The contribution of injection drug use to hepatitis C virus transmission globally, regionally, and at country level: a modelling study

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Summary

Background **WHO aims to eliminate the hepatitis C virus (HCV) as a public health threat by 2030. Injection drug use is an important risk factor for HCV transmission, but its contribution to country-level and global epidemics is unknown. We estimated the contribution of injection drug use to risk for HCV epidemics globally, regionally, and at country level.**

Methods **We developed a dynamic deterministic HCV transmission model to simulate country-level HCV epidemics among people who inject drugs and the general population. Each country's model was calibrated using country-specific data from UN datasets and systematic reviews on the prevalence of HCV and injection drug use. The population attributable fraction of HCV transmission associated with injection drug use was estimated—defined here as the percentage of HCV infections prevented if additional HCV transmission due to injection drug use was removed between 2018 and 2030.**

Findings **The model included 88 countries (85% of the global population). The model predicted 0·23% (95% credibility interval [CrI] 0·16–0·31) of the global population were injection drug users in 2017, and 8% (5–12) of prevalent HCV infections were among people who currently inject drugs. Globally, if the increased risk for HCV transmission among people who inject drugs was removed, an estimated 43% (95% CrI 25–67) of incident HCV infections would be prevented from 2018 to 2030, varying regionally. This population attributable fraction was higher in high-income countries (79%, 95% CrI 57–97) than in countries of low and middle income (38%, 24–64) and was associated with the percentage of a country's prevalent HCV infections that are among people who inject drugs.**

Interpretation **Unsafe injecting practices among people who inject drugs contribute substantially to incident HCV infections globally. Any intervention that can reduce HCV transmission among people who inject drugs will have a pronounced effect on country-level incidence of HCV.**

Funding None.

Introduction

Hepatitis C virus (HCV) is a blood-borne virus that causes substantial morbidity.[1] Globally, it is estimated that more than 70 million individuals are chronically infected with HCV, with around 400 000 HCV-related deaths occurring annually.[1,2] WHO has set ambitious targets to eliminate HCV as a public health threat by 2030,[3] which entail reducing incident infections by 80% from their 2015 levels and reducing HCV-related mortality by 65%. Injection drug use is an important risk factor for the transmission of blood-borne viruses, due to sharing of used needles and injecting equipment.[4] Although HCV prevalence among people who inject drugs is generally high (>30%), the prevalence of injection drug use in most countries is low (<1% of adults).[4] It is therefore generally assumed that injection drug use is usually only an important contributor to HCV transmission in low-prevalence settings, mainly high-income countries in Europe, Australasia, and North America.[5] Conversely, the role of injection drug use in countries of low and middle income, some of which have higher HCV prevalence than high-income countries,[2] is thought to be small.[6] In these settings, it is assumed that transmission is driven by other risk factors, such as unsterile medical injections, other medical procedures, unscreened blood transfusions, and community risks (eg, barbering, tattooing, and body piercing).[5–7]

In two analyses, researchers attempted to quantify the role of injection drug use in the transmission and disease burden of HCV.[8,9] These estimated two very distinct measures: the proportion of global prevalent HCV infections that are among people who have recently injected drugs (around 8·5%);[8] and the proportion of the global HCV morbidity burden attributable to injection drug use (roughly 39%).[9] Neither study measured full and future HCV transmissions resulting from injection drug use, and neither accounted for current or former injection drug users who were infected because of

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Research in context

Evidence before this study

We searched PubMed for published literature on the burden of the hepatitis C virus (HCV) epidemic attributable to injection drug use, with the terms ("IDU" or "PWID" or "IVDU" or "injection drug" or "injecting drug" or "intravenous drug" or "people who inject drugs") AND ("burden" or "PAF" or "population attributable") AND ("HCV" or "hepatitis C"). Four studies were retrieved by our search that have investigated the importance of injection drug use to the HCV burden nationally or globally in terms of infection or disease. In 2016, a modelling analysis estimated that around 39% of the 2013 HCV disease burden in terms of disability-adjusted life-years was associated with injection drug use, whereas a 2018 analysis calculated that 8·5% of prevalent HCV infections globally were among people with recent injection drug use. Nationally, a 2013 study estimated that around 28% of current HCV infections in the Netherlands were associated with injection drug use, whereas a 2018 study estimated that around 34% of the UK's current HCV burden was among people who currently inject drugs.

Added value of this study

Our study is the first to quantify the contribution of injection drug use to overall levels of HCV transmission globally, regionally, and at country level. 88 countries (85% of the global population) were modelled. Our findings indicate the substantial contribution that injection drug use makes to the global HCV epidemic.

Implications of all the available evidence

Globally, if we removed the risk for HCV transmission associated with unsterile needle and syringe sharing among people who currently inject drugs, 43% of incident HCV infections would be prevented between 2018 and 2030. The percentage of incident HCV infections that would be prevented is around twice as high in high-income countries (79%) compared with countries of low or middle income (38%). For many settings, scaling up HCV prevention and treatment interventions for people who inject drugs, including needle and syringe provision and opioid substitution therapy, will be essential to meet WHO 2030 elimination targets.

injection drug use, conferring additional transmission risk through iatrogenic or other routes. Iatrogenic or other transmission can be through routes such as tattooing in prisons,[10] mother-to-child transmission,[11] needlestick injuries to health-care workers,[12] and general access to health care leading to iatrogenic transmission.[13]

Policy makers should plan the most efficient use of resources to prevent and treat HCV infections in response to WHO's 2030 elimination targets.[3] For this objective, it is important to understand the future role of injection drug use in HCV transmission. To address this knowledge gap, we used country-specific HCV transmission modelling to estimate the contribution of injection drug use to HCV transmission globally, regionally, and at country level. We estimated the proportion of HCV infections that would be prevented from 2018 to 2030 if HCV transmission due to injecting risks were removed.

Methods

Model description

We used a dynamic deterministic HCV transmission model to simulate country-level HCV epidemics among the general population and people who inject drugs, incorporating age distributions, population growth, and HCV progression. We modelled three age groups: children aged 0–14 years, individuals aged 15–34 years, and adults aged 35 years or older. The 15–34 years age group was selected to approximate the age range at which individuals start injecting, using information from Degenhardt and colleagues.[4] We stratified adults (aged 15 years or older) into individuals who had never injected drugs, people who inject drugs (defined as people who currently inject drugs), and people who previously injected drugs (figure 1). Only individuals aged 15–34 years were assumed to initiate injecting. All people who inject drugs ceased to inject at a fixed rate to become people who previously injected drugs.

Most individuals enter the model susceptible to infection. HCV transmission occurs because of injection drug use among people who inject drugs or otherwise from risk factors representing medical and community risk factors for all people. Mother-to-child transmission of HCV results in some individuals entering the model chronically infected, which occurs at a rate dependent on the number of HCV-infected women of childbearing age (modelled as people aged 15–34 years) and their HIV co-infection prevalence.[14] Once infected, individuals either spontaneously clear their infection and become susceptible again or develop lifelong chronic infection. Those people who are chronically infected progress through different HCV-related disease stages (chronic, compensated, and decompensated cirrhosis). Individuals with decompensated cirrhosis have increased HCV-related mortality.

Modelled HCV treatment occurs at historical rates that are carried forward from 2017. A proportion of patients treated achieve a sustained virological response and become susceptible to re-infection, which occurs at the same rate as primary infection. In the remaining patients, chronic infection persists. After successful treatment, no further disease progression occurs if individuals had chronic infection.[15] Continued slower progression occurs among those with cirrhosis.[15] All individuals die at age-specific death rates. People who currently inject drugs are at increased risk of drug-related mortality.[16] The appendix (pp 3–7, 18) provides further details of the model.

See Online for appendix

Defining model parameters

Country-specific data from recent systematic reviews[2,4] and UN datasets were used to set parameters for and calibrate the model, including data for the prevalence of HCV among people who inject drugs and the general population, estimates for the proportion of people who inject drugs in the population, and data for population growth rates and age distributions. The appendix gives details of data sources (p 10) and estimates for country-level HCV prevalence and the proportion of people who inject drugs in the population (pp 39–42). We took most estimates of people who inject drugs in the population from the study by Degenhardt and colleagues,[4] which stated that they preferentially selected population size and HCV prevalence estimates that defined current injectors as individuals who have injected drugs in the previous 12 months. However, other estimates using alternative definitions (eg, injecting in the past 6 months) were still included in the systematic review in the absence of the preferred definition. For country-level HCV prevalence estimates, HCV antibody prevalence data were taken from systematic reviews,[2,4] and we adjusted these estimates using region-specific viraemic rates to estimate the prevalence of chronic infection in the survey year.[17] Historical treatment numbers were taken from various sources, which are described in the appendix (pp 32–36). All key parameters had uncertainty associated with them, with bounds generally obtained directly from studies. When bounds were unavailable for prevalence inputs, uncertainty bounds (±33%) were applied, which equate to the median level of uncertainty for those parameters that did have bounds. We did this step to avoid ascribing too much certainty to those estimates with no uncertainty bounds. Parameter estimates and country-level data are provided in the appendix (pp 6, 7, 21, 24–26).

Model calibration

The model was calibrated to 88 countries, including 85% of the global population, 92% of the population of high-income countries, and 83% of the population of countries of low and middle income. Only 43% of the population in sub-Saharan Africa was covered by the model, 62% in the Middle East and north Africa, and 64% in Latin America, whereas 95% or more of the population in remaining global regions was modelled.

A four-step calibration method using different sub-models was used to calibrate the overall model for each country, from 1990 onwards. For each step, we randomly sampled various model parameters and calibration data from their uncertainty bounds, then we estimated other unknown model parameters through calibrating specific submodels using the non-linear least-squares fitting function in Matlab version R2018a. This process of calibration builds on previous work by us,[18,19] using methods similar to those used by others.[20,21] Samples were generated until 1000 full model fits were obtained for each country. Runs were rejected if they could not fit the calibration data within the uncertainty bounds (±33%), thereby allowing the same level of uncertainty as for the model parameters. To ensure the quality of the calibration, resulting fits were checked and compared with target values, with the average error being in general less than 0·0001%.

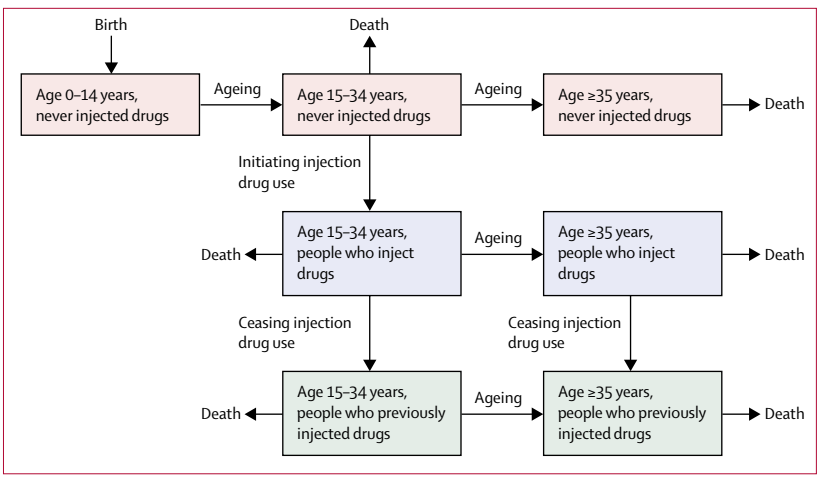

Figure 1: **Model schematic showing population ageing and progression through stages of injection drug use**

The first stage of the calibration process fit a population growth submodel (submodel 1) to calculate country-specific population growth rates between 1990 and 2015, fitting to population sizes in 2015. In the second stage, the model was adapted to include age demographics (submodel 2) to estimate age-specific death rates in 2015. These death rates were estimated by fitting submodel 2 to data for the proportion of the population in age groups 0–14 years, 15–34 years, and 35 years or older. For the third stage, this model was further adapted to include injection drug use (submodel 3). The rates that young adults initiate injection drug use was estimated by fitting submodel 3 to the country's proportion of people who inject drugs among adults. Lastly, the model was extended to include HCV infection (submodel 4). Submodel 4 was the full model. Sampled and fitted parameters from the previous submodels were used in the full model to estimate HCV transmission rates for injection drug use and the general population. We did this by fitting the full model to available chronic prevalence estimates among people who inject drugs and the general population for a specific year for each country (submodel 4). The calibration methods are described fully in the appendix (pp 8–17).

In view of improved blood bank screening[22] and a reduction in the re-use of medical syringes[23] over recent years, the HCV epidemics for each country were assumed to be in slow decline (about 1% annually), consistent with findings of a review.[2] This assumption was calibrated by seeding the initial epidemic in 1990 at a prevalence that was higher than the available survey estimate that was being calibrated to, but with considerable uncertainty (no decrease to 150% of this decrease). The HCV prevalence

among people who inject drugs was assumed to be stable between 1990 and the year of the survey estimate for all countries, because of evidence from a systematic review.[4] The proportion of adults in the population who inject drugs was also assumed to be stable between 1990 and the year of the estimate, except for in sub-Saharan African and eastern European countries, where we assumed increases (from 1990 onwards) in injection drug use, as suggested by available data.[24,25] The rationale underlying these assumptions are discussed in detail in the appendix (pp 19–23) and tested in various sensitivity analyses.

Model analyses

The calibrated models for each country were used to project the HCV epidemic for 12 years up to 2030, defined as the baseline projections for each country. To investigate the degree to which HCV transmission is driven by risks associated with injection drug use, the population attributable fraction (PAF) of HCV transmission (incidence) associated with injection drug use in each country, regionally, and globally, was estimated. To do this, the baseline model fits for each country were re-run with the transmission risk associated with injection drug use set to zero from 2018 onwards. For each paired parameter set, the PAF was estimated over 1 year and over 12 years as the relative reduction in the overall number of HCV infections over that period from setting the transmission risk associated with injection drug use to zero (from 2018), compared with the baseline projections. The projections for all paired parameter sets from each country were averaged to produce country-specific estimates, which were then combined to produce regional and global estimates with the average PAFs for each country weighted by that country's relative burden of HCV compared with the regional or global burden. The variation across the different model fits for each country were used to produce 95% credibility intervals (95% CrI).

Sensitivity analyses investigated the effect on PAF estimates of several scenarios: general population HCV prevalence being stable rather than declining from 1990; HCV prevalence among people who inject drugs decreasing at the same rate as HCV prevalence for the general population rather than being stable; the proportion of adults in the population who inject drugs in 1990 being stable in eastern Europe and sub-Saharan Africa rather than increasing; the same annual HCV treatment numbers but with half the treatment rate among people who inject drugs and double the treatment rate among people with cirrhosis; the rate of initiating injection drug use in the USA increasing 2·9-fold from 2010 onwards to capture the recent opioid epidemic;[26] varying temporal changes in HCV prevalence in the general population by region; and treating all infected people who inject drugs in 2018 and removing the additional transmission rate among people who inject drugs.

We used generalised linear regression models to ascertain the country-level factors associated with the PAF of HCV transmission associated with injection drug use. The 12-year PAF was logit-transformed (log[PAF / 1 – PAF]) because it is a proportion and was regressed on the covariables for the percentage of the adult population who inject drugs, HCV prevalence among people who inject drugs, HCV prevalence among the general population, the injecting duration of people who inject drugs in the country, the percentage of the country's prevalent infections that are among people who inject drugs, and the World Bank Gross National Income (GNI) per person (which could possibly act as a confounder for the amount of spending on a country's health-care system)—all from 2017. The non-linear association between the PAF of HCV transmission associated with injection drug use and the percentage of the country's prevalent infections that are among people who inject drugs was plotted using a fractional polynomial model.

Role of the funding source

No direct funding was received for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The model was successfully calibrated for 88 countries. For the countries simulated, the model predicted that, in 2017, 0·23% (95% CrI 0·16–0·31) of the global population were people who inject drugs, and 8% (5–12) of all HCV infections were among people who currently inject drugs.

Table 1 and figure 2 show global and regional estimates of the PAF of HCV transmission associated with injection drug use, with 12-year country-level PAFs shown in figure 3 and figure 4 (appendix pp 39–42). Globally, the model estimated 43% (95% CrI 25–67) of all new HCV infections could be prevented over 12 years (2018–30) if the heightened HCV risk associated with injection drug use was removed, varying from 14% (2–43) in sub-Saharan Africa to 96% (69–99) in eastern Europe. The 12-year PAF of HCV transmission associated with injection drug use was more than 50% for five other global regions—Australasia, east and southeast Asia, Latin America, North America, and western Europe—whereas it was less than 50% for central Asia, the Middle East and north Africa, and south Asia. The contribution of injection drug use to HCV transmission was greatest in high-income countries, where 79% (95% CrI 57–97) of new HCV infections could be prevented if the transmission risk associated with injection drug use was removed, compared with 38% (24–64) in countries of low and middle income. Compared with the 12-year global PAF, the 1-year global PAF for HCV transmission associated with injection drug use (2018–19) was slightly lower (39%, 95% CrI 21–64).

The appendix (pp 43–46) presents results of various sensitivity analyses, with the most important changes

	Fitted demographic data values			Prevalent infections among PWID (%, 95% CrI)	PAF of HCV infections associated with IDU	
	Adults who are PWID (%, 95% CrI)	Chronic HCV prevalence among PWID (%, 95% CrI)	Chronic HCV prevalence among the general population (%, 95% CrI)		2018–19 (1-year PAF)	2018–30 (12-year PAF)
Global	0·32% (0·23–0·42)	34·5% (25·8–42·0)	1·0% (0·7–1·4)	8% (5–12)	39% (21–64)	43% (25–67)
Central Asia	0·61% (0·44–0·81)	26·4% (21–29·8)	2·4% (1·5–3·3)	4% (3–6)	32% (16–69)	37% (19–73)
Eastern Europe	1·13% (0·71–1·61)	45·8% (34·0–53·6)	2·0% (1·2–2·6)	21% (12–31)	95% (64–99)	96% (69–99)
Australasia	0·60% (0·46–0·73)	35·7% (32·0–39·3)	0·8% (0·7–1·1)	19% (13–24)	58% (34–94)	66% (43–96)
East and southeast Asia	0·23% (0·19–0·28)	31·5% (23·8–38·2)	0·7% (0·5–1·0)	7% (5–10)	53% (26–98)	58% (32–98)
South Asia	0·09% (0·07–0·11)	30·3% (16·2–44·0)	0·9% (0·6–1·3)	2% (1–3)	10% (3–25)	14% (4–31)
North America	1·08% (0·63–1·51)	30·7% (22·2–40·7)	0·9% (0·6–1·2)	30% (16–47)	67% (43–100)	77% (56–100)
Western Europe	0·32% (0·23–0·40)	37·9% (27·3–44·7)	0·6% (0·3–1·0)	15% (10–20)	80% (45–93)	83% (53–94)
Sub-Saharan Africa	0·40% (0·26–0·55)	14·2% (10·5–17·7)	1·4% (0·9–2·2)	3% (1–4)	11% (2–39)	14% (2–43)
Latin America	0·44% (0·35–0·53)	49·7% (44·1–52·8)	0·8% (0·7–1·0)	18% (14–23)	66% (41–98)	71% (49–98)
Middle East and north Africa	0·24% (0·17–0·30)	31·7% (23·6–36·8)	2·5% (2·0–3·1)	2% (1–3)	13% (6–25)	16% (8–28)

PAF is the percentage of all new HCV infections that would be prevented if the HCV transmission risk associated with IDU was removed over the period. HCV=hepatitis C virus. PAF=population attributable fraction. PWID=people who inject drugs. IDU=injection drug use. 95% CrI=95% credibility interval.

Table 1: **Global and regional averaged fitted HCV prevalence estimates in 2017, model projections of the PAF of HCV transmission associated with injection drug use, and the percentage of prevalent infections in 2017 among people who inject drugs**

indicating the PAF could be lower (33%, 95% CrI 20–54) if HCV prevalence trends among the general population were assumed to be stable instead of decreasing, or 30% (15–51) if trends varied by region. Sensitivity analyses also showed that the PAF for the USA rose from 77% (95% CrI 56–100) in the baseline model to 85% (62–100) when we assumed an increasing epidemic of injection drug use since 2010. Other sensitivity analyses—in which we separately assumed a decreasing HCV prevalence among people who inject drugs, the population percentage of people who inject drugs in eastern Europe and sub-Saharan Africa was stable from 1990 (rather than increasing), and treatment rates were halved among people who inject drugs and doubled among people with cirrhosis—did not alter the global PAF estimate. The appendix (p 47) shows that the global PAF increased to 46% (95% CrI 26–65) if the heightened burden of HCV among people who inject drugs was also removed, as well as their elevated transmission risk.

Figure 5 shows a strong positive association between the 12-year PAF for each country and the percentage of the country's prevalent infections that are among people who inject drugs. In univariable regression analyses (table 2), the logit-transformed country-level PAF increased linearly with the percentage of a country's prevalent infections that were among people who inject drugs, the country's GNI coefficient, HCV prevalence among people who inject drugs, and the percentage of people who inject drugs in the adult population. In the multivariable model, only the percentage of a country's prevalent infections that were among people who inject drugs was associated with a higher 12-year PAF.

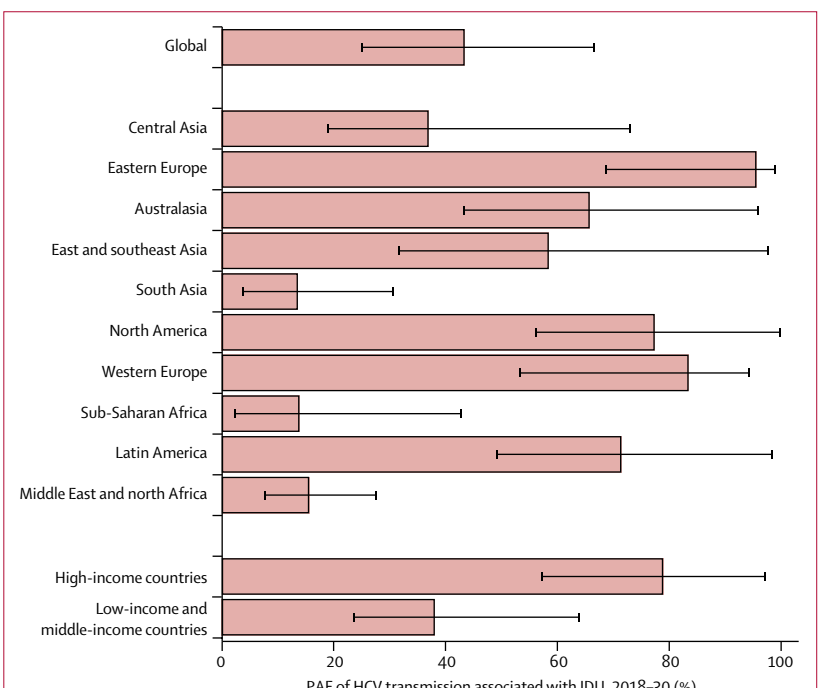

Figure 2: **12-year global and regional estimates of the PAF of HCV transmission associated with injection drug use, 2018–30**

Bars represent the median values and error bars the 95% credibility intervals. PAF=population attributable fraction. HCV=hepatitis C virus. IDU=injection drug use.

Discussion

Despite people who inject drugs comprising less than 0·5% of the global adult population and only contributing

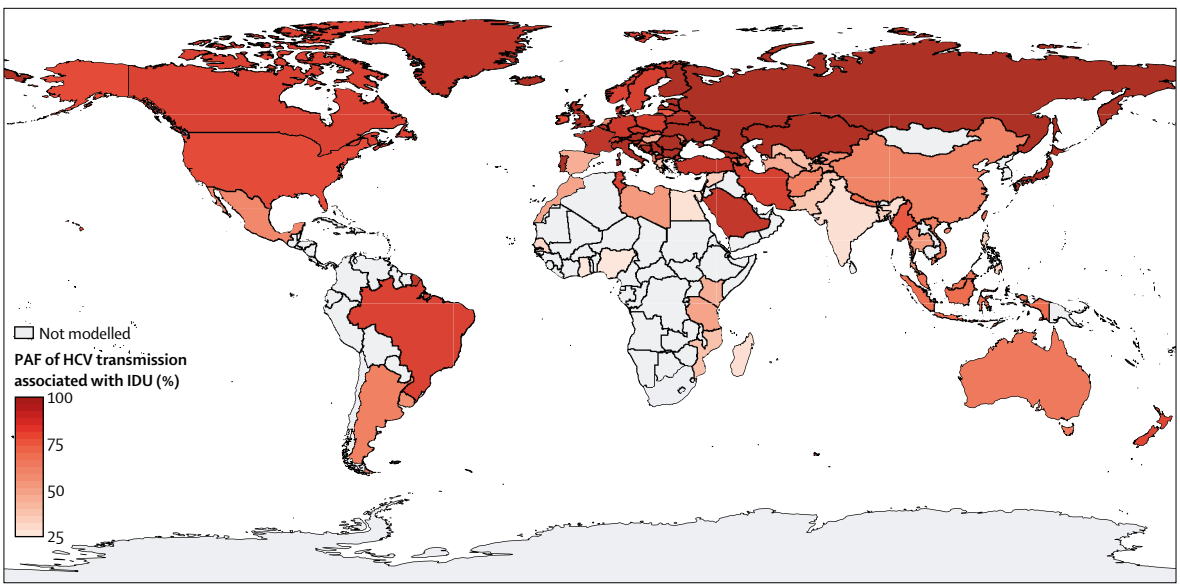

Figure 3: **Map of PAF of HCV transmission associated with injection drug use, 2018–30**
PAF is the percentage of all new HCV infections that would be prevented over the period 2018–30 if the additional HCV transmission risk attributable to IDU was removed. Countries in grey were not modelled because of a paucity of data. PAF=population attributable fraction. HCV=hepatitis C virus. IDU=injection drug use.

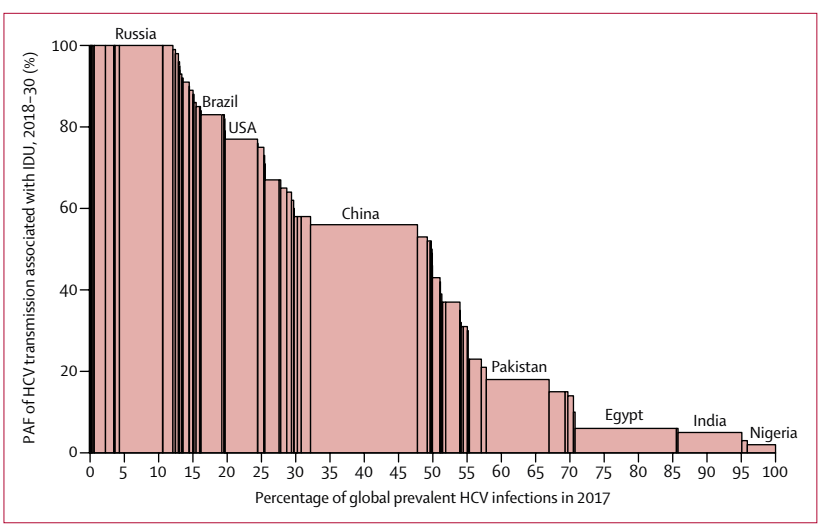

Figure 4: **PAF of HCV transmission associated with injection drug use, 2018–30, versus the percentage of global prevalent HCV infections in 2017, by country**
Countries with the largest chronic HCV burdens in 2017 are labelled. PAF=population attributable fraction. HCV=hepatitis C virus. IDU=injection drug use.

8% of prevalent infections, removing the transmission risk associated with injection drug use could prevent nearly half (43%) of all new HCV infections globally from 2018 to 2030. This reduction varied by country and regions. In sub-Saharan Africa, where the HCV epidemic is thought to be driven by medical transmission,[27] just over a tenth of infections were associated with injection drug use, whereas in eastern Europe, more than nine-tenths of infections were associated with injection drug use. In high-income countries, about twice as many infections (79%) would be prevented from removing the transmission risk associated with injection drug use than in countries of low and middle income (38%). The percentage of a country's prevalent infections that were among people who inject drugs was strongly and positively associated with the PAF, because this value accounts for the size of the population of people who inject drugs and the prevalence of HCV among them. For example, if 5% of the country's prevalent infections were among current injectors then the estimated PAF was 48%, increasing to 70% if 10% of prevalent infections were among people who inject drugs.

To our knowledge, no published report has estimated the future contribution of risk associated with injection drug use to HCV transmission at a global level. Two reports have estimated the current contribution of injection drug use to the global burden of HCV infection or disease,[8,9] but neither accounted for the chain of transmission that can occur in the general population because of individuals infected through injection drug use. Degenhardt and colleagues[9] estimated that 39% of disability-adjusted life-years for HCV in 2013 were associated with injection drug use, consistent with the magnitude of our estimate despite using a very different outcome and methodology. Grebely and colleagues[8] calculated 8·5% of all prevalent HCV infections globally were among people who inject drugs, which is comparable with our estimate of 8% for prevalent infections in 2017 (table 1). Grebely and colleagues' estimate is useful for guiding screening and treatment campaigns but does not address the importance of injection drug use to future HCV transmission. Otherwise, global modelling[2] simulated overall HCV epidemics in different countries but did not dynamically model HCV transmission or the role of injection drug use. Our results

seem to broadly agree with national estimates of the burden of HCV associated with injecting risks in the Netherlands and the UK,[28,29] with these analyses suggesting that 28% of current infections in the Netherlands are associated with injection drug use,[28] which is within the credibility interval of our estimate, and 34% of the UK's current HCV burden is among people who inject drugs,[29] which is very similar to our projections.

A strength of our modelling is that it is comprehensive in coverage: the analysis used data from HCV epidemics in 88 countries, comprising 85% of the world's population. We accounted for the role of heightened risk among people who inject drugs in these HCV epidemics, and we incorporated country-level demographic information, population growth, and vertical transmission. We also accounted for all incident infections that result from individuals infected with HCV because of injection drug use and the effect these incident infections have on HCV incidence and prevalence in the general population. This process enabled us to more accurately estimate the role that injection drug use has on the overall HCV epidemics in each country. Despite this strength, our analysis has limitations.

Data for the prevalence of injection drug use and the prevalence of HCV among people who inject drugs and the general population were variable in quality, possibly affecting our results. Data among people who inject drugs can vary in quality partly because of the illicit nature of injection drug use, which makes people who inject drugs a difficult population to study and to enumerate accurately. Data for the prevalence of injection drug use and the prevalence of HCV came from existing systematic reviews, and we modelled all countries that had an estimate for each. Thus, for some data estimates, it was unclear how they were compiled: some were old data and some were uncertain.

Taking data from disparate sources means some country-level PAF estimates could be imprecise. However, it is hard to quantify how this possible inaccuracy affects our results without additional data. Data-quality scores are shown in the appendix (pp 27–31). 46% of countries had a low data-quality score for general population HCV prevalence estimates. Data-quality scores were also low for country estimates of HCV prevalence among people who inject drugs (20%) and for the proportion of people who inject drugs among adults (39%). Although most of these key datapoints scored highly, only 19 countries (32% of the global population) had all three of these key prevalence estimates scored as moderate or better, and 66 countries (76% of the global population) had at least two of these estimates scored as moderate or better. It is possible that PAF projections for the remaining countries will change when better data become available, with improved data being most needed for HCV prevalence in the general population and for size estimates of populations of people who inject drugs. When only considering the 66 countries with better data, the global average PAF increases slightly to 49% (95% CrI 29–73) emphasising that not including projections from countries with low-quality data does not substantially affect our projections.

Some country's PAF estimates were lower than expected, including those for Spain (31%), Greece (23%), and Australia (62%). Previous evidence for these countries has suggested most transmission was among people who inject drugs.[5] This discrepancy could be attributable to data issues or HCV-epidemic factors—eg, historically high levels of injection drug use that have now decreased,

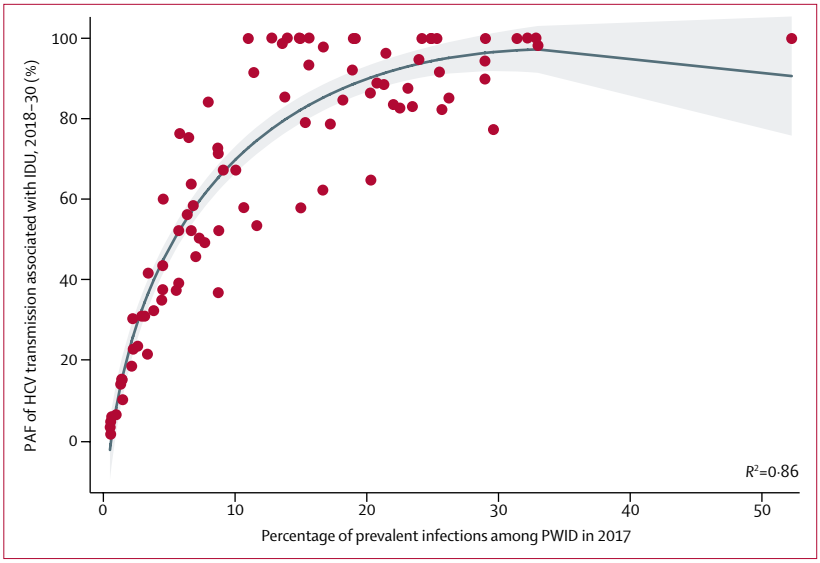

Figure 5: **Association between the PAF of HCV transmission associated with injection drug use, 2018–30, and the percentage of prevalent infections that are among people who inject drugs in 2017, by country**
The line represents the plotted line of best fit. Shaded area shows the 95% CI. Dots denote each country. Model equation is PAF=–0·3149 – (0·0372 × P_PWID) + (0·4376 × P_PWID1/2), where P_PWID is the percentage of the country's prevalent infections that are among people who inject drugs. PAF=population attributable fraction. HCV=hepatitis C virus. IDU=injection drug use. PWID=people who inject drugs.

	Univariable		Multivariable	
	Coefficient (95% CI)	p value	Coefficient (95% CI)	p value
GNI per person (per US$1000)*	0·05 (0·00 to 0·10)	0·039	0·01 (–0·04 to 0·07)	0·64
Population percentage of PWID in adults	2·62 (0·75 to 4·49)	0·0066	1·14 (–1·21 to 3·50)	0·34
HCV prevalence among PWID†	0·09 (0·02 to 0·17)	0·014	0·05 (–0·02 to 0·12)	0·12
HCV prevalence among general population†	–0·29 (–1·34 to 0·75)	0·58	–0·07 (–1·28 to 1·13)	0·903
Injecting duration (years)	0·21 (–0·00 to 0·42)	0·053	–0·22 (–0·46 to 0·02)	0·071
Percentage of the country's prevalent infections that are among PWID	0·26 (0·18 to 0·34)	<0·0001	0·26 (0·13 to 0·38)	<0·0001

All variables are from 2017 except for injecting duration, which is taken from surveys covering various years for each country. Dependent variable is PAF (logit-transformed). PAF is the percentage of all new HCV infections that would be prevented if the HCV transmission risk associated with IDU was removed over the period 2018–30. PAF=population attributable fraction. HCV=hepatitis C virus. IDU=injection drug use. GNI=gross national income. PWID=people who inject drugs. *Syria is missing data for GNI per person. †HCV prevalence measures are proportions, not percentages.

Table 2: **Associations between the 12-year PAF of HCV transmission associated with injection drug use and demographics and epidemic-related variables**

underestimates for the prevalence of people who inject drugs, or possibly high numbers of migrants with higher HCV risk than the background population. Other modelling from the Netherlands has suggested that most HCV infections were among migrants.[28] We did not incorporate migration into our model because of insufficient data and uncertainty around key assumptions such as HCV prevalence.[30] Although not explicitly included, we would consider incoming infections associated with migration as something that contributes to the non-injection drug use transmission aspect of the model, just as we would for medical and community transmission. Similarly, we were unable to include HCV epidemics among men who have sex with men within our model because of a scarcity of information around prevalence globally. However, studies indicate that although transmission among men who have sex with men is much higher than among heterosexual couples, incidence and prevalence is still low compared with people who inject drugs[31] and probably contributes little to the epidemic by comparison.[32]

We did not explicitly model what makes up the non-injection drug use component of HCV transmission, which could be due to factors such as medical injections, tattooing, body piercing, and barbering. Unfortunately, detailed country-level data for these factors were unavailable. Despite these issues, other country-level estimates seem to agree with our model,[28,29] with low PAFs of injection drug use in some high-income countries implying that our global PAF estimate for injection drug use could be conservative. Also, general insights about how the PAF is related to different country-level factors should still hold.

Another limitation of our analysis is that our deterministic models did not capture the network effects of how HCV transmits among people who inject drugs, which has been shown to be important for assessing the effect of interventions for HCV.[33,34] This point was outside the scope of our study; rather our main aim was to ascertain how the observed epidemic among people who inject drugs might contribute to overall levels of transmission in that country.

For almost all countries included, little to no published data are available to ascertain the likely ongoing evolution of each country's HCV epidemic. To counter this, we gathered available evidence on reductions in HCV transmission risks associated with improved blood transfusion safety[22] or reductions in unsafe medical injections,[23] thus assuming the modelled global epidemic was in decline, consistent with previous modelling.[2] However, there is considerable uncertainty in this assumption; therefore, we assumed wide uncertainty bounds and undertook sensitivity analyses in which we either assumed each country's HCV prevalence trends were stable or varied by region, which both projected lower PAFs (about 30–33%). Importantly, country-level HCV epidemic trajectories are highly uncertain, with only three countries having two repeated national surveys, highlighting the need for further data on this topic. Additionally, the systematic reviews used for this analysis, although from 2017, did not contain data from recent years when HCV outbreaks have occurred among people who inject drugs in some countries—notably the USA,[26] where a higher PAF is estimated when this is assumed. The paucity of robust data for HCV prevalence, particularly for the general population, also raises concerns about whether countries will be able to reliably ascertain their progress towards WHO's HCV elimination targets or develop plans to reach them. This dearth highlights the crucial role of good data for policy making. Importantly, one inaccurate datapoint could affect a country's results, implying that careful consideration of the assumptions made is needed before using our results to inform policy in specific countries.

Despite the limitations described above, it is important to note that our study utilises data from 12 reviews, synthesising data from thousands of studies and accounting for the uncertainty in these estimates in our projections. This process will have minimised data issues as far as is currently possible, with our extensive sensitivity analyses showing that the overall finding—that injection drug use is an important contributor to the global HCV epidemic—is robust despite data uncertainties.

To our knowledge, our study is the first to fully quantify the future contribution of injection drug use to the global HCV epidemic. The results show that the increased risks associated with injection drug use account for 43% of global HCV infections over the next 12 years, with this figure being even higher in high-income countries (79%). This information is primarily useful for policy makers who are uncertain about the importance of combating the HCV epidemic among people who inject drugs, particularly for meeting WHO's 2030 elimination targets.[3] Indeed, globally, our results suggest the incidence of HCV in people who inject drugs needs to be reduced by at least half to have any hope of reducing the overall incidence of HCV by 80%. A reduction in incidence can be achieved by reducing prevalence or transmission risks, for example via microelimination initiatives such as scale-up of HCV treatment for people who inject drugs or by prevention interventions[35] such as needle and syringe provision and opioid substitution treatment programmes. Newly synthesised data and modelling have shown that these interventions can strikingly reduce levels of HCV incidence,[26,36] can be cost-effective in various settings,[36,37] and can prevent other blood-borne viruses such as HIV.[38] However, the current coverage of needle and syringe provision and opioid substitution treatment is low in most countries,[39] as is the coverage of direct-acting antiviral treatment,[40] with people who inject drugs being frequently denied treatment.[41] Barriers restricting the coverage of these interventions need to be urgently addressed to achieve WHO's HCV elimination targets.

Contributors
AT developed the final model, which built on preliminary models developed by HF. AT did the analyses and wrote the first draft of the report, with guidance from PV. PV and NKM had the original idea for the study. PV, MTM, HF, AGL, and JGW supervised the analyses. HF, AP, SC, JL, JG, SL, NKM, LD, MH, and PV contributed to data collection. All authors contributed to data interpretation, writing of the report, and approved the final version.

Declaration of interests
JG is a consultant or advisor for and has received research grants from AbbVie, Cepheid, Gilead Sciences, and Merck/MSD, outside of the submitted work. In the past 3 years, LD has received investigator-initiated, untied, educational grants for studies of opioid medications in Australia from Indivior, Mundipharma, and Seqirus, outside of the submitted work. SL has received investigator-initiated, untied, educational grants from Indivior, outside of the submitted work. AP has received investigator-initiated, untied, educational grants from Mundipharma and Seqirus, outside of the submitted work. MH reports personal fees from Gilead, Abbvie, and MSD, outside of the submitted work. PV reports grants from Gilead, outside of the submitted work. HF has received an honorarium from MSD, outside of the submitted work. NKM has received unrestricted research grants and honoraria from Gilead and Merck, outside of the submitted work. AT, AGL, SC, JGW, JL, and MTM declare no competing interests.

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