Draft Final Report
Project to analyse impact and costs of HCV, HBV and HIV infection in injecting drug users in the EU

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Contents

1 Summary

This final report of project CT.98.EP.06 "Project to analyse impact and costs of Hepatitis B/C and HIV infection in injecting drug users in the EU" presents

- the results of a Workshop (June 1999) on the impact of HCV, HBV and HIV in injecting drug users (section 3),
- the outcomes of a literature search concerning impact and costs related to HCV infections (section 4, Appendix G),
- the identification, classification and estimation of the costs of HIV, HBV and HCV infections related to drug addiction (section 5),
- details concerning Working Group, project related projects and project related publications and contributions to conferences (Appendices A-D),
- an exploratory overview on impact and control of HIV/AIDS, HBV and HCV in injecting drug users in Europe (Appendix E), and
- a conceptual model covering the field of infectious diseases and drug abuse (Appendix F).

During the work the emphasis has shifted to the impact and costs of infections with HCV in view of the relatively little knowledge about HCV. The following conclusions have been stated.

- A conceptual model has been elaborated to cover the field of the drugs problem and inherent public health issues (see Appendix F). This model enables us to order current ideas, research questions, available data and data needs.

- A general overview of the spread of HIV/AIDS, HBV and HCV among IDUs in Europe shows that HIV, HBV and HCV constitute a major health burden for IDUs in Europe and are still not under control. Harm reduction has become an acceptable option in most EU countries, but coverage can be improved (section 3.2.2, Appendix E).

- Basic epidemiological research trying to elucidate the dynamics of the spread of HCV in IDUs is still inconclusive and motivates further epidemiological study. Data needs and methodological problems concerning the epidemiology of HCV have been identified together with necessary actions to solve these needs and problems by extension of surveillance, initiation of cohort studies, and development of backcalculation (e.g. from cirrhosis to incidence and prevalence of HCV). See: section 3.2.1, section 3.2.3 and section 3.5.1.

- Modelling approaches for transmission of HCV and related data needs have been defined (section 3.3.1, section 3.3.2, section 3.3.3). Modelling of the spread of HBV and subsequent economic evaluation of potential interventions (vaccination, screening) have already been elaborated. This work provides the format for the evaluation of interventions with repect to HCV (section 3.4.1).

- The literature review (263 publications) is an inventory of the basic knowledge on the impact and costs of HCV in IDUs. The majority of the articles addresses the

clinical and epidemiological aspects of the HCV in IDUs. Apart from articles on the ecomonic aspects of the treatment with Interferon, very few articles deal with economic aspects of HCV in IDUs per se (section 4).

- A preliminary cost estimate for incidence-based drug-addiction-related costs for infectious diseases (HIV, HBV, HCV) has been provided. Estimated drug-addiction-related costs of HIV/AIDS, HBV and HCV amount to 1871 million EUR for the EU as a whole. HIV takes account of the major part of these costs (71%), followed by HCV (24%) and HBV (5%; section 3.4.2, section 5).

- Further economic research should be devoted to prevalence-based estimation of costs, and the extension of the estimation of health care costs to social costs of drug addiction.

2 Background and Objectives

One important class of problems in the field of drug use concerns the adverse effects of infectious diseases on the health status of drug users, their treatment and their prevention. Especially, infection with HIV and Hepatitis B and C virus (HBV and HCV) is a serious problem in populations of intravenous drug users (IDU). As the transmission probability of HBV and HCV is higher than for HIV, the prevalence of HBV and HCV is usually much higher than HIV prevalence. This study is directed at the estimation of health care costs and relations of the underlying epidemiological processes to these costs.

The objectives of the project concern the questions

- What is the cost-of-illness related to HCV, HBV and HIV among IDU?
- What is the influence of epidemiological developments on resulting health care costs (cure/care/prevention)?
- What information is needed to ultimately construct cost-effectiveness scenarios for different interventions?

Further objectives were to construct an international network of experts (Working Group), to organise a meeting of the Working Group to discuss these questions and to develop relevant research.

Thus, the end products of the project are the assessment of an international Working Group and a study on the cost-of-illness of HBV, HCV and HIV in populations of injecting drug users. The study integrates health economics, epidemiology and modelling experience. Impact and costs related to HIV have already been widely investigated, while HBV seems to pose a lesser problem in IDUs than HCV. Therefore, the main emphasis of this report is on HCV, to a lesser extent on HBV, and only where necessary on HIV. The present document is the final report of project CT.98.EP.06 “Project to analyse impact and costs of Hepatitis B/C and HIV infection in injecting drug users in the EU”.

Section 3 presents results of the Workshop (June 1999). Section 4 presents the outcomes of a literature search concerning impact and costs related to HCV infections. Section 5 focuses on the identification, classification and estimation of the costs of infectious diseases related to drug addiction. Section 6 considers the results of the project and presents main conclusions.

Appendices A-D give details concerning Working Group, the Workshop (June 1999), project related projects and project related publications and contributions to conferences. Appendix E gives the text of a presentation on the impact and control of AIDS, HBV and HCV among IDUs in Europe. The study was also presented at a meeting organised by the National Institute of Drug Abuse, the National Institutes of Health and the US Department of Health and Human Services (Geneva, 1998). Appendix F presents a conceptual model covering the field of infectious diseases and drug abuse. This model was presented at the European Conference on Perspectives on

Infectious Disease Research (Dresden, February, 1999). Appendix G presents the references resulting from the literature search discussed in section 4.
The present project -emphasis on impact and costs related to infectious diseases in IDU- will be continued within the frame of a subgroup of the TSER project on Drug Use Modelling (see Appendix B). This subgroup (viz., the present Working Group) will develop cost-effectiveness scenarios concerning social costs of drug abuse. Therefore, the economists paid already attention to this aspect of problem drug use (see section 3.4.3, section 3.4.4 and 5).

3 Methodology and Results

3.1 Introduction

Methodology to be used in the project comprises literature reviews, epidemiological modelling, scenario analysis and cost-effectiveness analysis. Literature searches are directed to the cost-of-illness associated with drug related HBV, HCV and HIV infections. Cost-of-illness comprises direct health care costs and indirect costs (productivity losses) of these infections and associated diseases. Besides, intangible costs in terms of quality of life losses could be explored as well. An overview of available health-indexes and the feasibility to describe and value consequences of HBV, HCV and HIV infection with these health-indexes will be made in the future. The present work may be seen as a first step towards the estimation of Quality Adjusted Life Years (QALYs), a measures that allows for the expression of the impact of disease as a combination of reduction of both life-expectancy and quality of life.

One important area for research in the field of problem drug use is that of the cost-effectiveness of interventions in HBV, HCV and HIV prevention. A classification in terms of key variables and impact indicators will be one given in section 4. This classification presents the basic information for subsequent cost-effectiveness scenarios. Cost-of-illness results will be linked with the outcomes of epidemiological modelling of the spread of HIV and Hepatitis viruses in populations of drug users. Basically this means an extension of the traditional cost-of-illness methods, that could be labelled dynamic cost-of-illness assessment. Using this method guarantees that specific characteristics of infectious diseases (a.o. dynamic character of transmission; relation of cost-effectiveness of prevention with the incidence of the disease, which can change under the influence of the relevant intervention/prevention; proper choice of time horizon) are accounted for in costing. For instance, this means that costing will not be performed for a one-year period, but a longer time frame has to be chosen to obtain realistic results.

This project gives results that can subsequently be used for constructing cost-effectiveness scenarios. Cost-effectiveness scenarios reflect the relative economic attractiveness of different interventions in health care and public health. Cost scenarios as such will not be the product of this project, but recommendations for their construction are provided. Some guidelines for cost-effectiveness in infectious diseases will be specified. The present Section presents summaries of the presentations and discussions of the June 1999 Workshop of the Working Group.

3.2 Epidemiological and Social Impact

3.2.1 Epidemiology of HCV in UK - Matthew Hickman

Background

The estimates of prevalence and consequences of HCV are dramatic. The WHO estimates that 3% worldwide or 170 million people are infected. These figures are often quoted. Further, in industrialised countries it is estimated that HCV accounts for 20% of cases of acute hepatitis, 70% of chronic hepatitis, 40% of end-stage cirrhosis, and 60% of hepatocellular carcinoma and 30% of liver transplants. Since 1991 the risk of acquiring HCV through blood products at least in industrialised countries have been very slim. There is no substantial evidence for sexual transmission; the risk is probably low. Therefore, IDUs represent a major risk and route of transmission. They are a key target for prevention, both primary and secondary.

The evidence on the risk and prevalence of HCV among IDU has been consistently gloomy. Many studies found prevalence to be in the range of 50 to 90% in the UK and other European countries, Australia, and US. Nick Crofts and his colleagues suggest that HCV has been of the order of 60 to 70% in Australian IDUs since 1971. David Goldberg and Avril Taylor's studies found prevalence to fall in Scotland - from 90% in 1990 to 70% in 1995, though the fall was non-significant. And a recent study of injectors in Scottish prisons tested between 1994 and 1996 found 50% were positive. Studies in Ireland found prevalence of 60% among recent injectors presenting to treatment agencies between 1992 and 1997. Numerous studies in the States, e.g. Garfien in IDU recruited in 1988 and Hagan and colleagues with IDU recruited between 1994 and 1997, reporting prevalence of over 70%.

Incidence estimates are also high, that is 10 to 20 per 100 person years, e.g. 20 per 100 person years in US, and 12-16 per 100 person years in Australia with one extraordinary study suggesting that HCV incidence was 75.6 per 100 person years among IDU aged less than 20. In contrast, in several countries (notably UK and Australia) the evidence suggested that HIV prevalence had fallen and was continuing at low levels, and that HBV had fallen from estimates in the late 1980s.

Naturally this led to questions over whether harm minimisation measures were working for HCV; what else could and should be done? These questions were the subject of several anguished editorials, not helped by studies from the US and Canada suggesting that NEX do not offer any protective benefit.

Also, it led to attention on sharing practices in particular on the risk of indirect sharing - like spoons and filters, and back and front loading - and whether these conferred extra risk to HCV transmission.

The efficiency of HCV transmission is higher than HIV. Evidence from needle stick studies suggests that HCV infectivity (at 2%) is perhaps 7 times higher than HIV but still ten times lower than HBV. However, with over 50% of IDU carriers the probability of being exposed to HCV is high, and may by itself explain the persistently high prevalence rates.

Recent Study in England and Wales

We report findings of our recent survey of drug injectors not in contact with treatment agencies. The study was intended principally to look at the level of sharing using an instrument developed here called the IRQ, but with a subsidiary aim of collecting saliva to measure the prevalence of HIV, HBV and HCV. This study was combined with a further study carried out in the same study period that recruited IDUs from drug agencies for the Unlinked anonymous survey programme of HIV prevalence. The combined data included only those who had injected in the past four weeks.
The surveys were carried out by Professor Gerry Stimson, Gillian Hunter, Ali Judd and Steve Jones at CRDHB, and Dr Noel Gill and Dr Vivian Hope at CDSC. Dr John Parry at Virus Reference Laboratory carried out the testing.

Study Design

The community survey was carried out between October 1997 and June 1998.
Injectors were recruited in 7 cities in England, one in each Regional Health Authority, by indigenous interviewers selected and trained by the fieldwork co-ordinator.
Injectors were included if they had injected in the last four weeks, and had not been in contact with a specialist treatment agency or GP for treatment of their drug use in the last four weeks (they could be in contact with needle exchange).
Oral fluid specimens with informed consent were collected using the EpiScreen device, which has an estimated specificity of 99% and sensitivity for HCV of 77% and HBV of 93%.
The community sample collected 740 to 750 IDUs. And 2203 IDUs who had injected in the past four weeks and had given samples to the unlinked Programme were recruited through 47 drug agencies.

Sample

The sample characteristics are similar to most community recruited studies. There may be slightly higher numbers of IDUs who were never in treatment and more recent injectors.
The treatment sample was similar with respect to injecting career and age. Slightly more female IDUs were recruited in the community sample 29% versus 22% in the Programme sample, and less injectors of amphetamines.

Overall Findings

The HIV prevalence was low, that is less than 1% overall. It was slightly higher in London at 3%. No IDU found positive had been injecting for less than 5 years.
Overall infection with HBV was about 20%; in a similar study in 1992/3 it was 50%.
The HCV prevalence was lower than expected, that is 30% or 39.5% once adjusted for the sensitivity of the test.

Univariate results

Differences by some key characteristics have been established. Bearing in mind that the true prevalences are underestimated, they need to be multiplied by about 1.3.
There is a very strong relationship with injecting career; 7.4% in those injecting for less than 3 years, and over 60% in those injecting for 15 or more years. Not surprisingly, there is a similar relationship with age, with 6% of those under 20 infected with HCV compared to over 50% of those over 40.
There are no differences by sex in these combined data. In the community sample males did have a higher prevalence than females.
HCV prevalence was raised among those that had previously had a test, in residents of London, and those recruited from drug agencies. In the community sample alone, HCV prevalence was higher among those that had previously been treated (30% versus 15%).
The prevalence of having HCV was two to three times higher if infected also with HIV or HBV, though the adjusted odds were much lower, that is non-significant for HIV and just over 2 for HBV.

Multi-variable results

The odds ratios from the multi-variable model have been established. The strongest association is with injecting career, with the odds of HCV seven times higher in people with the longest careers compared to those injecting for less than 2 years. There is some association still with age, though most has been explained by years injecting. The odds of infection associated with other variables also have mostly diminished.
The odds ratio is raised for IDUs recruited in treatment, resident in London, that had a previous HIV test, and with evidence of previous HBV infection.
The findings for HBV are similar, with the strongest relationship with injecting career.

Sharing

Our data on sharing were surprising. The findings were higher than expected (especially compared to the old Government target of reducing sharing to 10% by 1998); 52% shared needles and syringes, and 74% shared injecting paraphernalia. There was a median of two sharing partners, and only 16% reported frequently sharing needles. This may signify a difference in risk, i.e. that people are sharing with fewer people and less frequently, but it needs corroboration with other studies assessing sharing and risk behaviour in more detail.
There were no differences by population sub-groups, and also no association with HCV or HBV. This is not unexpected given that the study pertains to the last four weeks and not to the time the person was exposed, and may be not focusing on behaviour that puts IDU at “greater” risk.

Conclusions

Our study is one of the first (or will be once it is published) to suggest that HCV prevalence is less than 40% among IDU, in contrast to previous estimates of above 50%.

HCV prevalence among recent injectors (0 to 2 years) was low at 7% (or 9% if adjusted).

It is likely that the incidence is also lower than previous estimates of 10 to 20% per annum, i.e. at about 6 per 100 person years (if we assume that those injecting for 1 or 2 years were exposed half way during their career).

This evidence is contrary to the argument that HCV is inevitable as it is acquired early on in IDU career and possibly at initiation.

This is the first piece of evidence to suggest that harm reduction activities in England may be working for HCV (though they do not seem to be having the same impact in Scotland).

These results have some corroboration – as the study consisted of two independent surveys – but more is needed. For example, we do not know when the HCV incidence declined or whether it will continue, or whether harm reduction activities need to be extended.

Further studies are required of incidence and further improvements to measure risk behaviour to identify and target preventable factors. And studies comparing levels of harm reduction and HCV infection between cities and countries to suggest why there are different prevalence estimates.

3.2.2 Injecting drug use, viral infections and responses in Europe - Lucas Wiessing (see also Appendix E)

Introduction

This study aims to give a general overview of the spread of HIV/AIDS, HBV, and HCV among IDUs in Europe by describing recent data collected by two European monitoring centres: EMCDDA and CESES. Also presented are relevant modelling data that were obtained in the framework of the European Union Concerted Action on Multinational AIDS Scenarios (BMH1-CT94-1723), co-ordinated by the Netherlands National Institute of Public Health and the Environment (RIVM). Because of the differences in geographic coverage of the available data and estimates, the main emphasis of this paper is on countries of the EU (Appendix E: tables 1 and 2). Information on reported AIDS cases is available from CESES also for Central and Eastern Europe (and Asian countries of the former Soviet Union). As results came from different studies and monitoring activities, a thematic structure was chosen for this overview. After a description of patterns of the spread of AIDS among IDUs, estimates are presented of historical HIV incidence derived by back-calculation from AIDS cases followed by recent data on seroprevalence of HIV, HBV, and HCV. Finally, a general impression is given of implementation and possible effects of harm-reduction measures in countries of the EU.

Objectives

To describe the current and historical spread of HIV/AIDS and the current spread of HBV and HCV among IDUs in Europe; to describe harm-reduction measures in countries of the European Union (EU).

Methods

Data were collected on AIDS cases and current levels of infection of HIV, HBV and HCV, and on harm-reduction measures, through national HIV/AIDS reports to the European Centre for the Epidemiological Monitoring of AIDS (CESES) and through National Focal Points within the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)/Reitox network. Estimates of HIV prevalence and incidence from reported AIDS cases and analyses by birth cohort were obtained by back-calculation within EU project BMH1-CT94-1723.

Results

New combination therapies have led to a sharp decline in AIDS incidence since 1996 in all EU countries but Portugal. Reported HIV seroprevalence data for 1995–96 show declining or stable prevalence in most EU countries. Back-calculation estimates from reported AIDS cases by country suggest that, up to 1994, HIV incidence was increasing in Portugal but already stable or declining in other EU countries. However, back-calculation estimates by birth-cohort show that new cohorts of young IDUs in the EU continue to be infected, even if at lower rates than in the initial phase of the epidemic. Although Central and Eastern Europe have low levels of AIDS among IDUs, some countries have reported rapid increases in HIV prevalence. HBV and HCV prevalence is extremely high in many EU countries (antibodies-HBV 21 to 63 percent; antibodies-HCV 19 to 92 percent), with an estimated total of about 500,000 HCV infections among IDUs in the EU. Most countries in the EU have introduced harm-reduction measures (information, clean needles and syringes, condoms, counselling and testing, methadone substitution treatment) but in most cases only since the 1990s and not nation-wide. Levels of injection drug use have decreased in many but not all countries, and rates of injection drug use among heroin users in treatment differ widely at present.

Conclusion

HIV, HBV and HCV constitute a major health burden for IDUs in Europe and are still not under control. Harm reduction has become an acceptable option in most EU countries, but coverage can be improved.

3.2.3 Brief overview HCV infection epidemiology among drug users - Erik van Ameijden

Epidemiology

Parenteral transmission. Parenteral transmission of HCV is highly efficient. HCV prevalence and incidence rates are generally high among IDUs (prevalence >60%; incidence >10%). Early after the start of injecting onset (<3 years), prevalences as high as 50% have been reported. Also, HCV prevalences can be very high in low HIV prevalence populations.

The main risk factors for HCV prevalence are duration of injecting (cumulative exposure), frequency of injecting and cocaine injecting (indicators of exposure), imprisonment (may indicate transmission in prisons), being female and black, and injecting with someone > 5 yrs older (indicative for mixing). Some studies found that sharing of injecting paraphernalia (e.g. spoons) is a risk factor.

Given that most of injectors are HCV infected, not only the number of current but also the number of former injectors are crucial for HCV cost and impact estimates. Future trends in injecting have to be anticipated to make projections. For instance, in Amsterdam the number of current injectors has halved, and as declining trends are exponential a further decline is expected (Van Ameijden, submitted).

Sexual transmission among IDUs. The importance of sexual transmission compared to parenteral is probably small. For instance, low HCV-prevalences have been observed among heterosexual partners of HCV-infected IDUs. The finding among non-injecting drug users of HCV-prevalences between 6% and 11% (e.g. Esteban, 1989; Van Ameijden, 1993; Neaigus, 1999) may also be explained by denial of injecting behaviour. However, among non-injecting groups such as prostitutes, visitors of an STD-clinic, HCV-prevalences as high as 10% were observed, risk factors being duration of prostitution, number of sex partners, and STDs (e.g. Nakashima, 1996; Salvaggio, 1993). Given that drug users are sexually active, especially female prostitutes, sexual transmission may be relevant.

Other types of transmission. Perinatal transmission occurs at a modest level; about 5%-10% of new-borns is HCV infected. Breastfeeding is not considered a significant factor. The number of HCV infected children is reduced as IDU women have low fertility rates. For example, one study showed that of 106 HCV-infected children, only 6% had an IDU mother (Bortolotti, 1998).
Transmission via household contacts is possible, but the likelihood is small. Through blood donations, (ex)injecting drug users may contribute to transfusion associated transmission.

Subtypes and transmission. IDUs are more likely to be infected with subtype 1a (and possibly 3) than other risk groups, and less with subtype 1b (Garcia, 1998; Kleter, 1998; Beld, 1998). It is unclear whether there is an effect of subtype on transmission efficiency.

Natural history of HCV

A recent infection with HCV is not often symptomatic (e.g. jaundice). Viral clearance with seroreversion does not often occur (<10%; Seeff, 1998; Beld, 1998). In time, about 80% develops chronic persistent hepatitis. The majority (>50%) has progressive liver disease, i.e. hepatohistological lesions. There may also be extra-hepatic manifestations. (e.g. glomerulonephritis). Ultimately, it is believed that after 20 years, 20% has developed liver cirrhosis. Hepatocellular carcinoma may also occur. It has to be noted that these figures vary widely between studies (e.g. progression to cirrhosis: Poynard, 1997: 33% after 20 years; Datz, 1999: 20% after 17 years; Walsh,1999: 2%).

Risk factors for progression of HCV infection include: old age, alcohol use, and male gender. Identified determinants in more recent studies are HIV induced immunosuppression (Thomas, 1996; Rockstroh, 1996; Beld, 1998), HAV infection (Vento,1998), subtype 1b (Beld, 1998, Tanaka, 1998; Costes, 1999). It should be noted that other studies did not find an effect of subtype (Kleter, 1998; Poynard, 1997; Verbaan, 1998).

HCV infection also has a more general negative impact on health, such as quality life, depression, physical function (Singh, 1999). For drug users it is difficult to quantify such effects.

To estimate the cost and impact of HCV among drug users, the natural course of HCV infection is crucial. However, it is concluded that important information is lacking:

- Wide variability progression rates to cirrhosis
- Maximum follow-up about 20 years: hereafter, there may be a large increase in progression rates given that age is a risk factor for progression
- IDUs may differ in progression from other risk groups, as there is substantial pre-liverfailure mortality, they have other subtypes, have high alcohol consumption, etc. One study found less hepatopathy (biopsies) among IDUs than among transfusion-associated patients (Lopez-Morante, 1998).

Primary prevention

At this time, there are no indications that a vaccine will soon be available. The development is difficult as there are several HCV subtypes and a considerable mutation rate. Therefore, behavioural interventions are important. At first sight, prevention appears difficult, given that HCV prevalences among recent initiates into injecting are very high (>50% after 1-2 years injecting use), and that HCV incidence generally exceeds 10%/year in the absence of extensive preventive measures. Teaching drug users who have not (yet) injected safe injecting practices is not an

option. In this respect, peer-based interventions appear most promising, e.g. targeting established injectors not to initiate others or in a safe way. Still, there are a few exemptions indicating that prevention is possible: in Geneva and Glasgow declining HCV-prevalences have been reported (Broers, 1998; Goldberg, 1998). However, prevention of injecting itself would be most efficient and may be feasible according to recent studies (Van Ameijden, 1995).

Treatment

In general, treatment of HCV infection is possible although results are not optimal. IFN mono-therapy is in 25% effective if >12 months given (viral clearance). If there is a sustained response to IFN Tx for >1 year, then HCV is probably eradicated (Camma 1998). Other studies show that IFN is cost-effective (Bisceglie, 1998) and that IFN has less effect in case of advanced disease and infection with subtype 1. The response for combination therapy with IFN and Ribavirin is higher, about 45%. New combination treatments are under development (e.g. corticosteroid priming, protease inhibitors). In late stage disease, survival after a livertransplant is high (90% after 1 year), but re-infection with HCV generally occurs (>90%).

The above studies are generally performed among non-IDU patients. Among IDUs, treatment outcomes may be poorer due to lower compliance with the treatment regimes. Furthermore, many background factors are unknown: the proportion of IDUs with known HCV serostatus, with regular ALT tests to determine liver function, access to treatment, and proportion actually receiving treatment.

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3.3 Modelling

3.3.1 Modelling epidemiological processes in IDU - Gordon Hay

Four main aspects of modelling epidemiological processes in IDU are considered; methods for estimating the prevalence of drug misuse, dynamic models of drug misuse prevalence, the spread of HIV via shared injecting equipment and the use of uncertainty and sensitivity analyses.

As a prerequisite for any modelling of drug misuse or its consequences, such as HIV or hepatitis prevalence, information is required on the number of people using or injecting drugs. The capture-recapture method is considered to be the most suitable method for estimating drug misuse prevalence at the local level, however a range of methods are being applied to obtain national prevalence estimates within an EMCDDA funded project. A related EMCDDA project which provides methodological guidelines for the use of capture-recapture methods provides a broad introduction to the methodology, but when examining health consequences such as the number of people infected with HCV, information is required on drug injecting rather than drug misuse. Unfortunately recent applications of the capture-recapture method within Europe have used the latter case definition, primarily as many contributing data sources cannot easily distinguish between drug misusers and drug injectors. Another main drawback of the capture-recapture methodology is that it usually only provides

information on drug misuse prevalence, and although the Jolly-Seber method is an extension to the basic method which examines open populations, the 'openness' of that method is perhaps better considered as a nuisance parameter rather than a serious attempt to quantify drug misuse incidence. In addition to incidence and prevalence data, information on the number of people who previously injected drugs but have now ceased may be required to provide accurate models of the future impact or costs of hepatitis or HIV in the European Union.

General population surveys, although often considered less useful than more advanced statistical techniques such as capture-recapture, may be useful in providing this information and a good example of how such a survey can inform research into health consequences is the National Survey of Sexual Attitudes and Lifestyles (Johnson *et al*. 1992), carried out in England and Wales in 1990 and 1991. Giesecke *et al*. (1994) combined information from this survey with data from unlinked anonymous HIV prevalence testing to provide estimates of the number of people infected with HIV.

Clearly the number of drug injectors in a population is not static, and while injector population sizes are influenced by the number of people beginning to or ceasing to inject, Caulkins and Kaplan (1991) demonstrated the impact that AIDS could have on the number of injecting drug users in the United States. Two models are examined, one which only considers a behavioural change by potential injectors and one which includes HIV transmission dynamics. Both models show the dramatic impact that AIDS could have, although it is important to remember that these simple models ignore many of the more complex processes acting on injector populations.

The original model, as described in Kaplan (1989), examines the spread of HIV between drug injectors who share needles within shooting galleries. Thus two populations are considered within a compartmental model, $\pi(t)$ which is the proportion of injectors who are infected at time t and $\beta(t)$ which is the proportion of needles / syringes infected at time. These proportions are abbreviated to π and β in the following set of differential equations.

$$\frac{d\beta}{dt} = \lambda\gamma\pi(t) - \lambda\gamma\beta(t)\{1 - [1 - \pi(t)](1 - \theta)\}$$

$$\frac{d\pi}{dt} = [1 - \pi(t)]\lambda\beta(t)\alpha - \pi(t)\mu$$

Five parameters are included in this model; λ is the rate at which drug injectors are assumed to be sharing needles, α is the probability that an injector becomes infected after using an infected needle, γ is ratio of injectors to needles, μ is the rate at which injectors leave the population (presumably through death) after becoming infected and θ describes the possibility that an injector cleans the needle. Again this model is

simple, and the deterministic solution to the differential equations suggests that the vast majority of injectors will become infected with HIV. Although such rapid disease spread has not occurred in many parts of the work, thus suggesting that the initial models may be flawed, such models can be used to evaluate control strategies and this model was used to justify introducing legislation to legalise needle exchanges in Connecticut.

Although this simple model only includes five parameters, uncertainty and sensitivity analyses following Blower and Dowlatabadi (1994) can be carried out. Using parameter values derived from behavioural research in Glasgow the sensitivity analysis suggests that the rate at which injectors share will have a comparatively strong influence on the spread of the disease.

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3.3.2 Prediction of future costs using various modelling techniques – Gloria Crispino O'Connell

Despite advances in understanding the basic biology of HIV and HCV, medical, public health and financial planning continues to be plague by uncertainties. There remain questions of an epidemiological nature to be answered. The questions to be addressed include, how many Irish injecting drug users are HCV of HIV seropositive now or will become positive; how many will develop chronic infection or AIDS and at what rate; and finally what planning and intervention is needed to curtail spread.

International and Irish studies highlight the uncertainties that exist and the need for refined estimates of prevalence based on age, sex and duration of drug use. Estimates

of the incidence of HCV among IDUs vary greatly. Smyth, Keenan, Dorman and O'Connor (1995) in a study of attendees at the National Drug Treatment Centre found prevalence varied with sex and duration of drug use. Similar results have been reported by Crofts et al (1993) and by Loxley (1995). Crofts, in a study of Australian drug users they found a seroprevalence rate of 68%, Loxley in a study of young drug users found a seroprevalence rate of approximately 6%.

In Ireland a HCV study has been completed by Smyth et al (1995) at The Drug Treatment Board. The authors found an overall seroprevalence rate of 84% with indications that in spite of needle exchange programs drug users continue to share needles. In addition they found that seroprevalence varied with sex and duration of drug use. Dusheiko and Roberts (1995) identified that the discounted costs per year of life saved when HCV is treated with alpha interferon ranged from £2,142 to £17,128.

In Ireland a total of 102,236 tests have been undertaken by the National Virus Reference Laboratory for HIV antibodies up to the end of August 1995 and 1,589 cases have tested positive. The HIV statistics show that intravenous drug users and non-IV drug using heterosexuals represent 62% of the total positive. In addition there have been 491 cases of full-blown AIDS and 259 deaths up to 30th. September 1995, (private communication with the Department of Health). These figures represent minimum incidence and their financial impact on health care resources cannot be denied. Dunne (1994) estimates that the cost of AZT therapy alone for a single case is in the region of £8,000 pounds per year.

In spite of the clear need for models of the transmission and spread of HCV the mathematical and statistical literature has to date concentrated on modelling the spread of AIDS initially in one sex communities and latterly in two sex communities, Comiskey (1993,1992), Anderson (1989). There are some exceptions to this, preliminary models for the spread of HCV have been discussed by Mather (1994) and Comiskey (1994).

We propose to extend the models already developed for the spread of AIDS in drug using communities. It is our intention to focus on deterministic models built by a set of partial or ordinary differential equations. Once developed the model will be solved by numerical methods using existing computer hardware available. Computer simulations of the spread of HCV and HIV through the population will be performed. These will concentrate on providing estimates of the prevalence of disease in the Irish drug using population. Such results will be used to estimate present and future costs of the disease and analyse the economical impact of various types of treatments. Finally, a qualitative analysis of the transmission dynamics will be undertaken to interpret the epidemiological impact of the infection and the threshold conditions for an epidemic.

Similar models developed in the past for AIDS in drug users and measles in children by Comiskey (1992, 1989) have shown with the advancement of time to produce reliable and accurate estimate and predictions of prevalence.

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3.3.3 Modelling approaches for transmission of HCV in IDU - Mirjam Kretzschmar

One theme of discussion in the project is the scope for using mathematical models for analysing the transmission and prevention of HCV in injecting drug users (IDU). To our knowledge there is no previous work done on this subject, but there has been work done on related subjects such as modelling the spread of HIV in IDU, and modelling the spread and prevention of HBV infection. Below the approaches used in that modelling work and to show how they could be applied to the problem of HCV in IDU are discussed.

Although a large part of the literature concerning the modelling of HIV concentrates on the sexual transmission route, there are some papers that deal specifically with the spread of HIV in IDU populations, where the main transmission route is via sharing of infected needles. A well-known paper by Kaplan (1989) investigates the effects of

needle exchange programs on the prevalence of HIV infection in an IDU population. The model is a relatively simple deterministic model. Kaplan's work has been extended by Greenhalgh & Hay (1996) to include different assumptions about the infectivity and possible effects of bleaching on HIV prevalence. A stochastic model that focusses on the effects of contact patterns and networks of IDU was developed by Kretzschmar & Wiessing, who used it to investigate the effects of different prevention strategies on HIV prevalence. This model required detailed data about sharing frequencies and the numbers of persons with whom risky sharing behaviour is practised. Finally, statistical models have been used by Rossi and Iannelli et al. (1997) for projecting future HIV and AIDS incidence.

Research in HBV modelling has concentrated on evaluating the effects of different vaccination strategies on HBV prevalence, especially the prevalence of asymptomatic HBV carriage. Williams et al. used an age-structured deterministic model to evaluate the effects of vaccination in a low-prevalence country and used the modelling results as a basis for a cost-effectiveness analysis of universal vaccination.

If one wants to use any of the above approaches for modelling HCV in IDU, it is first necessary to identify the research questions that should be answered. Based on those questions one can then chose the most appropriate modelling approach. As HCV is still a relatively unknown infectious disease, the first important question might be:

- How do prevalence and incidence of HCV depend on disease-specific and behavioural parameters?

An important step in answering this question is the design of a transmission scheme that describes the relevant stages of infection, the possible transitions between those stages, and the parameters that determines the speed of transition. If it is possible to estimate the durations of the various disease stages and the infectivity of individuals in those stages, one can then answer the question:

- What are threshold values for the establishment of HCV in a population of IDU and how do they compare to threshold values for HIV infection?

When this is achieved one also has an instrument for evaluation of prevention measures, if it is known how different prevention/intervention measures influence model parameters. One might then answer the question:

- What are the effects of intervention/prevention measures such as education to behaviour change, treatment of acute infection, or others on HCV incidence and prevalence?

In principle, one can distinguish two modelling approaches: deterministic models that describe flows between different population subgroups, and stochastic models that describe individuals, their contact patterns and the resulting transmission networks. Both approaches have their advantages and we showed some examples for the application of the different types of models. A deterministic model is more appropriate if one wants to describe the spread of infection in a large population such

as the total population of the Netherlands. If the model is not too complex, it is possible to get some analytical results, such as a formula for the basic reproduction ratio R_0. Furthermore, once the model is formulated, it can easily be solved numerically. As it is deterministic, only one simulation run is required per set of parameters, and so results can be obtained quickly. The disadvantage of deterministic models is that some of the assumptions that are influential for the outcome might be far from reality. This applies especially to assumptions about contact patterns, as in deterministic models it is usually assumed that a contact between two individuals lasts very short and that every contact is with a new individual. If we are dealing with a population where stable, small-scale contact networks are common, large discrepancies between model predictions and empirical observations can occur. In stochastic, individual based models information about local contact patterns and the duration of contacts can be used to get a good picture of the transmission networks and how they change with changing risk behaviour. The problem here is, that the detailed information necessary for estimating the model parameters is usually not available. Also, because of the stochastic nature of the model, there is a large variability in model outcome that makes it necessary to run large numbers of simulations in order to evaluate the outcome distributions. Advantage of the latter is that one does get information about the variability of the epidemic process, which is especially relevant when looking at small populations, like IDU populations in smaller towns.

In summary, we think that the above modelling approaches can be used to answer the following questions concerning HCV in IDU:

- What are the key parameters driving the epidemic of HCV in IDU?
- How do contact patterns of IDU influence the spread of HCV?
- How is the frequency of needle sharing linked to HCV prevalence?
- How do HIV and HBV transmission patterns compare to HCV?
- Which prevention strategies are the most effective in reducing HCV prevalence?

The data needed to estimate parameters for those models comprise:

- Disease specific parameters like transmission probabilities, duration of the infectious period, etc.
- Contact patterns and behaviour like sharing frequencies, mixing between different population subgroups, local network structure.
- Prevalence and incidence data for model validation.

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3.4 Economic impact

3.4.1 Progression of disease model for Hepatitis B and methodology for cost-effectiveness analysis -Ardine de Wit

Three topics were discussed:
1. A short introduction into economic evaluation methodology
2. A review of the literature on economic evaluation of HBV vaccination strategies
3. Methodology and preliminary results of a cost-effectiveness analysis on HBV vaccination strategies performed at the RIVM

Economic evaluation methodology
Economic evaluation of health care interventions is a young scientific discipline. Its aim is to compare the input and output of health care interventions, relative to other health care interventions. Economic evaluation methods have become mature over the past 10 years. Older studies often do not match current methodological standards. Three major types of economic evaluation are:

- Cost-benefit analysis (CBA): in a CBA, all effects of health care programmes are expressed in monetary terms. Therefore, we have to attach monetary values to (changes in) pain, suffering, mortality and functional status of patients. Because this is an extremely difficult task, CBA is not often performed.
- Cost-effectiveness analysis (CEA): in a CEA, effects are expressed in natural units, such as life years gained, % reduction of blood cholesterol, or number of averted infections. The outcome is expressed as cost per incremental change of the natural unit, e.g. cost per life year gained or cost per averted infection.
- Cost-utility analysis (CUA): this is a special type of cost-effectiveness analysis, with QALYs (Quality Adjusted Life Years) as the measure of effectiveness. This

is the most comprehensive outcome measure, incorporating both quality of life and survival information.

Review of the economic HBV literature

Many "economic" studies on effects of HBV interventions were published. More than 1000 entries were found in a recent literature review, but only 16 studies (15 CEA, 1 CBA) could meet with stringent quality criteria. Despite the fact that only high-quality studies were reviewed, big differences in methodology and assumptions were found. Completely opposite conclusions were reached in the selected studies: some studies characterise HBV vaccination as relatively cost-effective or even cost saving, while others describe such programmes as inefficient. In sensitivity analyses, the following parameters were found most often to influence study outcomes:

1. Vaccine costs
2. Discount rate
3. HBV incidence
4. In-/exclusion of indirect costs and effects
5. Percentage acute progressing to chronic
6. Discounting effects
7. Assumed lifetime costs of HBV infection

Cost-effectiveness analysis of HBV vaccination in the Netherlands

The aim of this CEA is to study the cost-effectiveness of different strategies to prevent the (spread of) HBV. Two major strategies under study are (1) the screening of pregnant women, followed by vaccination of their offspring if the mother is infected and (2) general vaccination of all new-borns (+ catch-up of adolescents). Future incidence of HBV infection is modelled with a dynamic epidemiological model that accounts for vertical and sexual transmission of the virus. The progression of disease after infection is modelled with a Markov-chain analysis. A matrix of transition probabilities (between the different stages of disease) has been constructed using literature and a panel of Dutch HHBV experts. The model predicts for each 5 years age group:

1. Future patient numbers per year per stage of the disease.
2. Expected life-time costs per infection
3. Expected loss of life-years due to HBV infection (account is taken of other causes of death).

The occurrence of events is modelled for a period of 50 years after infection, or until age 85. Costs were discounted at 0 % and effects both at 0 and 4 %. Vaccination costs have been excluded from the primary CEA model, but the influence of vaccination costs on cost-effectiveness was studied with sensitivity analyses.

The expected number of infections over the period 2000-2050 is 267.000 in the screen + vaccinate strategy and 121.000 under a general vaccination strategy. Future health care costs are expected to be 443 million guilders and 285 million guilders,

respectively. The predicted loss of life-years due to infection is 338.000 with the screen + vaccinate policy and 133.000 after the introduction of a general vaccination policy. Such a general vaccination programme would be cost-neutral (equal costs and savings over the study period) when vaccination could be offered at a total cost of NLG 31,50 (including administration, organisation and 3 doses of vaccine) per child. The outcomes of current CEA modelling appear extremely sensitive to one parameter in particular: the percentage of infected persons that is not able to clear the virus from the body and will become a chronic carrier of the virus. A general vaccination policy is expected to be 70 times as cost-effective if 10 percent of patients will become a chronic carrier, compared with a situation where “only” 3.3 percent will become a chronic carrier. The actual percentage of chronic carriage is unknown, but is thought to be much closer to 3.3 percent than to 10 percent. The cost per life year gained (not discounted) may be as high as NLG 120.000 if the percentage of chronic carriers is 3.3 percent.

It is concluded that the calculations presented must be seen as a demonstration of the model. Better data are needed, especially on the cost of disease and the percentage of patients becoming a chronic carrier.

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3.4.2 A Framework for the Social Costs of Drug Abuse; illustrated for the costs of drug-related infectious diseases - **Maarten Postma** (An elaboration of this study is given in Section 5)

In a pharmaco-economic approach of the drug problem one typically is interested in the costs related to drug abuse. This type of approach uses the cost-of-illness methodology developed for analysing disease impact. For example it is asked "what are the costs related to HIV/AIDS for the European Union?". Similarly: "what are the costs related to drug abuse in the European Union?" Next to similarity in methodology we notice that cost-of-illness is a part of costs related to drug abuse. For example, a part of the HIV/AIDS-epidemic is drug-related. In general, part of costs for treatment and care of infectious diseases is related to drug abuse. Social cost of drug abuse is however broader. Social costs also comprise addiction treatment, criminal acts, low performance in jobs and indirect costs. In this short note we address this broad framework and provide a preliminary estimate of direct health-care costs for HIV/AIDS en HBV/HCV.

The primary division for costs considered is private versus social costs. Private costs are those born by the individual (druguser), comprising effects at the individual level. The purchase of the drug, individual losses due to low job-performance and dropout from employment are private costs. Social costs are born by society. Next to effects at the individual level, unemployment causes welfare losses at societal level. Society pays for costs of addiction treatment and detoxification programs. Furthermore societal costs are incurred if drug use leads to criminal acts with property damage involved and traffic accidents. Finally, mortality due to substance abuse or drug-related disease causes life-years lost and therefore indirect costs.

Social cost of drug abuse is the value of opportunities lost by engaging resources in coping with the consequences of drug abuse. It equates to the benefit accruing by investing the same resources in the best alternative manner. Costs are involved as an activity prevents resources being used for some other purposes that enhance societal welfare. Obviously, if the drug abuse were not to occur, resources could be deployed in some other way.

As mentioned, social costing of drug abuse can methodologically be equated to cost-of-illness analysis. Cost-of-illness also provides a part of social costing of drug abuse. We can identify 5 steps in designing a cost-of-illness study. (i) A progression-of-disease model has to be constructed that comprises all clinically and economically relevant stages of the disease. (ii) Costing data - corresponding to these stages - have to be gathered. (iii) Discounting has to be applied to correct for time preference. (iv) Lifetime cost-of-illness per patient is modelled. (v) Lifetime cost estimated are linked to epidemiological information from (inter)national surveillance or extrapolated local studies. These steps imply that the incidence-based approach for cost-of-illness is favoured here. This approach attributes all (future) costs to the year of incident (HIV, Hepatitis infection, start of drug use) and is favoured for subsequent application in cost-effectiveness analysis. Its counterpart - the prevalence-based approach - is used for budget-year assessments and short-term planning purposes, but is less suited for cost-effectiveness assessments.

Cost-of-illness is preferably assessed in a bottom-up approach. A top-down approach would never be able to specify resource by disease-stage or risk-group (for example, drugusers). Bottom-up estimates for resource use should come from multi-healthcare-centre studies with sufficient sample size to assure representativeness. Studies should be designed as databases allowing in-depth analysis. For validation of bottom-up estimates (inter)national registrations can be used.

Cost-of-illness of drug-related disease in the European Union can be estimated for HIV/AIDS (Postma, 1998). Furthermore, data are available for the epidemiology HBV and HCV (see L Wiessing in this report). Finally limited data exist on the costing of

HBV and HCV. First, HIV/AIDS is considered. To comprise recent advances in farmaco-therapy the previously published progression-of-disease model (Postma, 1998) has been extended with a stage reflecting the life-years gained on new therapies, with hospital inpatient-days needs similar to those in symptomatic pre-AIDS stages (Tolley et al, 1998). One year on the new therapies costs US$8600 (AZT, lamivudine and ritonavir). Country-specific costing of a hospital inpatient day was done using healthcare-specific purchasing power parities and deflators (source: OECD Paris). An outpatient hospital contact is assumed to cost 30% of an inpatient day's costs and hospital costs are assumed to reflect 90% of total costs (Postma, 1998). Estimates of HIV-incidence for the mid 1990s are available from the Paris Centre for the Epidemiological Monitoring of HIV and AIDS.

Progression-of-disease for HBV distinguishes seven core-stages (see A de Wit in this report: section 3.4.1). Comprehensive costing is only available for Belgium (Beutels et al, 1996). Epidemiological information on prevalence is only available in convenience samples and pilot studies. This fragmentary information has been extrapolated to reflect country totals on HBV and HCV prevalence among drugusers. To crudely derive HBV/HCV incidence, prevalence figures were divided by 10.

All costing was done using a 4% discount rate. Estimated lifetime costs for HIV/AIDS vary from US$31,000 for Greece to US$104,000 for France. Total costs of drug-related HIV/AIDS is estimated at US1304 million in the European union as a whole. Spain accounts for up to US$600 million of this EU-figure. Estimated costs of drug-related HBV/HCV amounts to US$144 million. The total of both figures (US$1448 million) reflects approximately 0.30% of health-care expenditures in all EU-countries.

Our approach to drug-related infectious diseases will be extended to cover other fields of social costs. As a next step indirect costing should be considered as a comprehensive system for this calculation is available (see R Welte in this report). We already mentioned the need to include criminal justice and accidents in the social-costing framework. Also costs for other drug-related diseases should be considered, such as liver disease, bacteremia, heart disease and mental-health problems. Various outpatient support services and residential treatments can be costed. Methadone treatment provides an example of a service that is suitable for costing in a multi-national perspective.

In the end, cost-of-illness of social costs are not assessed perse. Often they serve the purpose of being used in subsequent evaluation, i.e. cost-effectiveness analysis. Then the costs become benefits, viz. that what has to be avoided by intervention (screening, therapy). Topics that emerge from the above analysis are screening drugusers and partners for HIV and HBV/HCV and cost-effectiveness of methadone-treatment programs. In conclusion, a preliminary assessment of health-care costs for drug-related HIV/AIDS and HBV/HCV has been done as part of a broader framework for

social costs. Accurate measurement of social costs provides the basis for pharmaco-economic evaluation.

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3.4.3 Model for Indirect Cost Estimation (MICE) - Robert Welte & Reiner Leidl

Introduction

Costs are becoming increasingly important in health policy decision making. Indirect costs considerably contribute to the total costs of many diseases. However, indirect costs are time consuming to estimate and the calculation is often not well documented. Quality problems may thus exist. Keywords in this study are: indirect costs, computer module, paid work, unpaid work

Objective

The Ulm module for indirect cost estimation (MICE) was designed to provide scientists and policy makers with a tool that allows rapid and precise estimation of the indirect costs of morbidity and mortality. It has been developed for Germany with other countries to follow.

Methods

MICE consists of a Microsoft Excel spreadsheet and documentation. The current reference year is 1995 but it can be easily updated. MICE provides calculations according to the human capital approach or to the friction cost method. Losses of paid and unpaid work can be included. Paid work is valued according to the average net product per capita, specified by age and sex categories. This is derived from the labour costs of employees in trade and industry that are adjusted for unemployment, part-time employment and the labour force participation rate. Unpaid work can be valued with (a) the average labour costs of employed housekeepers (substitution approach) or (b) with the net income of employed housekeepers (as minimum opportunity costs). The

average time spent on unpaid work, specified by age and sex, is obtained from a time budget study.
When applying the human capital approach, the present value of the future net product (PVFNP) of paid and unpaid work is needed for estimating the indirect costs of early retirement and premature mortality. The PVFNP is calculated by multiplying the survival probabilities with the corresponding expected yearly net product. An appropriate discount rate can be chosen.

Results
Multiplying the number of persons in each age and sex group with the respective net product and adding these up approximately yields the income from employment in Germany according to national accounts. This finding underlines the assumption that the method used renders valid results. In the basic calculation for a person aged 31 in 1995, the loss of one effective working day of paid work is 155 DEM for females and 284 DEM for males while the loss of one day of unpaid work is 156 DEM for females and 77 DEM for males (substitution approach).

Conclusions
MICE is a feasible, quick, transparent and flexible instrument to calculate indirect costs.

3.4.4 Ideal and practical model to compute the social costs due to drug abuse - Fernando Antoñanzas, Roberto Rodriguez, Joan Rovira

In this section, we present a survey of several studies that deal with the calculation of the social economic costs derived from unhealthy consumption behaviours. We investigate the different methods used to measure these costs in order to identify similarities in data treatment and cost measurement, to help us calculate the social costs caused, in particular, by drug consumption and its related diseases (HCV, HBV and HIV).

This section is based on the description of a general theoretical model that embodies several studies focussing on the social costs derived from unhealthy consumption behaviours. The studies reviewed here are part of a broader analysis that considered other unhealthy behaviours (alcoholism, obesity and reckless driving). From an initial sample of 41 studies, we have selected 5 of them, related to drug addiction, that are presented in this review.

Social costs are generated by the consumption of certain products (e.g. drugs and alcohol) that cause externalities. In general, empirical studies tend to consider the negative effects (costs) although a few of them focus on the net effects: the difference

between the positive economic effects from unhealthy habits (for example, a reduction in medical care expenditures due to a higher mortality rate) and the negative ones. Externalities introduce a divergence between the social costs and benefits and the private ones. While the latter refer to those accruing to the people involved in the activity, the former are borne by society as a whole. Social cost calculations usually consist of the quantification of the effects derived from behaviours that, supposedly, have a negative impact on social welfare.

The empirical studies appear to convey the idea that public intervention to limit these behaviours is useful or justifiable. Buchanan (1969) pointed out the confusion about the concept of cost. He makes a distinction between the cost that influences a decision (the opportunity cost) and the costs influenced by that decision. Certainly, the studies under revision here do not attempt to distinguish between these; they assume, however, that the latter should induce the public authorities to intervene in order to reduce or eliminate them. In any case, the results from these studies can not legitimately be used to justify any given intervention. The potential benefits of public intervention arise from the reduction in the negative effects of unhealthy behaviour.

However, the desirability of such intervention must be justified, not only on the basis of its benefits, but also on its costs. Public intervention would only be justified if the elimination or reduction of the negative effects gave a greater saving than the costs of the intervention and also compensated for the reduction in the positive effects derived from the, supposedly, unhealthy behaviour (for example, the pleasure of drinking a glass of wine). Empirical studies on unhealthy behaviours have to be considered as informative elements, indispensable for analysing the desirability of public intervention, because they provide a methodology to calculate the social costs involved and can therefore help to characterise which kind of intervention is more efficient (economic evaluation). Nevertheless, they should separate carefully the private negative effects from those borne by the rest of society. This is done rigorously in very few studies. In general, health costs are presented in an aggregated form, without differentiating the fraction paid by the individual as a private cost. A more serious drawback found in the empirical studies is the lack of an explicitly defined social welfare function. In this sense, it would be desirable that this kind of analysis clarifies all the implicit assumptions used in the calculations, so that other researchers could replicate the results or modify the criteria used.

Although the studies under consideration focus on drug addiction, they differ in their objectives, theoretical models and hypotheses. It is, therefore, a difficult task to

compare them. In this review, we propose a theoretical framework within which all the studies fit. This will imply that some of the articles reviewed do not fully calculate the social costs.

In order to calculate the costs derived from consuming unhealthy substances, we need an epidemiological base (number of individuals facing the risk) and the costs derived from the risk (medical expenditures). The precision of the studies will depend on exactly how both elements are measured. We saw in the articles reviewed that multiple problems exist in relation to a precise cost calculation. As well as deficiencies in epidemiological data, in some circumstances there is no precise knowledge of the causal relationships between the consumption of certain products and the associated medical care problem. Causal relationships are sometimes known but quality data are lacking.

Due to the above-mentioned problems, empirical results will depend on the author's ability and calculation method. As an example, for products whose consumption generates addiction, most of the studies try to include the value of lost production, medical care costs, the value of property damages, the cost of fires, the criminal activity costs and the addiction treatment costs. These costs are difficult to calculate. For example, how to calculate the cost of a human life? It is clear that the researcher plays an important role. Even when there is a clear valuation such as, for example, the income losses derived from unhealthy behaviours, the economic literature does not agree whether the income loss, given the existence of unemployment, is a social cost or not.

References

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3.5 Plans and Perspectives

3.5.1 Subgroup Epidemiological & social impact

Definition of data needs and available data sources / Methodological problems
HCV epidemiology

- more data on HCV incidence are needed (cohort studies); trends in HCV-prevalence are difficult to interpret
- risk factor measurement of HCV-incidence have to be refined to identify more causal factors
- coverage HCV surveillance in rural settings is poor

- transmission rates are not well known; Variable infectivity? Effect Tx?
- contact rates (sharing) and mixing patterns are not well known
- Can sexual transmission be ignored?
- an estimation on the number of former injectors is needed but lacking; in some places only the total number of drug users is available (injectors and non-injectors combined)
- data on trends in injecting behaviour are often lacking

Necessary actions:
- extension surveillance
- initiation cohort studies

Natural history HCV
- Progression rates to cirrhosis and death due to HCV are unknown
- Long term progression rates are not available
- The effect of subtype and pre-cirrhosis mortality is unknown
- Possible effects of HCV infection on general physical and mental well being are unknown
- Interaction between HCV and other infections not known (HBV, HIV, HAV)
- The mean duration (stadium) of HCV infection is unknown (possibly increasing progression rates, age)

Necessary actions
- retrospective multi-centre cohort study, using stored serum samples
- develop backcalculation methods (hepatocellular carcinoma, cirrhosis)

Treatment HCV
- Effectiveness Tx unknown in real world setting
- Effectiveness may be lower among IDUs (compliance, subtype 1, etc)
- Proportion of IDUs who are HCV tested, under surveillance, and in treatment: unknown

Necessary action:
- observational cohort study

Primary prevention
- Effectiveness preventive measures unknown, but probably low (e.g. information/education, bleach, needle exchange, testing and counselling, methadone)
- Which factors are responsible for declining HIV-prevalences?

Necessary action:
- evaluation studies (however probably not feasible for ethical and methodological reasons)

Coverage of EU member States
- Southern countries are underrepresented

Other potential participants

- A clinician/ fundamental researcher is needed (natural history, treatment)

Plans for papers

- A number of the presentations will be published.

3.5.2 Subgroup Modelling impact

The issues discussed are listed below and were discussed jointly:

1. Definition of data needs and available data sources.
2. Methodological problems.
3. Coverage of EU Member States.
4. Other potential participants: suggestions for extension of the Working Group.
5. Plans for Papers (author, content, timing).

In order to provide estimates of prevalences and incidences useful to evaluate the costs of the epidemics related to (problem) drug use (HIV/AIDS, HBV, HCV) it is necessary to properly model the spread of the diseases among the target population and, first of all, to estimate the size of such hidden population of susceptibles. Thus, various different models are required, namely:

1. A model to estimate the size (prevalence) of the susceptible population (problem drug users).
2. A model to estimate the dynamics (incidence) of the susceptible population.
3. A model to estimate the spread of HIV/AIDS.
4. A model for hepatitis.

A model to estimate the size (prevalence) of the susceptible population (problem drug users)

Is already available from the NPEA project. Rossi and Ravà will apply the method to the countries were suitable data exists. Data needed for the analysis comes from the European Monitoring centre for AIDS in Paris (AIDS incidence data) and from local surveys among problem drug users (prevalence of HIV among drug users). The estimation method has already been applied for Italy, Belgium, France, Luxembourg, Portugal, Spain and Ireland. Problems exist for the application to the other countries, which might be overcome using the model jointly with other estimation methods. This issue will be further investigated.

A model to estimate the dynamics (incidence) of the susceptible population

Is already available from the EMCDDA Pilot project on Time trends and incidence of problem drug use but needs some modifications which will be treated by S. Heisterkamp in the framework of the TSER working group on Time trends and incidence. To estimate the incidence curve of problem drug use therapy data are

necessary, namely the incidence of new treatments for opiate users in aggregated form periodically recorded. The estimation of the latency time distribution, which is needed to apply the model, will be performed by the group on Time trends and incidence of the TSER project (University of Rome Tor Vergata). The model can be applied in countries were data are available for estimating the latency period distribution (Italy, Belgium, UK, The Netherlands, Ireland).

A model to estimate the spread of HIV/AIDS

Such models are also available from the Concerted Action on AIDS but need to be modified to incorporate the impact of the triple therapy for HIV patients. This aspects is presently under investigation in the framework of a national project in Italy, such project is conducted jointly by the University of Rome Tor Vergata, The Ospedale San Bortolo of Vicenza and The Istituto Superiore di Sanità, estimates will be available at the beginning of the year 2000. The subgroup will investigate about other similar studies already published in the literature. Data needed for the analysis come from follow up of treated patients.

A model for hepatitis

Such models need to be developed and expertise from at least one expert medical doctor is necessary (extension of the Working Group). Catherine Cominskey, Gloria Crispino, Gordon Hay and Mirjam Kretschmar will investigate this issue in details and explore the literature.

The subgroup decided to collaborate by e-mail and address the plans for paper issue in the future.

3.5.3 Subgroup Economic impact

The subgroup was satisfied with the coverage of EU-member states. Extension of the group is not required. The group supports inclusion of Andrea Tramarin, also because of his AIDS-economics experience (but do remind that Roberto Mollica is participating, although not present at the June workshop 1999).

Methodological problems concern the classification of costs of drug abuse. Several of the talks (in particular Prof. Antoñanzas) gave some insight in the topics involved. These talks will be integrated into a first paper (paper 1; principal author Antoñanzas). A preliminary estimate for a part of the framework will be done (paper 2; principal author Postma).

Data needs are primarily found in HBV/HCV costing figures over Europe. HIV/AIDS provides a relatively comprehensive data availability. Currently only Belgium data

for HBV seem appropriate. Furthermore, the work on indirect costing presented by Welte can only be transferred to other EU-countries if "time-budget" studies are available.

This is not the case for all countries. Work to extend HBV/HCV costing and transfer of the indirect costing module to other costing is in progress anyhow and papers result from ongoing projects (paper 3; principal author De Wit and paper 4; principal author Welte)

The current RIVM work on cost-effectiveness of HBV vaccination strategies depends mainly on English parameters on infectivity of the virus in the general population and on Belgian cost data. The cost data will be updated for the Netherlands in the Fall of 1999. Early 2000, the dynamic model for spread of the virus will be updated with Dutch data on sexual behaviour. Also, the influence of migration from more endemic countries will be explored. As a result, one will be able to update the current cost-effectiveness analysis with data that are better adapted to the Dutch context. So far, one has only explored the cost-effectiveness of general vaccination of all newborns in comparison with screening of all pregnant women. In the Spring of 2000, the cost-effectiveness of prevention in risk-group (IDU, homosexuals) will be explored. New results are expected for May 2000.

The current work at the RIVM is mainly concerned with HBV. In the context of the EMCDDA project, the progression of disease model and cost information has to be adapted to HCV. Considering the similarities between HBV and HCV, it is expected that the work on HBV will be expanded relatively easy to HCV.

4 Impact and costs of HCV in Intravenous Drug Users; a literature review - Wien Limburg

4.1 Introduction

The assessment of HCV-related costs of illness in IDUs requires data on the number of current and former injectors, unhealthy behaviours and transmission routes and dynamics, the course of the disease in IDUs and related health care needs, treatment effectivity and costs, the effectivity and costs of transmission preventing interventions including screening, partner identification programmes and drug treatment, indirect costs and effects, private and social costs, and discounting (this report). In an attempt to fulfil the need for such data a literature search was performed, which is reported on in this section. It starts out with a description of how the search was performed and in what databases. Subsequently the results of the searches are discussed. These results concern the disease, the prevalence and incidence of the disease in IDUs, and some of the costs involved. The results of the searches are presented in Appendix G.

4.2 Literature search

Databases

As the literature on HCV in IDUs and in particular the economic literature was expected to be scarce a number of databases have been consulted. Literature searches have been performed in the following databases: MedLine, EconLit, Heed, PsychLit and Social Abstracts.
The databases EconLit, PsychLit and Social Abstracts all yielded a very few references only, the majority of which was also found in MedLine.

Search strategies

In MedLine the following search strategies were used:

- to find studies on HCV in IDUs including studies on the epidemiology, riskfactors, diagnosis and treatment in the western world:
  'Hepatitis C' and 'Substance abuse, intravenous' and 'Europe not Eastern Europe or Transcaucasia', result 100 references, included 59
  Hepatitis C' and 'Substance abuse, intravenous' and 'North America not Mexico', result 26 references, included 20
  'Hepatitis C' and 'Substance abuse, intravenous' and 'Australia or New Zealand', result 43 references, included 34
- to find studies on the costs of HCV in IDUs:
  'Hepatitis C' and 'Substance abuse, intravenous' and 'Economics', result three studies
- to find studies on the costs of HCV:
  'Hepatitis C' and 'Economics', result 101 references, included 77
- to find studies on the costs of IDU:
  'Substance abuse, intravenous' and 'Economics', result 77 references, included 50.

Search strategies involved MESH headings with related terms and all subheadings.
In the Heed database (Health Economic Evaluations Database) the following search strategies were used:

- to find studies on HCV in IDUs:
  'Hepatitis C' and 'Drug abuse', results nil
- to find economic studies on HCV:
  'Hepatitis C' in all data, result 63 references.
  The majority of these references were also found by the MedLine searches. The remaining were included in the list of references of costs of HCV.

Exclusion criteria

General exclusion criteria concerned countries with less fortunate health care systems than in Western Europe and the USA, that is Eastern Europe and Transcaucasia, and Mexico, respectively; language, that is not Dutch, English, French or German; year of publication, that is before 1990 and after week 2 of October 1999; and unavailability in Dutch libraries.
Those references in which either 'costs', 'HCV' or 'IDUs' were merely mentioned but were not discussed were also excluded from the lists.

4.3 General information on HCV

Disease course

Hepatitis C is a bloodborne infection, which affects the liver. The symptoms in the acute stage, if any, are fatigue, malaise, loss of appetite and jaundice. Within 1 to 2 weeks after exposure HCV RNA becomes detectable in the serum, and in about 6 weeks serum alanine aminotransferase (ALT) levels begin to increase. Still, in the acute stage HCV infection may often go unnoticed (66%) (1). It hardly ever is fulminant but when it is, it is often lethal. Recent estimates of the percentage of acute HCV infection becoming chronic are 80 to 85%. In the chronic stage the ALT levels tend to fluctuate and may be intermittently normal. About 20 to 30% of those with chronic HCV develop liver cirrhosis with a heightened risk of developing hepatocellular carcinoma (1,3,4,8). Complications of cirrhosis mark end-stage liver disease. HCV may also manifest itself in nonhepatitic symptoms like arthritis and essential mixed cryoglobulinemia. The chronic stage is often indolent and symptoms may show only in an advanced stage of liver cirrhosis decades after the initial infection (1,4).
There are at least 6 genotypes and many subtypes of HCV. It is not yet clear what influence HCV genotypes have on the course of the disease. Co-infection with HIV, alcohol consumption (24) and older age at time of infection promote the progression of HCV. HCV in IDUs is mainly associated with genotypes 1a and 3a with genotype 3a being far more frequent in IDUs than in other populations (32,34,47).
It should be noted that very little is known about the course of the disease in IDUs

specifically. Not one study was found that dealt exclusively with this subject. May be not surprisingly so, as the disease usually progresses very slowly which would mean many years of follow-up in a difficult population. It is not known whether the disease progression and time of progression differs essentially between IDUs and non-IDUs.

Diagnosis

Hepatitis C was initially referred to as non-A-non-B hepatitis. Its agents have been identified only in the late 1980s. Because the symptoms of HCV are not disease-specific, HCV infection is diagnosed by testing for the presence of antibodies to the virus or by testing for the presence of the virus RNA. The antibody test involves an enzyme immunosorbent assay, if positive followed by a confirmation test with a radioimmunoblot assay. To test whether a person is an HCV-carrier, two types of tests are used, qualitative and quantitative. As a qualitative test, a polymerase chain reaction (PCR) assay is most sensitive for detecting HCV in the blood, but because it is not standardised, it may be unreliable. Quantitative RNA tests measure the level of viral RNA in the blood. They are less sensitive than qualitative PCR and therefore not to be used for screening (4). A liver biopsy may be used to confirm the HCV diagnosis and to determine the severity and stage of the diseases. People can be carriers without having antibodies.

Treatment

Treatment of HCV infection in terms of virus eradication has proven unsuccessful in five out of six patients and if successful mainly in the acute stage (1,4,15). Slowing down the disease is therefore an important treatment goal. Treatment modalities are recombinant interferon alpha 2b for 6 up to 24 months, recombinant interferon alpha 2a for 12 months and 'consensus' interferon for 6 months. Treatment is recommended for patients who as yet do not have but are likely to develop liver cirrhosis. Discontinuation of treatment is often followed by relapse. 15 to 20% shows a sustained response in the serum ALT level, and only 10 to 15% HCV RNA disappearance (1). A combination therapy with interferon and Ribavirin may be more effective than just interferon, especially in reducing the risk of relapse. Liver transplantation is about the only treatment option in end-stage liver disease due to chronic HC.

Interferon, however, is contraindicated in HCV patients with alcohol or drug abuse. Whether IDUs are likely candidates for liver transplantation is unclear but quite unlikely.

Transmission

HCV is predominantly parenterally transmitted. HCV is far more infectious than HIV in terms of bloodborne transmission and because of higher seroprevalences. Risks groups are intravenous drug users (IDUs) through sharing of syringes and other preparation equipment, those receiving blood transfusions or blood products, health care workers with needlestick accidents, those with tattoos and piercings, people with

multiple sex partners especially if also HIV positive (57), long-term prisoners (1,3,112), and more men than women are infected. Transmission through sexual intercourse is far less common than with HBV, as is perinatal transmission from mother to child (6% vs 90%) (25). HCV is not spread by sneezing, sharing eating utensils or casual contact (2). Because of its asymptomatic manifestation and because not all HCV carriers develop chronic hepatitis, there is an unidentified group of HCV carriers that may for years constitute a potential source of transmission.

Prevention

There is as yet no vaccine against HCV, so pre-exposure prophylaxis is impossible. To curtail the spread of HCV, prevention of transmission is therefore the main pre-exposure strategy. Prevention interventions include education, testing and counselling, safe sex, and clean syringes and needles in IDUs. Because of the high prevalences of HCV in recent IDUs, it is being suggested that it is may be a better strategy to get IDUs off the needle than off drugs (113,115).

4.4 Epidemiology

Introduction

Since the introduction of the blood test for HCV the incidence of HCV infections due to blood transfusions has decreased dramatically, at least in the western world. It is estimated that at present about 60% of new infections are related to illegal drug using. A positive HCV status in IDUs seems to be associated with syringe sharing, number of injecting years, older age, level of drug consumption, imprisonment, and male gender (17,39). The prevalence of HCV among IDUs is high although percentages differ between countries.

Western Europe

Stark et al (39) found that in Berlin 83% of 405 IDUs were anti-HCV positive, with HCV spreading rapidly among young IDUs (80% after 1 year). In France 2 out of 3 IDUs are estimated to be HCV infected, amounting to 15-20% of all HCV-infected (40). Of a Greek population of 106 IDU prisoners, 63.2% was found to be HCV positive (30). In different Italian cities prevalences of 65% (69), 58.3% (70), 63.4% (78), and 81% (54) were reported. In Amsterdam, the Netherlands, prevalence rates of 70% (50), 73% (63) and 74% (75) in IDU populations were found. In Valencia, Spain, 85.5% of 1704 IDUs tested positive for HCV antibodies and 69% of IDUs who had been injecting for less than 1 year (46). Gran Canaria shows a similar prevalence rate of 87.6% (28).

Smyth et al reported 61.8% of 733 IDUs (24), 52.1% of 353 IDUs, with a lower percentage in recent injectors (19), 84% of 272 IDUs (48) in Dublin, Ireland, to be HCV infected. In a population of Scottish inmates, 50% of the IDUs were HCV positive, with relatively more ‘older’ injectors testing positive (22). HCV prevalences in IDU populations in two regions in England were 59% (49) and 53% (61). Hickman

reports a prevalence of less than 40% in populations of IDU from 7 English cities with higher percentages in 'older injectors' and in case of coinfection with HIV (this report).
An Icelandic study showed a prevalence of 63% in 152 IDUs (56). A Swiss study showed a dramatic decline from 91.6% to 29.8% in HCV positive IDUs who entered a treatment programme before 1988 or after 1993 (29).

North America

In a population of 2513 patients visiting an emergency department of a hospital in Baltimore in 1988, 18% was HVC positive and 83% of the 175 IDUs (95). In a Baltimore cohort of 225 IDUs, 192 (85%) were HCV positive. Being HCV positive was associated with number of injection years, although as much as 70% of recent injectors was HCV positive within a year after starting injecting (96). In the same town in 1991, 1356 IDUs were tested for anti HCV markers, 89% tested positive increasing to 94% after 10 years of injection. Other risk factors include injecting daily, sharing needles in- or outside shooting galleries especially with multiple sharing partners, injecting cocaine, and a history of drug treatment (89). In the framework of the same project (ALIVE study), viral infections in short-term IDUs were investigated. The overall HCV prevalence was 76.9% (up to 6 years of injecting) and 64.7% in recent (less than 1 year) injectors. In new injectors incidence is related to injection frequency, injecting cocaine, and use of unclean needles (88). Another cohort of this project, 147 IDUs who were anti-HCV negative at enrolment, was followed from1988/9-1995. 47 became HCV positive (versus 13 HIV positive), with the highest incidence in the first 2 years (84). A Baltimore community outreach study, involving 229 young adult IDUs, confirmed the finding that recent injectors are at a high risk for HCV infection. Risk factors included injecting cocaine and speedball, injecting daily, injecting with more than 1 partner, sharing syringes and other drug use paraphernalia, and backloading. With very young injectors seroprevalence was also associated with having an initiator who was 5 years older and with receiving help with injecting. At baseline 86 IDUs were seropositive, at follow-up 13 of the 105 IDUs showed seroconversion (83). In Sacramento, California in 1987 72% of 585 IDUs enrolled in a drug treatment programme was HCV positive. The prevalence of serologic markers correlated with the duration of IDU, ethnic group and drug used with heroin being most risky (94).
In 1992 13.997 people were screened for HCV, 9.270 of which could be analysed as to the risk factors. The overall prevalence of HCV infection was 7.0%; the prevalence in IDUs was 66.6%. The main risk factors proved to be IDU, haemodialysis, blood transfusion, sex with an IDU, and sex with multiple partners (134). Nation-wide in 1995 the prevalence of HPC in the general population was assessed to be 1.8%, amounting to about 3.9 million people. Highest rates of infection are found in IDUs and haemophilia patients, viz. 60-90%. Since 1989 the incidence associated with IDU has been declining, although still 43% of newly HCV infected are (primarily young) injectors (81).

Australia and New Zealand

Prevalences of HCV in IDUs in Australia have repeatedly found to be high in comparison to HIV prevalences. Fairley et al. report a prevalence of 61.9% in an IDU population of 431 attending a Melbourne hospital between 1979 and 1989. Back then the proportion of HCV positives in haemophiliacs was still higher, that is 75.6% (132). In Sydney 59% of 201 IDUs had HCV antibodies, with a significant increase in 'older' injectors from 26% in those injecting less than 3 years to 94% in those injecting more than 10 years (122). Crofts and colleagues report a prevalence of about 68% in a population of Victorian IDUs, with an incidence rate of 20% (125,121). IDUs in a prison population showed prevalences of 63.6% in men and 84.8% in women, with an incidence rate as high as 41% in young men (120). Over a 5-year period a decline in the percentage of HCV positives among IDUs in a methadone maintenance programme at first test was found, that is from 71.1% in 1991 to 52.3% in 1995 (109). Crofts et al present an overview of studies on the prevalence and incidence of HCV in IDUs in various field and clinic-based studies in Australia. Overall, the prevalence rate is found to be high, 60-70% since at least 1971, and the current incidence is assessed to be 15% with up to 40% in certain subpopulations. Unlike HBV and HDV, HIV prevention interventions have resulted in only a little, if any, decrease in the incidence of HCV in IDUs since the mid 1980s (107). They repeatedly stress the importance of identification of transmission routes and transmission preventive measures (107,103). Van Beek (104) found that in a cohort of 1078 IDUs in a HIV prevention centre the overall prevalence rate was 45% and the incidence was 20.9% with those under 20 years showing an incidence as high as 75.6%.

In New Zealand in a group of 92 IDUs enrolled in a needle exchange programme, 77 proved HCV positive with the highest number of 45 out of 52 in those injecting for over 11 years (119). Less high a prevalence was found in 116 persons attending a methadone treatment clinic, that is 54.3% with again the rate increasing with number of injecting years (118). 64% of 241 IDUs recruited from treatment centres and the community was tested anti-HCV positive. The study again confirmed the finding that the rate increases with number of injecting years (106).

4.5 Costs

Costs of HCV in IDUs

The most striking result of the literature searches is that only three studies were found on the costs of HVC in IDUs and that only one of these studies (133) made a concrete attempt to estimate the direct health care costs of HVC in IDUs. The remaining two studies were on the costs of screening for HCV in risk groups of which IDUs is just one (134), and on the (costs of) prevention of HCV transmission by addiction treatment (135).

Through modelling of the disease progression and its different stages in hypothetical

cohorts of 1000 newly infected IDUs over an extended period of time by the Markov model, Brown and Crofts (133) estimate that the cumulative direct health care costs for treatment of HCV in IDUs over a period of 60 years will reach approximately $0.5 billion (1994 dollars). Not included are the costs of interferon, which is contraindicated in IDU, and (in)direct private costs as the available epidemiologic data are limited. Currently the incidence of chronic HCV in IDUs is estimated to be about 6.500 to 8.000 per year. If correct, the present epidemic is generating direct health care costs of the order of $90-$115 million per year.

Costs of HCV

Because of this limited number of studies found on costs of HCV in IDUs, additional searches were performed for the costs of HCV and of IDU separately. Almost half of the studies found on costs of HCV, that is 35, deal with the costs of treatment with interferon. Ironically, Brown and Crofts exclude these costs from their study because being IDU may be a contraindication for α-interferon treatment and because of the poor efficacy and efficiency of the treatment.

The remaining studies are on pathology services like diagnostic tests (9), population screening (9), screening of blood and other blood-related issues (12; 3 of which touch on the issue of compensation) and prevention (3), and general editorials (5).

Interferon treatment

Studies on the cost of interferon treatment use models that make assumptions, often based on the Markov chain model, about the annual risk of moving from one stage of the diseases to the next, and about the response rate to and the efficacy of interferon. If these assumptions are not entirely right, this may have a major impact on the cost-effectiveness of the treatment; a higher response rate to the treatment would raise its cost-effectiveness and might even make it cost saving. Important variables to be included in a cost-effectiveness analysis of α-interferon treatment are stages of the diseases, the time it takes for the various stages to develop, long-term response rate and cost of interferon, costs of health care services, when treatment is discontinued, duration of model, and discount rate (136). Social costs, like loss of income or value of life, are not always included. The current standard dose of interferon is 3 MU 3 times a week for at least 12 months.

Ancos et al (212) compared the costs of α-interferon treatment of 2 groups of hypothetical patients with chronic HBV and HCV with a latency period for developing cirrhosis of 10 years if untreated and with a response rate of 32%. Included in the costs are costs of diagnosis and α-interferon for 6 months, of follow-up like fees of health care professionals and tests, of complications likely to occur between the latency period and cirrhosis complications, and social costs like costs due to loss of work and life. Aggregated costs for HCV treatment are estimated at £ 3.584.300 and £ 5.443.456 (including costs for lives lost) for patients in the same stage of the disease and patients in different stages of the disease, respectively. Under a number of assumptions the treatment is claimed to be cost-effective, but these assumptions need

to be substantiated for this claim to be confirmed. To evaluate the costs of α-interferon treatment, Dusheiko and colleagues (197) compared cohorts of 1000 hypothetical treated patients with HCV and HBV with an untreated cohort over a period of 30 years. They used a transitional probability model to estimate the progression of the disease. The disease path is supposed to go from chronic hepatitis to cirrhosis to sequelae of cirrhosis to death or transplantation for some. Included in the costs are medical costs, social costs like cost for travel and time of patients or work loss, value of lives, QALYs, and discounting. When values for life were included treatment is suggested to be cost effective compared to no treatment. By means of a decision analysis model Bennett et al (175) make projections about the long-term benefits and costs of 6 months of interferon treatment of mild chronic HC. A Markov model is used to estimate lifelong clinical and economic outcomes. It is assumed that a 6 months sustained HCV RNA negativity equals cure and that cure is for life. They show that treatment increases life expectancy with a marginal cost-effectiveness, which compares favourably with screening for breast cancer or cholesterol reduction programs especially in younger patients. Kim and colleagues (174) compared the cost-effectiveness of 6 and 12 months of α-interferon treatment versus no treatment for patients with chronic HC. They also used the Markov model. Costs include costs of α-interferon plus, treatment costs of decompensated cirrhosis, hepatocellular carcinoma and liver transplantation and of follow-up, and discounting (3%). 6 months of therapy proved clinically less effective than a 12 months course, and only slightly more cost-effective ($ 4000 versus $5000 per QALY gained). A 12 months course has become common practice (173,136). In a recent publication Shiell et al (136) evaluate the costs and effects of 12 months of interferon-α in a cohort of 1000 hypothetical patients with chronic HCV infection aged 40 years at the start of treatment over a period of 30 years by means of a decision-analytic model (Markov). Costs pertain to costs of interferon and treatment of complications of cirrhosis including liver transplant and terminal care. The incremental cost per life year saved was $15.835 and per QALY gained it was $8.250 (Australian 1996 dollars). These outcomes change with different discount rates or quality of life weights.

Population screening

As treatment of HCV with α-interferon is most, although limited, effective in an early stage of the disease, screening seems warranted. Kaur et al (192) estimate the costs of screening to be $917-$1.246 for each detected case of HC, which compares favourably with the costs for screening for colorectal or breast cancer. To determine the screening strategy with the best cost performance rate, Lapane et al (168) compared the costs and performances of 4 screening models. Model 1 calls for blood test when the mathematically predictive probability exceeds 7%. Model 2 calls for blood test if people have a significant risk based on a comprehensive questionnaire. Model 3 omitted socially intrusive questions that may not be answered truthfully. Model 4 involves ALT testing followed by confirmation HCV testing. Model 2 seems preferred in most medical settings and should be strongly considered in IDUs or those

who had sex with an IDU, haemodialysis patients, aged 30-49, men, and recipients of blood transfusion (before 1990). Models 1-3 are more cost-effective than model 4.

Blood screening
A French study (178) evaluated the relative costs of screening blood donations for HC. Through a decision-analysis model the cost-effectiveness of a transaminase assay and tests for antibodies to HBc and to HCV was compared to that of transaminase and anti-HBc screening alone. For 100.000 donors the costs of the two approaches were FrF 2.760.405 and FrF 626.864 respectively. Costs included the tests plus overhead. With the first approach 285 infected donors were detected versus 105 with the second. The incremental cost ratios were FrF 30.549 and FrF 13.365, respectively. With a lower prevalence than 0.3% the cost of detecting an additional infected donor would rise.

Costs of IDU
On the basis of primary data compiled by the Research Triangle Institute, extensive literature searches and a variety of other sources, French et al (229) make an admirable attempt to provide a common source of published cost estimates for drug abuse consequences. Nine broad categories are identified: medical service costs; perinatal costs; drug abuse treatment costs; drug-associated disease costs; cost of alcohol, illicit drug and mental health comorbidity (ADM); crime related costs; foster care payments; special education and early intervention costs; and costs to Aid of Families with Dependent Children (AFDC). Of all these categories quantitative economic data are available. For each individual category the costs are presented in tables (in 1994 American dollars). HCV related costs are not included although other infectious diseases are.
The evaluation of the Tacoma Syringe Exchange program (224) shows a positive relation between the use of syringe exchange and a reduced risk of HCV and HB. It is estimated that the programme has led to a 61% reduction in HBV and a 65% reduction in HCV among local IDUs.
Gold et al (226) present an economic evaluation of a local (Toronto, Canada) needle exchange programme aiming to prevent HIV infection in IDUs. Important factors in the cost-effectiveness analysis are the incidences of HIV in IDUs with and without the programme, the costs incurred by the programme and non-market costs, the costs of treating HIV infection, and the discount rate. By means of a constructed incidence model the incidence was assessed to decrease by 24 in a period of 5 years due to the programme. If so, $ 1.292.444 (1995 Canadian dollars) would be saved, which would mean a cost savings ratio to cost of 4:1.
Hurley et al (228) evaluate the effect of needle exchange programmes for prevention of HIV. Seroprevalence studies involving at least 50 IDUs in cities all over the world were included in the evaluation. The rate of change of seroprevalence was calculated between the first and the last survey for cities without and with programmes established during the period spanned by the surveys. The increase in seroprevalence

was 5.9% versus 5.8%; the average annual change was 11% lower in cities with a programme. It is concluded that needle exchange programmes are effective and therefore to be recommended to prevent transmission of infection by the use of injected drugs.

5 Pharmaco-economics of drug addiction; cost impact of HCV, HBV and HIV for IDU in EU-countries – Maarten Postma & Hans Jager

Acknowledgement
The authors benefited from discussions with and information provided by Fernando Antoñanzas, Lucas G. Wiessing and Ardine de Wit.

Introduction
Pharmaco-economics covers the research field of allocating scarce resources to drugs and drug-related activities.[1] The primary field of pharmaco-economical applications covers the medical applications of drugs, with relevant fields such as pharmaceutical costing studies and cost-benefit analysis of pharmaceuticals. The methodology though can directly be applied to "unhealthy" applications of drugs as well. Summarised as reflecting the "drug problem"[2] this refers to smoking and injecting drugs such as opiates, benzodiazepines, amphetamines and cocaine.

Pharmaco-economics has been applied to the drug problem previously in only few studies. For example, Kim *et al* analysed costs and benefits of drug prevention programs for the USA over the period 1979-92.[3] They estimated a very favourable cost/benefit-ratio: there is a saving in direct and indirect costs of US$15 for each US$ spent in drug addiction prevention. Rice *et al* estimated the costs of drug-addiction-related illnesses within a broader social costing framework.[4] This framework comprised the indirect costs and the costs of crime as well.

For the drugs problem the concept of social costs is very suitable to approach the pharmaco-economic aspects. Social costs reflect the total burden of costs for the society as a whole. This societal perspective on the burden of costs for the drug problem is the most relevant approach from the pharmaco-economic point of view and is often the viewpoint that policy-makers are most interested in. Pharmaco-economic approaches are increasingly desired by policy makers. These evaluations assist policy-makers in deciding on the allocation of resources and generic methods developed allow valid comparisons to be made between different programs.[5] For example, the pharmaco-economics of infectious diseases prevention enjoys a growing interest. For example, in the Netherlands investigations in the pharmaco-economics of HBV vaccination and HIV-screening programmes are explicitly required by the Ministry of Health before implementation of a program.[6]

The importance of pharmaco-economic evaluation of the drug problem is not limited to national levels. At local levels authorities are becoming aware of the relevance of a scientific approaches to their portfolios of prevention and treatment programmes, such as needle-exchange programmes and methadone treatment. Pharmaco-economic evaluation at multinational levels is important in situations where health problems are not restricted to countries or cultures but present themselves at, for example, EU-

level. The drug problem and related infectious diseases present an obvious example of the latter.

This chapter presents a methodology derived from pharmaco-economic theory to classify the costs related to the drugs problem and to estimate parts thereof. The classification draws on general economic principles of costing and the estimation procedure has previously been used to HIV/AIDS-related costs at the European Union (EU) level.[7] The estimation is directed to the direct medical costs of HIV/AIDS and Hepatitis epidemics among drug users in the EU. This can be considered as an illustration of using the classification system on social costs of the drug problem. The preliminary estimate provided only covers part of all costs for drug-addiction-related diseases. This chapter does not consider indirect costs of the infectious diseases considered and the costs of other (non-infectious) diseases. Furthermore, costs of addiction treatment, criminal acts, low performance in jobs and indirect costs of substance-addiction related mortality (SARM) are currently left for further research.

This chapter does however produce a crude estimate for the costing of infectious diseases in the EU through drug addiction that has previously not been attempted.

Linking Epidemiology and Pharmaco-economics

Results of epidemiological models and pharmaco-economics have to be linked prevalence-based or incidence-based to estimate direct medical costs related to the drug problem. Traditionally, pharmaco-economic research uses two basic methods for expressing the impact of drugs and disease, labelled incidence-based and prevalence-based methods. The first concerns accounting lifetime costs to the year of incidence of disease. The second method concerns an annualization of these lifetime costs and these are linked to prevalence estimates.[7]

To cover the full pharmaco-economic impact of the drug problem, it is necessary to analyse the lifetime costs consequences incurred by a representative incident (HCV/HBC/HIV-infected) drug user. For direct medical costs this incidence-based approach does however assume that the future health-care technologies will remain the same as in the analysis. Also all other assumptions are extended up to the time until the last incident infection in drug users has been dealt with. If the assumption of everything staying equal holds true for the period of analysis, and the full pharmaco-economic impact is what is being referred to in a decision context the incidence-based approach is the more appropriate one. This could be the case if the decision context, for example, refers to investments and allocating budgets in prevention of drug-addiction related problems. As the latter is often the case, this chapter reports results using the incidence-based approach. Potentials of the prevalence-based approach are considered in the Discussion.

Data and Assumptions

Estimated incidence of HIV among drug users in the EU varies from approximately 200 per million population in Spain and Portugal to less than 10 per million in Germany, Greece, Netherlands and the UK (source: EU Concerted Action on Multinational AIDS Scenario Analysis, RIVM/CEDES, 1997; missing data for Luxembourg and Ireland; these countries were neglected in the model).

Hospital-bed needs incurred by HIV/AIDS vary over the different stages of disease. Furthermore, hospital costs and costs of pharmaceuticals are the major cost drivers for health-care costs of HIV/AIDS. In particular, the terminal phase of AIDS goes along with a relatively high intensity of hospital-bed needs. For this purpose previously two stages were differentiated for AIDS: a final stage of maximally 6 months before death (late stage; LS) and a stage for the foregoing period (chronic stage; CS). Application of the staging concept to the Netherlands, Italy, France, Greece, Spain and the UK has shown that per person-year (ppy) inpatient days in LS are at least twice those in CS. Inpatient-day needs in symptomatic pre-AIDS stages equal 20% of those in CS. Information on inpatient days was available for the 6 countries mentioned.[7]

To comprise for recent advances in pharmaco-therapy the previously published progression-of-disease model was extended with a stage reflecting the life-years gained on Highly Active Anti-Retroviral Therapy (HAART), with hospital inpatient-days needs similar to those in the symptomatic pre-AIDS stages.[7]

One year on HAART costs approximately 10 000EUR for the package of pharmaceuticals (AZT, lamivudine and ritonavir). Country-specific costs per acute-care day were used, varying from 420EUR (UK) to 600EUR (France). For countries with missing data 500EUR was assumed. Costs per acute-care day include average outpatient costs (we assumed 30%). It was assumed that outpatient care for HIV/AIDS patients is more resource-intensive than average resulting in an assumed doubling of the costs per outpatient contact for HIV/AIDS. Finally hospital costs for HIV/AIDS were assumed to reflect 90% of total costs excluding the costs of HAART.[7]

A multiplier on HIV incidence was used to estimate HCV incidence in drug users (annual HCV incidence ranging from 305 in the Netherlands to 13580 in Spain). The multiplier was based on HCV prevalence estimates in populations of drug users divided by HIV prevalence estimates in the same populations (ranging from 3 in the UK to 72 in Greece).[2] This rate was multiplied by 0,5 to provide the appropriate multiplier for HCV incidence (derivation of the factor can be obtained by the authors).

As similar procedure was followed for HBV (annual HBV incidence ranging from 4704 in Greece to 241347 in Spain). The multiplier for prevalence of HBV relative to HIV ranged from 2 for France to 37 in the UK.[2] In absence of this multiplier, 0,5 times the prevalence multiplier for HCV was used.[2] The appropriate multiplier for

incidence resulted after multiplication of the prevalence multiplier by 1,25 (derivation of the factor can be obtained by the authors).

Crude cost estimates for HCV and HBV were derived from a progression-of-disease and costing model for Hepatitis (developed by A de Wit and MJ Postma at the National Institute of Public Health and Environmental Protection). For HCV a progression to chronic Hepatitis of 75% was used. For HBV a progression to chronic Hepatitis of 3% was used.

Results and Discussion

Using a 4% discount rate, lifetime costs for HIV can be estimated for France, Greece, Italy, Netherlands, Spain and UK (Figure 1). Estimated lifetime costs for HIV vary from 47.530EUROs for the UK to 110.890EUROs for France. Subsequently, incidence-based costs can be estimated for these 6 countries. Costs of drug-addiction - related HIV for the EU as a whole is estimated by raising costs for the six countries proportional to incidence figures. Discounted lifetime cost estimates were 10.000EUROs for HCV and 1300EUROs for HBV.

Estimated drug-addiction-related costs of HIV/AIDS and HBV and HCV amount to 1871 million EUR for the EU as a whole. HIV takes account of the major part of these costs (71%), HBV is only minor (5%; Figure 2). Figure 3 shows the cost distribution over the six countries for which detailed HIV/AIDS resource-utilisation data were available.

Our current model uses the incidence-based approach. If on the other hand the budget impact of the drug problem were the focus of analysis, and if this impact is expected to change with new technologies, the prevalence-based approach - applied over a well-defined period of analysis - is more appropriate to support decisions from the pharmaco-economic point of view. With respect to the long-term social costing or full pharmaco-economic impact incidence and prevalence-based approaches are myopic.

On the short-term however, the incidence and prevalence-based approaches may differ even if applied to the same dataset. As an example, the recent introduction of HAART in HIV treatment may serve. On the short-term HAART causes major improvements in health and related cuts in hospitalisations. As a consequence, prevalence-based assessment for budgeting purposes one or two years ahead indicates reductions in hospital budgets for HIV/AIDS-care. However, resource-intensive and costly late stages of HIV/AIDS are merely shifted a few years ahead and on a lifetime basis costs will probably rise because HAART is relatively expensive. An incidence-based approach would typically show the latter development, whereas a prevalence-based approach might focus on the short-term cost reductions only. In consequence, implications drawn for health policy might differ depending on the approach and presentation used. Obviously, the framework for linking epidemiology and pharmaco-

economics should encompass the possibility of using both types of assessments and projections. Further work on our model will be directed to developing a prevalence-based approach for estimating drug-addiction-related costs of infectious diseases.

Further model development will also be directed to other cost categories. The primary division for costs considered here is private versus social costs. Private costs are those born by the individual (drug user), comprising effects at the individual level. The purchase of the drug, individual losses due to low job-performance and possible dropout from employment are private costs. Social costs are born by society. Next to effects at the individual level, unemployment causes welfare losses at societal level. Society pays for costs of addiction treatment and detoxification programs. Through social security and private health-care insurance society pays - at least for parts - of health care for drug-related diseases. Also SARM causes life-years lost and therefore indirect costs.

Furthermore societal costs are incurred if drug use leads to criminal acts with property damage involved and traffic accidents. A typical pharmaco-economic viewpoint concerns the conceivement of theft: property going from one person to another - even in criminal act - is considered as merely reflecting transfers, as taxes are considered to be transfers. Transfers are not considered as costs as they do not influence total societal welfare.

Social costs of drug addiction reflect the value of opportunities lost by engaging resources in coping with the consequences of drug addiction. It equates to the benefit accruing by investing the same resources in the best alternative manner. Costs are involved as an activity prevents resources being used for some other purposes that enhance societal welfare. Obviously, if the drug addiction were not to occur, resources could be deployed in some other way.

In conclusion, a preliminary cost estimate for incidence-based drug-addiction-related costs for infectious diseases has been provided. Further model development will be directed to designing a prevalence-based approach and estimating other cost categories.

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Figure 1: Lifetime costs of HIV-infection in EUROs for six EU-countries.

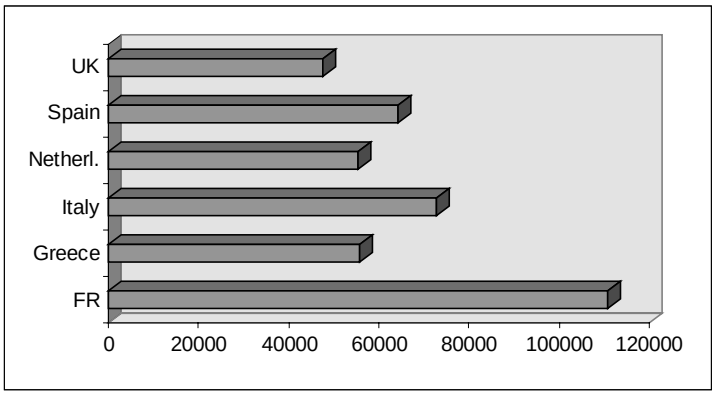


Figure 2: Distribution of the costs for HCV (24%), HBC (5%) and HIV (71%) in 1995 for the EU as a whole.

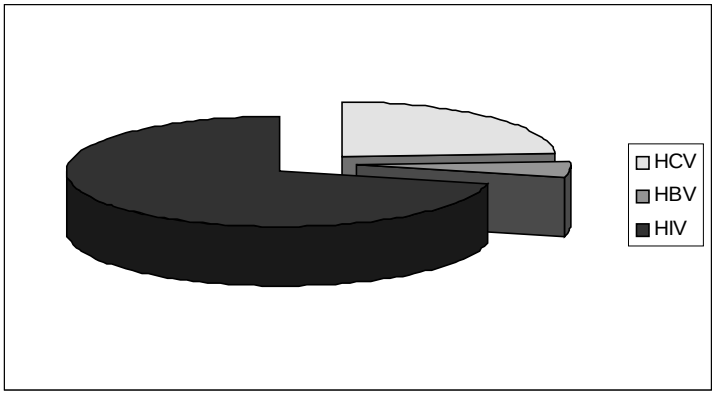
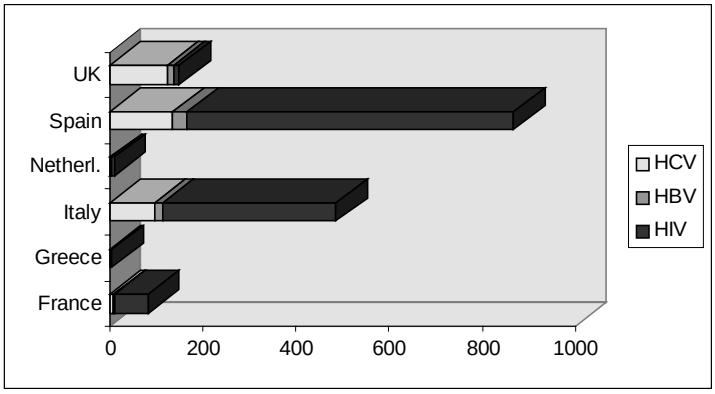


Figure 3: Costs of HCV, HBV and HIV in millions of EUROs for six EU-countries.



6 Discussion and Conclusions

The project seeks to develop a quantitative picture of the *impact and costs* of some important infectious diseases in subpopulations of IDUs, in particular HIV/AIDS, HBV and HCV. 'Impact' concerns *epidemiological* aspects, such as the prevalence, incidence and the routes of transmission of infectious diseases in these subpopulations. 'Costs' involve the *economic* consequences of infectious disease control and the allocation of health care resources.

Because the focus is on the impact and costs, the present study can be regarded as a 'cost-of-illness' study attempting to estimate the burden of infectious diseases on health care resources. The estimate of the cost of illness, however, is not the ultimate goal of the subsequent projects. Eventually, we would like to be able to construct cost effectiveness scenarios (cost-effectiveness analysis) for potential interventions (care and prevention). The goal is to express intervention related costs in units of health effects, e.g. the costs of an intervention expressed per averted infection. The approach of the present project has been adapted to this future goal. Essential to this approach is to come through a bottom up procedure to a linking of epidemiological and economic data using models for disease transmission and economic decision models (see: e.g. work of A. de Wit on interventions for hepatitis B, section 3.4.1).

Next to the aim to go from cost-of-illness approach to a cost-effectiveness analysis (from 'descriptive' to 'what-if'), the scope will be extended from health care costs to social costs. Some of the studies presented (workshop June 1999) prepare the ground (see: section 3.4.2, section 3.4.3 and section 3.4.4).

The conceptual model for the drugs problem and inherent public health, social and legal issues presents the total scope research needs to address to allow for rational policy choices regarding drug interventions (see figure 2 in Appendix F). On the basis of the factors (preventive interventions, risk factors related to life style and drug related behaviour, the physical and social and legal environment) that could affect drug use, the model illustrates how the consequences of drug use present themselves at the individual level (individual effects of drug use: undesired health effects, adverse social and legal events) and the population level (social burden of drug use: use and costs of health care services, use and costs of social and legal institutions). The conceptual model enables us to position the present issues (impact and costs of HIV, HBV and HCV in IDUs) within a much wider framework of policy supporting research devoted to the fight against the drugs problem.

As the present knowledge about HCV proved to be lacking in essential epidemiological and health economic aspects, the exploration within the project focussed in particular on the consequences of HCV infections.

This report presents

- the results of a Workshop (June 1999) on the impact of HCV, HBV and HIV in injecting drug users (section 3),
- the outcomes of a literature search concerning impact and costs related to HCV infections (section 4, Appendix G),

- the identification, classification and estimation of the costs of HIV, HBV and HCV infections related to drug addiction (section 5),
- details concerning Working Group, project related projects and project related publications and contributions to conferences (Appendices A-D),
- an exploratory overview on impact and control of HIV/AIDS, HBV and HCV in injecting drug users in Europe (Appendix E), and
- a conceptual model covering the field of infectious diseases and drug abuse (Appendix F).

In view of the overlap between issues discussed in the several sections and the different objectives as formulated in this report, the global conclusions with reference to the relevant sections for more detailed conclusions are summarised below.

- A conceptual model has been elaborated to cover the field of the drugs problem and inherent public health issues (see Appendix F). This model enables us to order current ideas, research questions, available data and data needs.

- A general overview of the spread of HIV/AIDS, HBV and HCV among IDUs in Europe shows that HIV, HBV and HCV constitute a major health burden for IDUs in Europe and are still not under control. Harm reduction has become an acceptable option in most EU countries, but coverage can be improved (section 3.2.2, Appendix E).

- Basic epidemiological research trying to elucidate the dynamics of the spread of HCV in IDUs is still inconclusive and motivates further epidemiological study. Data needs and methodological problems concerning the epidemiology of HCV have been identified together with necessary actions to solve these needs and problems by extension of surveillance, initiation of cohort studies, and development of backcalculation (e.g. from cirrhosis to incidence and prevalence of HCV). See: section 3.2.1, section 3.2.3 and section 3.5.1.

- Modelling approaches for transmission of HCV and related data needs have been defined (section 3.3.1, section 3.3.2, section 3.3.3). Modelling of the spread of HBV and subsequent economic evaluation of potential interventions (vaccination, screening) have already been elaborated. This work provides the format for the evaluation of interventions with repect to HCV (section 3.4.1).

- The literature review (263 publications) is an inventory of the basic knowledge on the impact and costs of HCV in IDUs. The majority of the articles addresses the clinical and epidemiological aspects of the HCV in IDUs. Apart from articles on the ecomonic aspects of the treatment with Interferon, very few articles deal with economic aspects of HCV in IDUs per se (section 4).

- A preliminary cost estimate for incidence-based drug-addiction-related costs for infectious diseases (HIV, HBV, HCV) has been provided. Estimated drug-addiction-related costs of HIV/AIDS, HBV and HCV amount to 1871 million EUR for the EU as a whole. HIV takes account of the major part of these costs (71%), followed by HCV (24%) and HBV (5%; section 3.4.2, section 5).

- Further economic research should be devoted to prevalence-based estimation of costs, and the extension of the estimation of health care costs to social costs of drug addiction.

Appendix A
Address List of Members of Working Group of Project to Analyse Impact and Costs of Hepatitis B/C and HIV Infection in Injecting Drug Users in the EU

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Appendix B
Related Projects, Project Related Papers and Reports, and Contributions to Conferences

Related Projects

EMCDDA project: Study options to develop dynamic models of drug use and related problems using epidemiological data. University of York

EMCDDA/DG XII project: European network to develop policy relevant models and socio-economic analyses of drug use, consequences and interventions (short title: Drug Use Modelling)

Subprojects:

1. Prevalence estimates of problem use
    - 1a. Prevalence of problem drug use at the national level (IFT, DE)
    - 1b. Prevalence of problem drug use at the local level (University of Glasgow, UK)
2. Temporal and spatial spread of problem drug use
    - 2a. Time trends and incidence of problem drug use (University Tor Vergata, IT)
    - 2b. Geographic spread of problem drug use (University of Keele, UK)
3. Costs/cost-benefits and economic markets
    - 3a. Costs and cost-benefits of drug use and interventions (RIVM, NL)
    - 3b. Analyses of economic markets and policy measures (York University, UK)

Viral hepatitis (243680), RIVM, NL

HIV surveillance in Dutch IDU (441100), RIVM, NL

Quantitative analysis and exploration of effectivity of intervention and prevention strategies in infectious diseases (431511), RIVM, NL.

Subproject:

Modelling of vaccination strategies against Hepatitis B

Cost-effectiveness analysis of interventions in care and prevention (403505), RIVM, NL

Project Related Papers and Reports

EMCDDA project: study of options to develop dynamic models of drug use and related problems using epidemiological data (CT.96.EP.05), Centre for Health Economics, University of York, York, 1997

Jager JC, Postma MJ, Achterberg P: Towards multinational scenario analysis on health impacts of druguse. In: EMCDDA project: study of options to develop dynamic

models of drug use and related problems using epidemiological data (CT.96.EP.05), Centre for Health Economics, University of York, York, 1997

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Godfrey C et al (eds.): Monograph on Dynamic Modelling, York/EMCDDA (in preparation)

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De Wit A, Welte R: Hepatitis B vaccination strategies. Literature Review. RIVM report, 1999

Contributions to conferences

Jager JC, Achterberg PW, Wiessing L, Hartnoll R, Postma MJ: Infectious diseases and drug abuse: conceptual modelling of consequences and interventions. Poster

presentation. European Conference Perspectives on Infectious Disease Research, Dresden, February 1-3, 1999

Postma MJ, Wiessing L, Kretzschmar M, Hartnoll R, Jager JC: Costs of drug related infectious diseases in EU-member States (Geneva 21-25 March 1999)

Wiessing L, Rossi C, Houweling H, Downs AM, Jager JC, Hartnoll R: Injecting drug use in Europe: estimating extent, viral infections and response (Geneva 21-25 March 1999)

Appendix C
Management Structure (Working Group)

The "Project to analyse impact and costs of Hepatitis B/C and HIV infection in injecting drug users in the EU" (proposal CT.98.EP.06; RIVM projectnumber 4035) is funded by the European Monitoring Centre on Drugs and Drug Addiction (EMCDDA) and co-ordinated by the RIVM, the Trimbos Institute (Utrecht, the Netherlands) and the University of Rome Tor Vergata (Rome, Italy).

Working Group
- Project team
  - Project co-ordinators
    - JC Jager/RIVM
    - E van Ameijden/Trimbos
    - C Rossi/Tor Vergata
    - Wiessing/EMCDDA (also contactperson for EMCDDA)
  - Project assistant
    - BJM Zuidema - van Gerwen/RIVM
  - Principal Investigators
    - M Kretzschmar/RIVM
    - MJ Postma/RUG
    - L Rava/Tor Vergata
  - Research assistants
    - R Welte/RIVM
    - A de Wit/RIVM
- Experts
  - Epidemiology
    - M vd Laar (represents M. Berns and others)
    - D Goldberg/Glasgow
    - M Hickman/London
  - Modelling
    - G Hay/Glasgow
    - C Comiskey/Maynooth
  - Economy
    - F Antoñianzas/Rioja
    - R Leidl/Ulm (represented by R Welte)

Appendix D
Meeting of Working Group

Dates: 24 and 25 June 1999; place: National Institute of Public Health and the Environment (RIVM), Bilthoven, the Netherlands

Projects & co-ordination framework

- Impact and Costs of Hepatitis B/C and HIV in IDU in the EU
  * funded by EMCDDA
  * co-ordinated by EMCDDA, RIVM, Trimbos & Univ Rome
- European Network to Develop Policy Relevant Models and Socio-Economic Analyses of Drug Use, Consequences and Interventions
  Short Title: Drug Use Modelling
  * funded by TSER/DG XII/EC
  * co-ordinated by EMCDDA

Subprojects drug use modelling

1 Prevalence estimates of problem drug use
  1a At the national level (IFT)
  1b At the local level (Univ Glasgow)
2 Temporal and Spatial spread of problem drug use
  2a Time trends and incidence (Univ Rome 'Tor Vergata')
  2b Geographic spread (Univ Keele)
3 Costs/Cost-benefits and Economic Markets
  3a Costs/cost-benefits of drug use/interventions (RIVM)
  3b Economic markets and policy measures (Univ York)

Aims

Project: impact and costs of HIV, HBV and HCV in IDU in the EU

- To assess cost-of-illness related to HBV, HCV and HIV
- To assess influence epidemiological developments on health care costs
- To assess data/methodological needs for construction of cost effectiveness of potential interventions

Project: Costs/cost benefits of drug use and interventions in EU

- To estimate costs for society of drug use
- To assess cost-effectiveness of different forms of intervention using models

Global objective

- Formation of Working Group
- Expertise Required at Three Levels
  *Epidemiology and Social Aspects
  * Mathematical Modelling

    * Economic Evaluation
- Size
    * Start with Core Group (15 experts)
    * Extension of Core Group in view of data needs and expertise as established by Core Group

Programme for working group

- Present Meeting
    * Exploration of research area at three levels in three sessions
    * Discussion in subgroups
    * Final Report & Joint Publications
- Further Meetings (Core Group and Invited Guests)
    * Spring 2000, RIVM/Bilthoven
    * Fall 2000, EMCDDA/Lisbon (with other TSER groups)

Issues for discussion in subgroups

- Identification of data needs and available data sources
- Methodological problems
- Coverage EU Member States
- Other participants: suggestions for extension of Working Group
- Plans for Papers (authors, content, timing)

Programme of Workshop Meeting 24th – 25th June 1999

Opening - Prof. Dr G. A.M. van den Bos
Introduction - Hans Jager & Lucas Wiessing

Epidemiological and Social Impact
Chair: Erik van Ameijden

> *Surveillance concerning Hepatitis C infections* - David Goldberg
> *Prevalence of HIV, Hepatitis B/C in IDU and related risk factors* - Marita van de Laar
> *Epidemiology of HCV* - Matthew Hickman
> *Injecting drug use, viral infections and responses in Europe* - Lucas Wiessing
> *Epidemiology of Hepatitis B/C in a Dutch cohort, potential interventions and methodological comments* - Erik van Ameijden

Modelling
Chair: Carla Rossi

> *Modelling epidemiological processes in IDU* - Gordon Hay
> *Methods and estimates of incidence and prevalence of IDU populations in the EU* - Lucilla Rava & Carla Rossi
> *Prediction of future costs using various modelling techniques* - Catherine Comiskey
> *Modelling approaches for transmission of Hepatitis C in IDU* - Mirjam Kretzschmar

Economic impact
Chair: Maarten Postma

> *Progression of disease model for Hepatitis B and methodology for cost-effectiveness analysis* - Ardine de Wit
> *Model for Indirect Cost Estimation (MICE*) - Robert Welte
> *Ideal and practical model to compute the social costs due to drug abuse-* Fernando Antoñianzas
> *A Framework for the Social Costs of Drug Abuse; illustrated for the costs of drug-related infectious diseases* - Maarten Postma

Subgroup Meetings & Reporting by Subgroups*
> Epidemiological & social impact
> Modelling impact
> Economic impact

Close of meeting

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*for issues discussed see text

Within the frame of the TSER project (see section 2) the Working Group will be extended and will continue the scientific work started in the current project. Several meetings will be planned, viz. Spring 2000, RIVM (TSER) and Fall 2000, EMCDDA/Portugal (with other TSER groups).

Appendix E

Wiessing LG, Hartnoll R, Houweling H, Jager JC, Downs AM, Hamers F: Impact and Control of AIDS, HIV, and Hepatitis B and C Among Injecting Drug Users in Europe: An Exploratory Overview. Also in: inaugural meeting report. National Institute of Drug Abuse, National Institutes of Health, US Department of Health and Human Services: 1999, 23-35

Introduction

This paper aims to give a general overview of the spread of HIV/AIDS, HBV, and HCV among IDUs in Europe by describing recent data collected by two European monitoring centres: EMCDDA and CESES. Also presented are relevant modelling data that were obtained in the framework of the European Union Concerted Action on Multinational AIDS Scenarios (BMH1-CT94-1723), co-ordinated by the Netherlands National Institute of Public Health and the Environment (RIVM). Because of the differences in geographic coverage of the available data and estimates, the main emphasis of this paper is on countries of the EU (see tables 1 and 2). Information on reported AIDS cases is available from CESES also for Central and Eastern Europe (and Asian countries of the former Soviet Union). As results came from different studies and monitoring activities, a thematic structure was chosen for this overview. After a description of patterns of the spread of AIDS among IDUs, estimates are presented of historical HIV incidence derived by back-calculation from AIDS cases followed by recent data on seroprevalence of HIV, HBV, and HCV. Finally, a general impression is given of implementation and possible effects of harm-reduction measures in countries of the EU.

AIDS Among IDUs in Europe

Data on all AIDS cases reported in Europe are collected by CESES (1998). Among IDUs, a northeast to southwest gradient exists in AIDS incidence (figure 1), and differences between countries are large (Hamers et al. 1997). Highest incidences are reported in France, Switzerland, Italy, Portugal, and Spain (incidence rates of 7 to 73 cases per million total population in 1997) and much lower incidences in other countries (incidence rates of 0 to 5 per million). In the countries with high AIDS incidence among IDUs, the high levels of HIV are an important source of heterosexual transmission to non-IDUs (Downs, Hamers et al. 1998). In 1990, IDUs became the predominant transmission group among AIDS cases, surpassing homosexual and bisexual men (figure 2). After a slowdown in the rate of increase, AIDS incidence among IDUs increased substantially in 1993 and 1994 because of the widening of the AIDS case definition to include pulmonary tuberculosis (TB). This broader definition had a particularly marked effect in Spain where there is a high prevalence of TB infection among HIV-infected persons. Since mid-1996, however, strong declines in AIDS incidence have occurred, in part because of the effectiveness of highly active antiretroviral treatments that delay AIDS onset in HIV-infected patients (CESES 1998, Termorshuizen and Houweling 1997). These declines have not occurred in all countries, which might indicate differences in the uptake of pre-AIDS treatment. In Portugal this seems to be practically non-existent among IDUs (Portugal National Focal Point, personal communication). However, the fact that the epidemic in Portugal is still in its early phase makes interpretation difficult.

Birth Cohort Analysis of AIDS among IDUs

Plotting the incidence of AIDS among IDUs by 5-year birth cohort (each group born in successive 5-year periods) can show the effect of AIDS over "generations" of IDUs (Stoneburner et al. 1993). This has been done with data from 12 Western European countries up to 1994 (figure 3) (Houweling et al., in press). The incidence curve for the oldest birth cohort, born between 1950 and 1954, shows that this cohort was never very much affected by AIDS. Among IDUs born between 1955 and 1959, incidence still does not show a steep increase but already reaches much higher levels. The next birth cohort, IDUs born between 1960 and 1964, has been most affected by the epidemic. They moved from ages 15 to 20 to ages 25 to 30 between 1980 and 1990, so the years of highest HIV incidence probably coincided with the ages of maximum drug use. However, more important for current prevention policy is the fact that in recent years the two youngest birth cohorts still show strong increases in AIDS incidence although maximum levels are lower so far. These lower levels indicate that the levelling off or even decline of total incidence in some countries may mask continued rising incidence in new cohorts of young drug users. Over the years, the epidemic appears to have been continuously reaching young people, resulting in important increases in incidence in these subgroups.

Estimation of the HIV Incidence Curve for IDUs by Back-Calculation

Because of the AIDS virus' long and variable incubation time, AIDS incidence gives a delayed and diffuse picture of the transmission dynamics of HIV. However, using modelling techniques, it is possible to estimate the most likely historical HIV incidence curve on the basis of reported AIDS incidence and the incubation time distribution as estimated in cohort studies. Within a multinational EU project (BMH1-CT94-1723, Jager and Ruitenberg 1997) and using the European AIDS data corrected for reporting delay, the underlying HIV incidence curves were reconstructed (Downs, Heisterkamp et al. 1998; Houweling et al. 1998) using a nonparametric back-calculation model (Heisterkamp, Downs, and van Houwelingen, in press; Downs et al. 1997) modified to include age as a covariate and effects of the 1993 change in the AIDS case definition [details to be published elsewhere (Downs et al., submitted)]. Disease progression was modelled by a 7-stage Markov model with parameters estimated from a Dutch cohort of IDUs (Hendriks et al. 1998) and age factors derived from the Multicohort Analysis Project Workshop (1994). From the results (figure 4), the first thing that becomes apparent is that HIV-incidence curves have a shape different from AIDS-incidence curves, showing during the first years the peaked epidemic curve of many nonsexually transmitted infectious diseases. In general, HIV incidence rises very quickly, infecting the most susceptible individuals in a few years, after which it declines rapidly because of the decreasing number of susceptible IDUs in the population. However, as long as HIV prevalence remains high, any newly susceptible (i.e., needle-sharing) IDU entering the population will have a high risk of infection. It is difficult to distinguish the effects of behaviour change from those of saturation, particularly as the total population size of (susceptible), IDUs is unknown. However, it is clear that any behaviour change has to be rapid and timely to prevent early massive HIV infection rates among IDUs.

Back-calculation estimates by birth cohort show that in EU countries the oldest birth cohorts (born between 1950 and 1960) experienced the peak of HIV incidence at

about the same time. In other words, at the beginning of the epidemic the virus infected susceptible IDUs rapidly without much distinction by age. In contrast, the younger cohorts started to become infected later, only after entering the IDU populations. The cohort born between 1965 and 1969 and especially the one born between 1970 and 1974 were mainly infected after 1990. This infection incidence again reflects how young and new drug users entering the population continued to become infected even at a time when the total HIV incidence rates among IDUs were declining greatly after the first epidemic phase of the 1980s.

Back-calculation estimates by country show very large differences, of the same order of magnitude as those seen in the reported AIDS cases on which the estimates are based. Figures 5a and 5b show results for some EU countries with low incidences of HIV, (Belgium, Germany, Denmark, United Kingdom [UK], Netherlands), and some countries with high incidences (Portugal, Spain, Italy, France). The less affected countries have an estimated peak HIV incidence of between 5 and 16 cases per million total population per year, whereas the most affected countries have peak incidences of 100 to 400 cases per million. Such large differences cannot be explained by differences in the prevalence of injection drug use only. There are certainly differences in prevalence of drug use between countries but not to such an extreme extent, as available estimates of problem drug use (mostly injection usage) prevalence differ by a factor of only about 3 to 5 (EMCDDA 1998). The differences in HIV incidence must therefore be related to (inter-related) differences in risk behaviour, other risk factors, or the public health response. Especially disturbing is that HIV incidence in Portugal appears to have begun to rise only after 1990, long after awareness of AIDS and the possibility of prevention existed in Europe. Furthermore, it seems not to have started levelling off until 1994 although it must be borne in mind that back-calculation estimates for the most recent years are uncertain. In Spain the second peak in the estimated HIV curve seems to be unsupported by national trends data of HIV seroprevalence (not shown) and may be the result of allowing for the change in the AIDS case definition or some other factor in AIDS reporting.

Data on HIV Prevalence among IDUs in the EU

HIV seroprevalence data for IDUs in all EU countries (table 1) were collected for the first time by the EMCDDA in 1997 and updated in 1998. These data are reported by the National Focal Points, which together with the EMCDDA form the Reitox network. It is still not possible to consider these data comparable because they are from different types of sources, ranging from IDUs in treatment in several countries to opiate overdose deaths in Austria and self-reports of test results in France and Greece. However, even if sources are heterogeneous and sometimes only local or clearly biased, the low HIV prevalence of 0 percent from self-reports of IDUs attending a syringe exchange program in Finland, 0.6 percent from the Unlinked Anonymous surveillance system in England and Wales, and 0.5 percent (screening) to 2.0 percent (self-reports) in Greece, contrast sharply with the 16 to 20 percent in France, 16 percent in Italy, and 30 percent in Spain. It is therefore clear that there remain large differences in HIV prevalence between countries. Trends in prevalence are again derived from different sources and show stable or declining HIV prevalence in most countries of the EU. From Portugal, although a rise in seroprevalence among IDUs in drug treatment in 1995 was initially reported (EMCDDA 1997), consistent with other

information such as the results from back-calculation, the trend appears to have reversed in 1996 and may at present be considered stable (1994: 14 percent; 1995: 18 percent; 1996: 14 percent). From Belgium also a temporary strong increase was reported in HIV notifications of young IDUs, and more recent data from drug users in treatment indicate a stabilisation.

AIDS and HIV in Central and Eastern Europe

Unlike the situation in Western Europe, the AIDS epidemic in IDUs in Central and Eastern Europe is still barely visible, except for Poland and the former Yugoslavia (CESES 1998). Strong increases in HIV prevalence have recently been recorded in Poland and in some countries of the former Soviet Union, such as Ukraine, and circumstances favouring a rapid spread among IDUs have been described (Khodakevich et al. 1997). These include non-existence or limited coverage of syringe exchange programs, police enforcement of laws prohibiting the carrying and distribution of syringes, dangerous injection practices, and widespread needle sharing. Also, there have been reports about the contamination of opiates with HIV during the production phase before distribution (Alcabes et al. 1998). Although AIDS incidence among IDUs in Central and Eastern Europe is low, reliable HIV data are scarce, and the developments in Poland and the former Soviet Union suggest that it may be a matter only of some years before epidemics occur in more countries. Therefore, HIV prevention programs are urgently needed.

HBV and HCV among IDUs in the EU

At the beginning of the 1990s there was some confusion whether the high levels of HCV found among IDUs reflected a new epidemic. Antibody tests have been available only since 1989, and the high prevalences found since then in different parts of the world, as well as some retrospective analyses of stored sera of IDUs, indicate that the virus probably began to spread before the HIV epidemic. It appears further that HIV prevention is not sufficient to prevent the spread of HCV because it is much more easily transmitted than HIV, not only through blood or needle-sharing, but also through sharing other equipment used for injecting drugs (spoons, cotton, water). In view of its extremely high prevalence, HCV may, for IDUs, be as important as HIV in public health terms; HCV infection can cause liver cirrhosis and cancer that may lead to premature death.

Seroprevalence data on HBV and HCV among IDUs, collected through the EMCDDA/Reitox network of National Focal Points, are presented in table 2. To our knowledge these are the first available seroprevalence data on HBV and HCV among IDUs in EU countries, and even if they are assembled from incomparable sources, they can give a crude impression of the spread of these viruses. In general the levels of HBV are lower than those of HCV. Besides a possible difference in infectivity, this is probably due for the most part to the fact that a much larger proportion of those infected with HCV than HBV develops chronic infection and remains able to infect others. The prevalence of antibodies against HBV ranges from about 20 percent in Denmark, Luxembourg, and the UK to about 60 percent in treatment samples in the Netherlands and Spain. Vaccination of IDUs is currently increasing so that these data are turning into an indicator for the potential of further vaccination rather than of

levels of those ever infected. For HCV, much higher levels of prevalence are reported, ranging from about 50 percent in several countries to more than 90 percent in Sweden and Greece (the very low prevalence in Luxembourg may be unreliable because it is based on self-reports). These data indicate that HBV and HCV have spread widely among IDUs in Europe as in other parts of the world. A French study estimated that roughly 500,000 current IDUs in the EU were infected with HCV in 1996 (Nalpas et al. 1998). This may still be a gross underestimation of all prevalent IDU-related infections because it does not take into account infections in former IDUs.

Harm Reduction in the EU

Whereas traditional demand reduction focused on reducing drug consumption through prevention and treatment, the first aim of a harm-reduction approach is to minimise adverse health and social consequences of drug use. A broader vision of harm reduction includes substitution treatment to reduce injection drug use. A more limited implementation in the area of infectious diseases at least encompasses the availability of syringes through pharmacies and syringe exchange programs, provision of condoms, and HIV counselling and testing. The data presented in table 3 were extracted from qualitative descriptions in the 1997 national reports on the drug situation provided by the National Focal Points. Where possible the time when these measures were implemented and whether they have national coverage were assessed. Furthermore, some information was available on injection drug use trends and rates of injection drug use among opiate users in treatment.

From table 3 it becomes clear that in practice harm reduction has become the norm in most countries of the EU. This is interesting in itself, given the different impression arising from some recent political controversies on national drug policies. Syringes are available in all countries, and condoms and HIV counselling and testing seem to be widely available. Substitution treatment also exists in all countries (EMCDDA 1998), mostly in the form of oral methadone. Even heroin trials have started in the Netherlands following Switzerland, which is not an EU country. However, coverage and intensity of harm-reduction measures vary considerably and can probably still be improved. From the national reports it appears that syringe availability is not always nationwide and that it depends much on local or regional initiatives, although these may be more frequent in high-risk areas. Sweden and Finland have only very limited syringe exchange programs, and Finland recently restricted the availability of syringes in pharmacies. In France, substitution treatment, although strongly increasing, mostly involves buprenorphine, which is often injected although methadone programs are also developing. In Germany, large differences exist between regions and cities in the implementation of harm-reduction measures.

If harm-reduction measures are becoming common practice, this has mostly been occurring in recent years. Can harm-reduction measures therefore have had much effect on the HIV epidemic in the EU? From table 3 it appears that in several countries harm-reduction measures have been implemented only in the 1990s, years after widespread HIV infection of IDUs had already occurred. A recent evaluation of syringe exchange programs in Spain, France, and Italy, the most affected countries in Europe, found that these programs have mostly been introduced after 1993, although the unrestricted distribution of syringes through pharmacies has existed in France

since 1987 (PESESUD 1998). In these countries the effects on seroprevalence may start to become visible in the years to come. Other countries, however, were more timely in implementing harm-reduction measures. The first countries to introduce syringe exchange programs were the UK, the Netherlands, and Sweden (which, however, always remained limited to only two programs). Substitution treatment was available early in the UK, the Netherlands, Italy, and Denmark. In the UK, the early and strong response has probably helped to avert a large HIV epidemic (Stimson 1996), but in the Netherlands syringe exchange programs were introduced only after the initial epidemic among IDUs in Amsterdam had already occurred. Nevertheless, in a well-documented cohort study it was concluded that the combined harm-reduction measures in Amsterdam had decreased injection risk behaviours (van Ameijden et al. 1994). Harm-reduction measures have thus most probably prevented many infections in some countries such as the UK and the Netherlands, but in other countries they were introduced too late and on a too limited scale to prevent major HIV epidemics.

Even when it is difficult to assess what the specific contribution of harm-reduction measures has been in the EU, in general, risk of infection has decreased since the 1980s as shown by age-specific HIV incidence by back-calculation (figure 4). This may partly be the result of the early harm-reduction measures, partly the result of autonomous behaviour changes by IDUs in response to information and awareness of AIDS in the general media, and partly because those at highest risk were already infected (saturation effects or depletion of susceptibles). It is not possible to disentangle the relative effects of these factors. Declines in injection drug use have been reported over the past 10 years from several countries and were perhaps greater in countries with either a high prevalence of HIV or an early-occurring HIV epidemic. For example, Greece, which never experienced an HIV epidemic among IDUs, still reports a figure of 82 percent IDUs among opiate users in treatment. In contrast, in the Netherlands, which was affected early in the 1980s, injection drug use among opiate users in treatment decreased a great deal to a current rate of about 14 percent. However, other factors seem to play a role, too. In Spain, IDUs have been widely infected, and strong declines in injection drug use have been reported (De La Fuente et al. 1997). These declines were similar in areas with high or low prevalence of HIV and may have been associated with the type of heroin on the market (smokable or injectable) rather than with HIV prevalence levels. Moreover, no important decreases in injection drug use have been reported in Italy and France, although the IDU populations in these countries are among the most heavily affected by HIV. In Austria, injection drug use even increased after 1990, and this was apparently associated with new heroin transport routes after the opening of the borders to Eastern Europe.

Indeed, although the effect of harm-reduction measures has become visible in some countries, and they are now being increasingly implemented on a larger scale, coverage at the EU level also seems insufficient if judged by data on rates of infection reported in the previous sections of this paper. Back-calculation by country and by birth cohort suggests continuing HIV transmission in new generations of IDUs, even though at lower levels than in the 1980s and with large differences between countries (see figures 5a and 5b). In Portugal, AIDS incidence continued to increase until at least 1997 (data from CESES, presented in EMCDDA's 1998 annual report), whereas the back-calculation estimates also suggest that the HIV epidemic in Portugal started after 1986 and kept growing until at least 1992–1993. Account should further be taken

of the continuing very high rates of HIV in seroprevalence data from southwestern European countries (Spain, Italy, Portugal, and France), even though prevalence among IDUs is slowly declining in Spain, Italy, and France. From available seroprevalence studies, we know that rates of HBV and HCV are extremely high among IDUs all over the EU, while other studies indicate the high risk of transmission of HIV, HBV, and HCV in prisons (Weilandt and Rotily 1998).

Conclusion

AIDS incidence in IDUs is strongly declining due to new treatments. However, different sources of data indicate that HIV, HBV, and HCV infections are not under control and still constitute a major health burden for IDUs in Europe. Transmission of these viral infections continues into new generations of IDUs in Europe. Harm reduction has by now become an acceptable option in most EU countries, but coverage can still be improved.

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Table 1 Prevalence of HIV infection among injecting drug users in EU countries, EMCDDA 1998

	Year	Data	Number tested	Percent HIV infected	Trend in prevalence
Austria (1)	1997	Opiate overdose deaths	132	1.5	(Stable)
Belgium (French) (2)	1996	First treatments, self-reports	294	1.4 *	Stable
Belgium (Flemish) (3)	1993	Antwerp: Study treatment/streets	217	(5)	___
Denmark (4)	1995	Estimate from HIV notification	____	4	___
Finland (5)	1997	Helsinki: Needle exchange, self-reports	131	(0)	(Stable)
France (6)	1995	Survey treatment centres, self-reports	6429	16-20	Decrease
Germany (7)	1996	Drug users in treatment, self-reports	2074	3.9 *	Stable
Greece (8)	1997	Treatment, screening/self-reports	708	0.5-2.0	Stable
Ireland (3)	1993	Dublin: Study treatment/streets	185	(8)	___
Italy (9)	1997	Treatment in public services	73,784	16 / 1-28	Decrease
Luxembourg (10)	1997	Treatment reporting system, self-reports	280	2-4	Stable
Netherlands (11)	1995-97	Repeated treatment/street studies	1333	2-26	Stable
Portugal (12)	1996	Survey treatment centres, self-reports	379	14	Stable
Spain (13)	1996	Survey treatment centres	871	30	Decrease
Sweden (14)	1997	Study 9 prisons	196	3	Stable
United Kingdom (England and Wales) (15)	1996	Unlinked Anonymous	3,373	0.6	Decrease

* refers to all problem drug users; percentage among IDUs is not known but is almost certainly higher.
Information based on local data is given between parentheses.
Data based on self-reports may be unreliable.

1) Austria National Focal Point 1998a
2) Belgium National Focal Point 1998 [C. Preumont and L. Bils, Comité de Concertation sur l'Alcool et les Autres Drogues, de la Communauté Française de Belgique (personal communication, 1998)]
3) Papaevangelou and Richardson 1995, pp.73-82
4) Denmark National Focal Point, 1997 (Smith 1997)
5) Finland National Focal Point 1998 (Ovaska, Holopainen, Annala 1998)
6) France National Focal Point 1998 (Antoine and Viguier 1998)
The range given is not geographical: upper limit gives the seropositives among all known test results while the lower limit assumes those who do not know their test results are seronegative.
7) Germany National Focal Point 1998 (Zahn et al. 1996).
8) Greece National Focal Point 1998 (Screening drug free treatment: n=409, 0.48%; treatment reporting system, self-reports: n=299, 2%).
9) Italy National Focal Point 1998 (Prevalence of HIV antibodies in SER.T users by Region 1990-97, Ministry of Health). National average and range of seroprevalences by region.
10) Luxembourg National Focal Point 1998 (Origer, 1998) Two percent assumes all with unknown test results are seronegative, 3% is prevalence in all those with known test results, 4% if also corrected for 79% IDUs and assuming all seropositives are IDUs.
11) Netherlands National Focal Point 1998 (1995: Arnhem 2%; 1996: Amsterdam 26%, Utrecht 5%; 1997: Heerlen 16%, Maastricht 3%, Rotterdam 9%) (Wiessing et al. 1996; Wiessing, van Rozendaal, Scheepens, Schat et al. 1996; Wiessing et al. 1997; Carsauw et al. 1997; Berns et al. 1998)
12) Portugal National Focal Point 1998
13) Spain National Focal Point 1999
14) Sweden National Focal Point 1998 (Trend in prevalence based on notifications of IDUs) (Käll and Thorstensson)
15) Public Health Laboratory Service 1998

Table 2: Prevalence of antibodies against hepatitis B (HBV) and hepatitis C (HCV) among IDUs in EU countries, EMCDDA 1998.

	Hepatitis B			Hepatitis C		
	Year	Data	Percent anti-HBV +	Year	Data	Percent anti-HCV +
Austria (1)	1996	Vienna: Hospital, low threshold treatment	(50-56)	1996	Vienna: Hospital, low threshold treatment	(72-79)
Belgium	-	-	-	-	-	-
Denmark (2)	1995	Estimate	21	1995	Estimate	50
Finland (3)	1997	Helsinki: Needle exchange, self-reports	(34)	1997	Helsinki: Needle exchange, self-reports	(53)
France (4)	-	-	-	1995	Survey treatment centres, self-reports	53-70
Germany (5)	1996	Dortmund: Treatment	(48)	1996	Dortmund: Treatment	(63)
Greece (6)	-	-	-	1997	Methadone/drug free treatment	50-94
Ireland (7)	-	-	-	1992/93	Dublin: Treatment	(84)
Italy (8)	1997	Treatment	40	1997	Treatment	67
Luxembourg (9)	1997	Treatment, self-reports	22	1997	Treatment, self-reports	19
Netherlands (10)	1994/96	Rotterdam/Heerlen/Maastricht: Treatment	(59-63)	1994/96	Rotterdam/Heerlen/Maastricht: Treatment	(74-84)
Portugal (11)	-	-	-	1996	Treatment, self-reports	74
Spain (12)	1996	Treatment	59	1996	Treatment	83
Sweden	1997	Study 9 prisons, saliva (13)	55	1994	Stockholm: Study prison/treatment (14)	(92)
United Kingdom	1996	Unlinked Anonymous, England and Wales (15)	22	1994	Survey treatment centres (16)	48-77

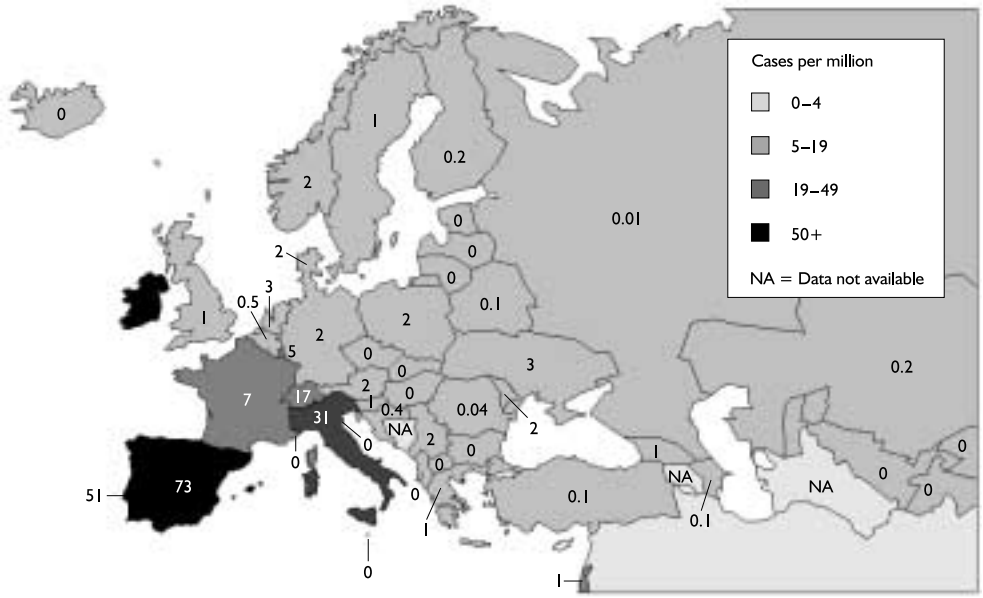
Hepatitis B antibodies partly reflect ever being infected with HBV and partly vaccination; the proportion of seronegative IDUs indicates the population at risk or the potential for vaccination. Information based on local data is given between parentheses. Self-reports on hepatitis infection may be unreliable.

1) Austria National Focal Point 1998b
2) Denmark National Focal Point 1997
3) Finland National Focal Point 1998
4) France National Focal Point
5) Germany National Focal Point 1998 (Bätz and Reymann 1997)
6) n=140 tested, Greece National Focal Point 1998 (Center for Control of AIDS and STDs of the Ministry of Health 1998)
7) n=272 tested (Smyth et al.)
8) n=66,623 tested; Italy National Focal Point 1998
9) Luxembourg National Focal Point 1998
10) Netherlands National Focal Point 1998
11) Portugal National Focal Point 1998
12) (Only heroin IDUs) National Plan on Drugs: Survey of Heroin Users in Treatment, 1996
13) Sweden National Focal Point 1998 (Käll and Thorstensson 1998)
14) Sweden National Focal Point 1998 (Krook et al. 1997)
15) Public Health Laboratory Service 1998
16) n=2,081; test results reported by treatment centres in the survey (Waller and Holmes 1995)

Table 3. Harm reduction measures in EU member states, as described in the 1997 national reports provided by the Focal Points in the EMCDDA/Reitox network

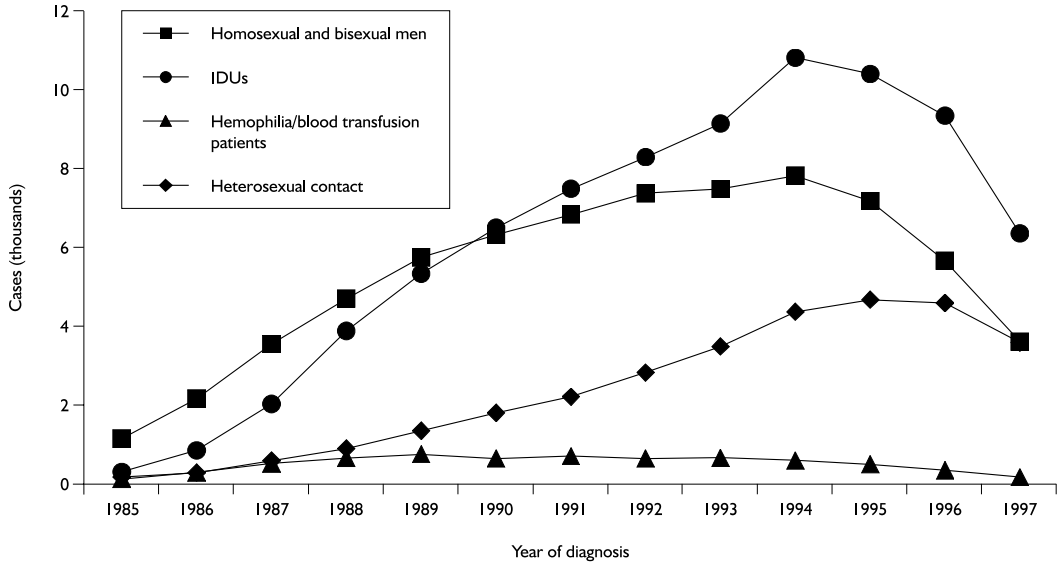
	Syringe exchange programs	Syringes available in pharmacies	Distribution of condoms	HIV counseling and testing	National coverage	Implemented since
Austria	Many, low threshold	Yes, nationally	Low threshold	Low threshold	Yes	1990's
Belgium	Some	?	?	NGOs?	No	?
Denmark	Yes	Yes	Yes	Yes	Yes	?
Finland	Rare	Recently stopped	?	?	No	?
France	51	Yes	Yes	Yes?	Yes	Recent
Germany	Most cities	Yes, free	Low threshold	Yes	?	?
Greece	Yes	Yes	Yes	Yes?	Yes	?
Ireland	Yes	?	Yes	Yes	Yes	?
Italy	Some regions, mostly machines	?	Some regions	Yes	No	Recent
Luxembourg	Yes	Yes	Yes	Yes	Yes	1993
Netherlands	Yes	Yes	Yes	Yes	Yes	1984-1987
Portugal	Yes	Yes	Yes	Yes	Yes	1993
Spain	Yes	Yes	Yes	Yes	Yes	Recent
Sweden	n=2	No	?	Yes	No	1986
United Kingdom	Yes, n=300	Yes, n=2000	Yes	Yes	Yes	1980s

Figure 1. AIDS cases diagnosed in injection drug users in 1997 per million total population (WHO European Region)



Source: CESES, Saint-Maurice, France
Data reported to 30/06/98, adjusted for reporting delays

Figure 2. Adult and adolescent AIDS cases by transmission group and year of diagnosis (WHO European Region)*



Source: CESES, Saint-Maurice, France
Data reported to 30/06/98 (n=204,065)
*Adjusted for reporting delays (1995–1997)

Figure 3. Yearly AIDS incidence per 100,000 persons in 5-year birth cohorts 1950–1974, injection drug users, 12 European countries 1978–1994, adjusted for reporting delay (Houweling et al., in press)

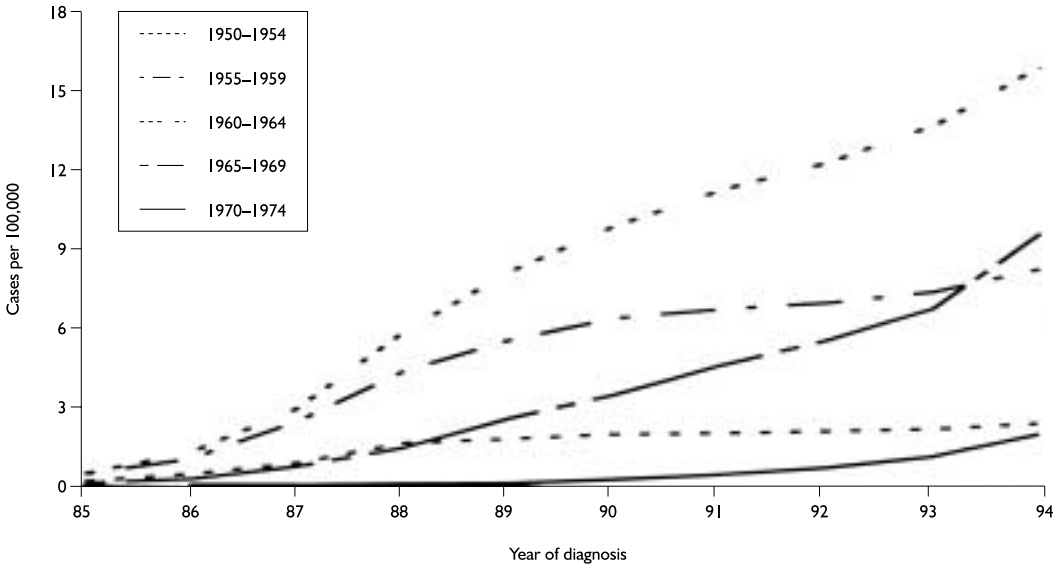
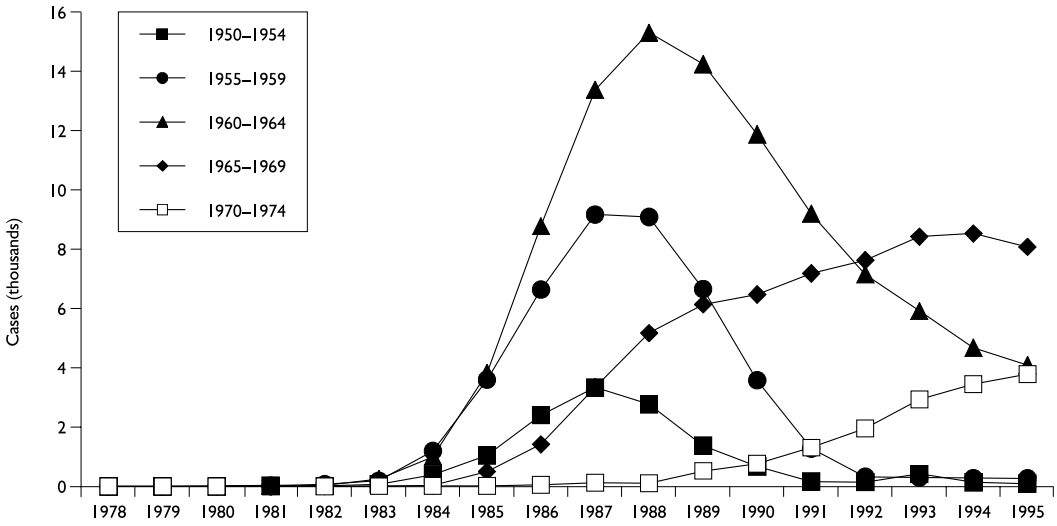
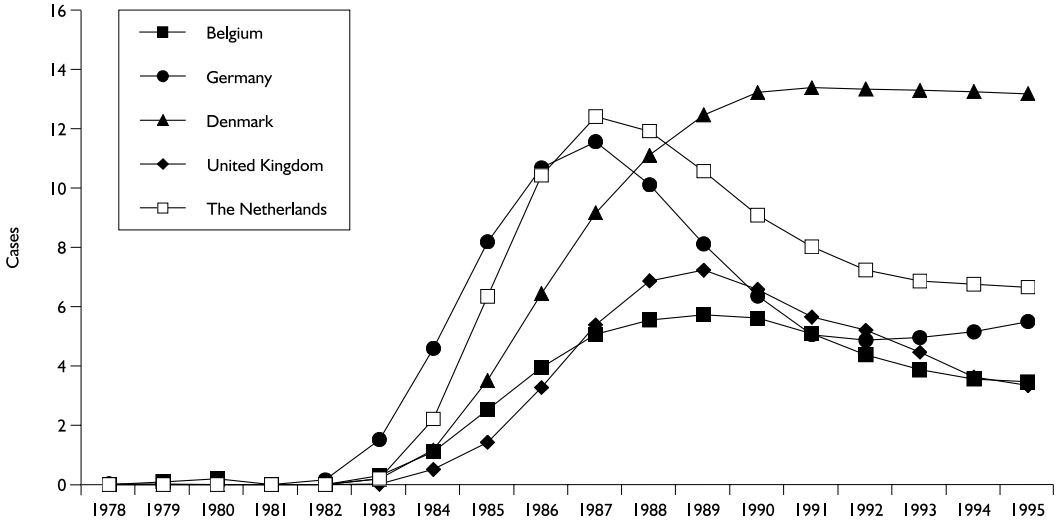


Figure 4. HIV incidence in injection drug users in the European Union, back-calculation estimates by birth cohort



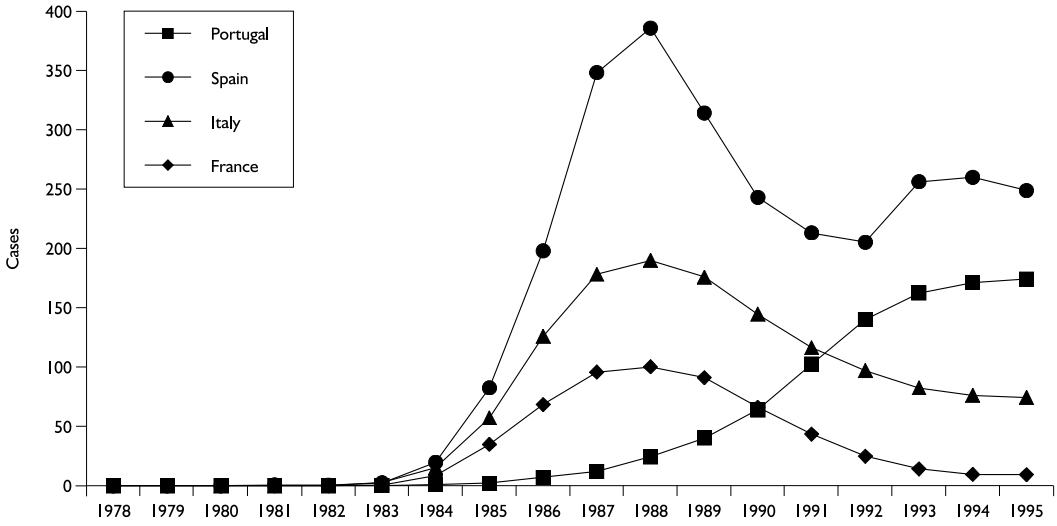
Source: Jager and Ruitenberg 1997

Figure 5a. Yearly HIV incidence in injection drug users per million population, back-calculation estimates by country



Source: Jager and Ruitenberg 1997

Figure 5b. Yearly HIV incidence in injection drug users per million population, back-calculation estimates by country



Source: Jager and Ruitenberg 1997

Appendix F

Jager JC*, Achterberg PW, Wiessing L***, Hartnoll R***, Postma MJ*: Infectious diseases and drug abuse: conceptual modelling of consequences and interventions. Poster presentation. European Conference Perspectives on Infectious Disease Research, Dresden, February 1-3, 1999**

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Background

The drugs problem and its consequences for society represent a complicated research field. The consequences of drug abuse comprise among many others the adverse effects of infectious diseases. Measuring their impact and simulating potential (cost-) effectiveness of policies and interventions are required to support public health strategy development. A conceptual (theoretical) model will help

- to provide a structure for the development of ideas and mathematical models,
- to define the boundaries of the field under study,
- to offer a structure for orderly handling the subject matter i.e. the classification of data sources, key variables and impact indicators, the ordering of research questions and research projects (cf: Jager & Ruitenberg, 1997; Ruwaard & Kramers, 1997).

Thus, a conceptual model can be a bridge between the various actors and representatives of the different disciplines involved in an integrated study of the impact of infectious diseases on populations of drug users.

Objective

To develop a conceptual model for the drugs issue and the interrelationship with infectious diseases.

Conceptual model

A conceptual model is proposed which departs from five basic components, i.e. drug use, policy related to drug use, determinants of drug use and effects, individual effects of drug use and the social burden of drug use (see Figure 1).

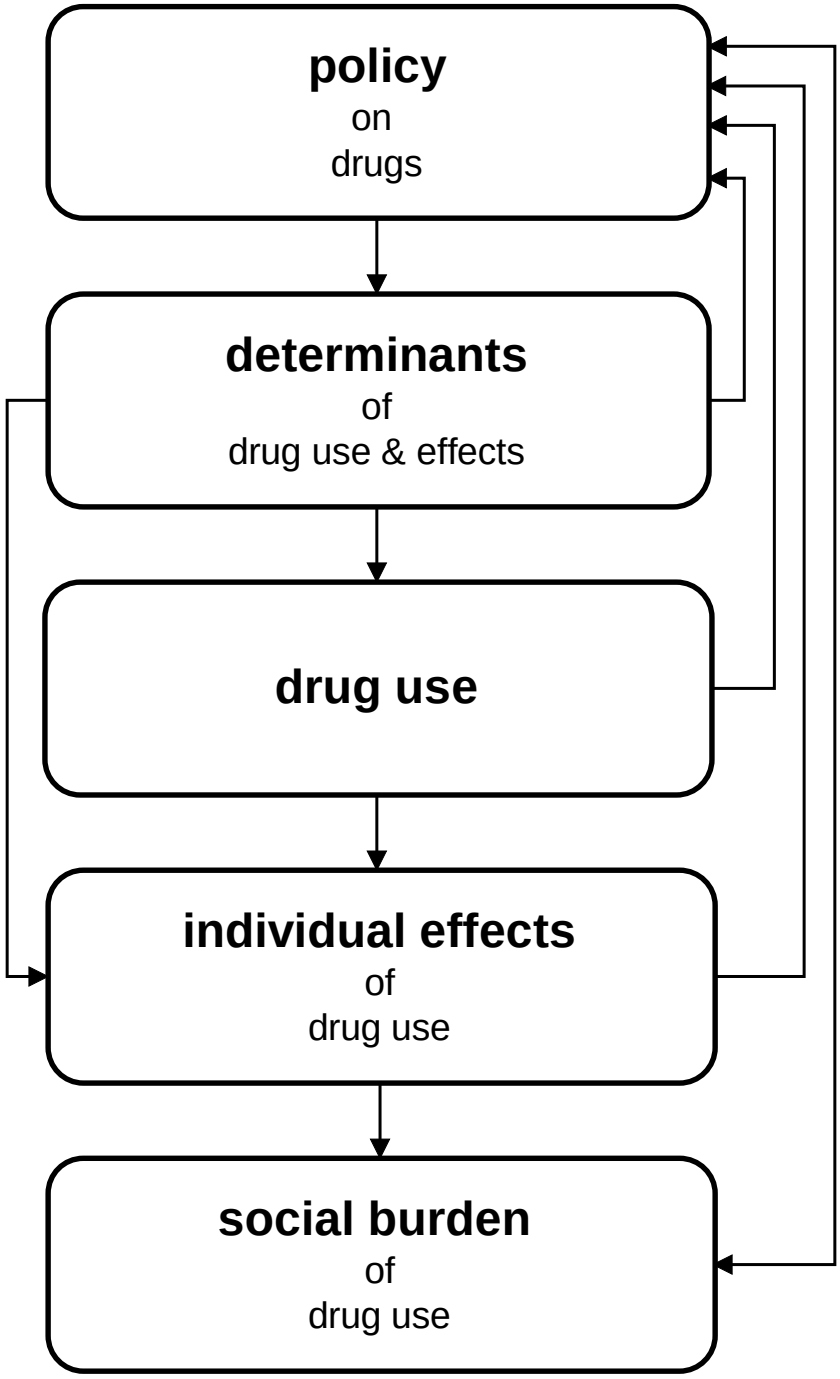

Figure 1. Conceptual Basic Model for the Drugs Problem

The components shown in Figure 1 are detailed into subcomponents (second detail level) and placed in a scheme that shows the main interrelations (see Figure 2).

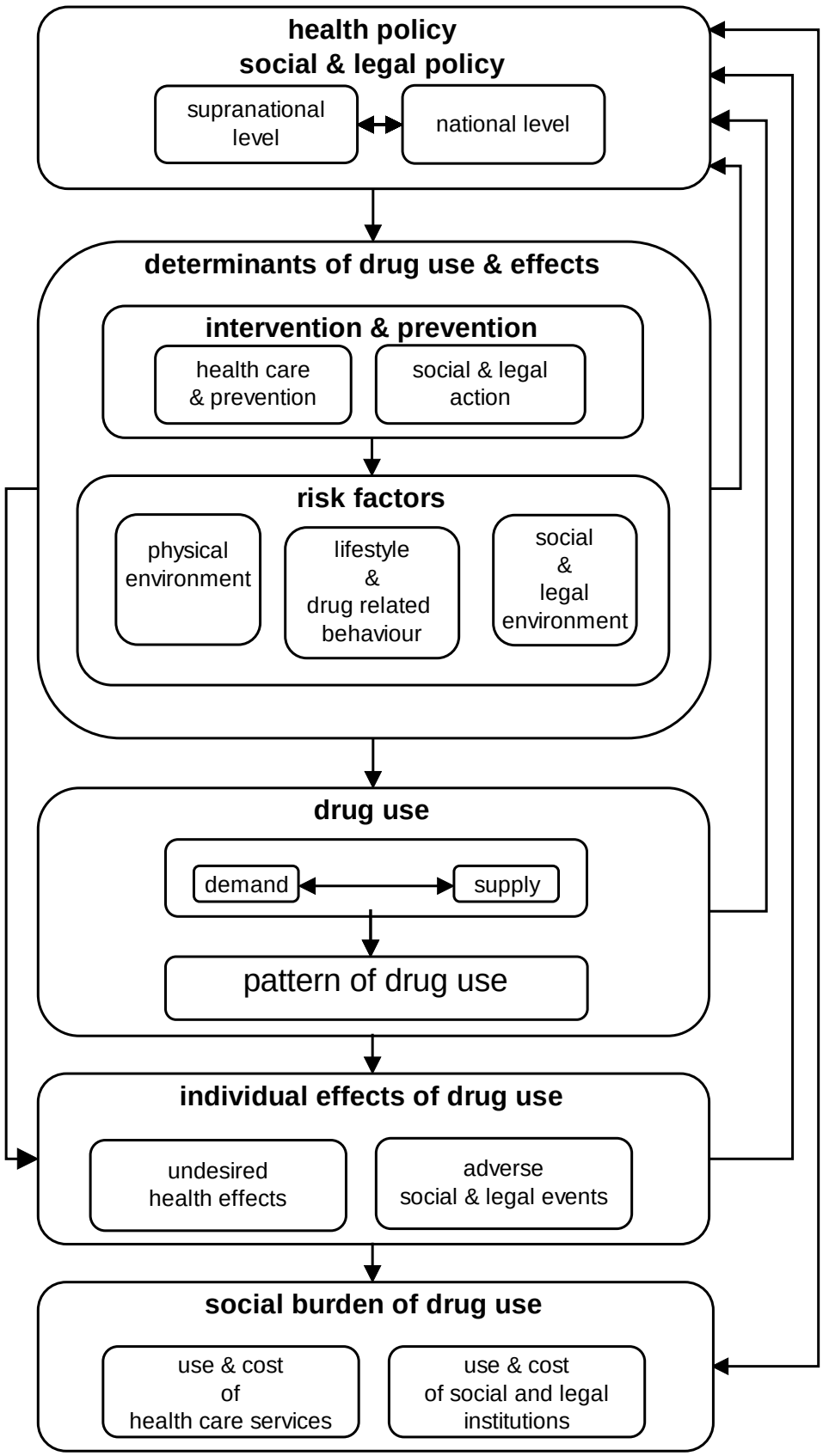

Figure 2. Conceptual Model for the Drugs Problem and Inherent Public Health, Social and Legal Issues (see Table 1 for some further detail)

The policy box comprises supranational and national policies concerning health and social and legal policies, which try to affect the determinants of drug use and effects.

The second box concerns the determinants of drug use -e.g. life style and the social environment- and the determinants of effects of drug use on health and social events -e.g. attraction of infectious diseases-. There is a division between the interventions in health care or prevention and in the social or legal fields and the risk factors. This is clearly a complex box where each area can be further broken down into different aspects containing numerous potential interactions.

The central box represents the core of the drugs problem, i.e. drug use. The model expresses that drug use is defined by determinants. It also shows that drug use plays a role in giving direction to policies on drugs (see relevant arrow).

The boxes below the box for drug use deal with individual (adverse) effects (fourth box) and social burden of drug use (fifth box).

The conceptual model is elaborated and completed with concrete examples of interrelated issues in terms of policies and interventions, undesired health effects, adverse social and legal events and use and costs of health care services and social and legal institutions (see Table 1).

Table 1. Components for Conceptual Modelling the Drugs Problem and Inherent Public Health, Social and Legal Issues

- **Health policy**
- **Social & legal policy**
  - National level
    - National drug laws (legal vs illegal drugs)
    - Drug specific strategies
    - Research (focal points/EMCDDA)
  - Supranational level
    - United Nations Conventions
    - Treaty of European Union 1993
    - European Action plan on Drugs (EC)
    - Co-ordination of research activities (EMCDDA)
- **Determinants of drug use and effects**
  - Intervention & prevention
    - Health care & prevention
      - Health care (somatic and mental care)
        - Substitute prescribing (methadon)
        - Detoxification
        - Out/inpatient treatment
        - Counselling
      - Prevention
        - Health protection
          - Syringe & needle exchange
        - Disease prevention
          - Vaccination
          - Screening for drug related diseases
        - Health promotion
          - Education (safe sex/needle hygiene)
    - Social and legal action
      - Social intervention
        - Demand reduction activities
        - Rehabilitation of drug users
        - Targeted programmes/mass media campaigns
      - Legal intervention
        - Law enforcement
        - Supply reduction
        - Prohibiting & punishing possession, arrests and drug seizure
        - Control of trade
  - Risk factors
    - Physical environment
      - Exogenous (biotic, physical, chemical) factors
        - Biological agents like HIV, HBV, HCV, *M. tuberculosis*
        - Quality of drugs
      - Endogenous factors (acted on by exogenous factors)
        - Genetic factors
      - Life style & drug related behaviour
        - Needle sharing
        - Sexual; behaviour/prostitution
        - Alcohol
        - Lack of hygiene/dental care

Table (continued)

		Social & legal environment	
			Mobility/immigration/ethnicity
			Social profiles of users
			Subpopulations like schoolchildren students and intellectual circles
			Geographic patterns/urbanizations
			Attitudes/public opinion
			Criminal justice systems
Drug use			
	Demand & supply		
		Demand	
			Demographic developments
		Supply	
			Macroeconomic developments
			Technological developments
			Geopolitics/geographical patterns of drug supply
			Control of trade
	Pattern of drug use		
		Type (qualitative aspects) of use	
			Kind of drug
			Hard vs soft drug use
			Route of administration (by mouth, smoking, injecting, sniffed)
		Quantity of drug use	
			Frequency of drug use
			Prevalence/incidence of drug use
			Drugs career
Individual effects of drug use			
	Undesired health effects		
		Drug addiction	
			Drug careers, dependence and poly drug dependence
		Drug related diseases and conditions	
			Infectious diseases: AIDS, Hepatitis B and C, endocarditis, Tuberculosis
			Neurologic/psychiatric disorders
			Comorbidity
		Drugs related mortality	
			Drug related diseases, overdose, accidents, suicides
	Adverse social & legal events		
			Drugs related crime (public safety)
			Social disapproval
Social burden of drug use			
	Use & cost of health care services		
			People needing/seeking help
			Hospital beds
			Patient related and general program costs
			Lost productivity
			Unemployment
			Potential years of life lost
	Use & cost of social and legal institutions		
			Drug offences
			Drug seizures
			Prison use

Perspective

The authors feel that, analogous to earlier work in the area of AIDS-related policy research (cf: Jager & Ruitenberg, 1997) conceptual modelling may be effectively used to order current ideas, research questions, available data and data needs. It also supports necessary interdisciplinary Cupertino. The present conceptual model for the drugs problem and inherent public health issues might be used as a starting point for a discussion about the set-up of a multinational and interdisciplinary concerted action investigating the impact of infectious diseases in populations of drug users. Some focusing will be necessary to reduce the inherent complexity of the problems involved.

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Appendix G
Wien Limburg: References on impact and costs of HCV in Intravenous Drug Users; a literature review (see section 4)

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