)	(5.4-11.9)	(7.1-10.4)	(6.5–11.3)	(2.6-13.1)	(9.4-17.6)	(13.6-18.0)	(17.9-25.3)	(26.9-50.1)
Six EMCDDA drug-treatment agency cohorts (summed)								
Deaths	151	490	191	31	237	869	434	116
PY at risk	20503	59451	23195	2981	20503	59450	23195	2981
Rate per1000	7.4	8.2	8.2	10.7	11.6	14.6	18.7	38.9
(95% CI)	(6.3- 8.6)	(7.5- 9.0)	(7.1- 9.5)	(7.0-14.5)	(10.2-13.1)	(13.7-15.6)	(17.0-20.6)	(31.8-46.0)
Drugs-related deaths by sex	**Females**				**Males**			
France								
DR deaths	37				144			
PY at risk	11177				52570			
Rate per1000 (95% CI)	3.3 (2.2 – 4.4)				2.7 (2.3 – 3.2)			
Scotland								

DR deaths	42	153
PY at risk	6459	16211
Rate per1000 (95% CI)	6.5 (4.5 – 8.5)	9.4 (7.9- 10.9)
Six EMCDDA drug-treatment agency cohorts (summed)		
DR deaths	157	707
PY at risk	24785	81367
Rate per1000 (95% CI)	6.3 (5.4 – 7.4)	8.7 (8.1- 9.4)

* Footnote: Current age 15-24 = from "15th birthday plus 1 day" to 25th birthday; results sensitive to

cut-point; minor discrepancies in totals compared by sex and current age 15+.

Table 3: Poisson regression limited to current age < 45 years: Scotland and France [1]; for drug treatment cohorts [2]; and pooling of all cohorts [3].

Follow-up	Overall		
Cohorts	Scotland and France [1]	Drug Treatment Cohorts [2]	Pooling all cohorts [3]
Covariate	**Relative Risk, RR (95% CI)**		
Male	1.17 (0.90 – 1.51)	1.46 (1.22 – 1.75)	1.36 (1.17 – 1.58)
Current age 25-34	1.46 (1.04 – 2.05)	1.07 (0.87 – 1.32)	1.17 (0.98 – 1.40)
Current age 35-44	1.72 (1.18 – 2.51)	0.99 (0.78 – 1.25)	1.16 (0.95 – 1.42)
Barcelona		Baseline	Baseline
Lisbon		0.39 (0.31 – 0.48)	0.40 (0.32 – 0.49)
Rome		0.40 (0.33 – 0.48)	0.40 (0.33 – 0.49)
Vienna		0.44 (0.35 – 0.55)	0.44 (0.35 – 0.56)
Dublin		0.19 (0.13 – 0.27)	0.19 (0.13 – 0.28)
Denmark		0.66 (0.50 – 0.88)	0.66 (0.50 – 0.88)
France	Baseline		0.17 (0.14 – 0.21)
Scotland	3.11 (2.52 – 3.84)		0.58 (0.48 – 0.69)
2nd follow-up epoch (2nd six months of follow-up)	0.90 (0.71 – 1.14)	0.72 (0.61 – 0.85)	0.77 (0.67 – 0.88)
3rd or later 6-month epoch	0.42 (0.29 – 0.61)	0.44 (0.36 – 0.53)	0.44 (0.37 – 0.52)

Table 4: Synthesis from European Monitoring Centre for Drugs and Drug Addiction Annual Report 2003

Member State & population aged 15-64 (in millions)	Drugs-related deaths [D]			Problem drug users initiating treatment [P]		Male users' RR of drugs-related death	Older users' RR of drugs-related death
	In two years: mainly 2000+01	% male [Dm]	% 35+ years old [Dold]	% male [Pm]	% 35+ years old [Pold]		
Austria 5.5	306	84%	37%	72%	19.7%	2.0	2.4
Denmark 3.5	505	82%	61%	77%	21.8%	1.4	5.6
Finland 3.4	140	84%	19%	73%	6.6%	1.9	3.3
Germany 55.1	3865	84%	*	80%	9.6%	1.3	*
Greece 7.1	625	93%	23%	86%	17.8%	2.2	1.4
Ireland 2.3	233	76%	45%	77%	7.0%	0.9	10.9
Italy 39.0	1841	89%	42%	87%	42.7%	1.2	1.0
Netherl. 10.7	174	85%	53%	80%	31.0%	1.4	2.5
Portugal 6.9	598	90%	28%	83%	28.0%	1.8	1.0
Spain 27.2	494	82%	49%	85%	23.9%	0.8	3.1
Sweden 5.6	205	85%	47%	64%	31.1%	3.2	2.0
Median RR						**1.4**	**2.4**
Pooled RR						**1.4**	**2.4**
England & Wales ~ 35.0	3286	81%	41%	*	*	*	*
France 38.1	226	90%	28%	80%	42.0%	2.2	0.5

Footnote 1: Dm denotes the percentage male among drugs-related deaths, Dold the percentage older than 35 years; Pm denotes the percentage male among problem drug users who initiated treatment, Pold is the percentage aged than 35 years or older among treatment initiates. Relative risk, RR, of drugs-related death for males versus females was approximated by

$$\text{Relative Risk (males)} = Dm/Pm * [100-Pm]/[100-Dm];$$

and for older versus younger problem drug users by

$$\text{Relative Risk (older)} = Dold/Pold * [100 - Pold]/[100-Dold].$$

Data from France are presented, but not included in the weighted summary of observed relative risks, which uses the number of drugs-related deaths as weighting.

Footnote 2: with acknowledgement to data providers in member states for source Statistical Tables 7, 24 and 25; * indicates not available; Spain's 494 drugs-related deaths pertained to five cities only with population of 4.2 millions aged 15-64 years.