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Supplementary appendix

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Supplementary material to: 'Methods and indicators to validate country reductions in incidence of hepatitis C virus infection to elimination levels set by the WHO'

Note: This supplementary material is based on a technical working paper prepared for the World Health Organization entitled **Use of modelling to help develop alternative indicators for documenting elimination of HCV incidence**

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1.0 Introduction

In different countries, it is likely that there will be different levels of data availability for determining how a country is progressing towards HCV elimination. Although the gold standard should be to collect empirical incidence data, it is likely that many countries will be unable to directly monitor incidence reductions at the national level. Indeed, more likely than not, incidence data will either be unavailable or limited to localised studies that only focus on specific subgroups and/or have insufficient power to accurately monitor trends.

Although available incidence data will be a crucial part of the story for determining whether a specific country has achieved elimination, it is likely that countries will also have to rely on more indirect data, which can be collected more easily at the national level, for assessing whether a country has achieved the elimination targets set out by WHO. The following types of data have been proposed:

- Trends in HCV prevalence. This is likely to include changes in chronic prevalence (and possibly antibody prevalence), or changes in chronic prevalence amongst those with positive antibody response. This could come from serial surveys amongst the general population or specific subgroups at risk of HCV infection (e.g. PWID, MSM or prisoners) or routine testing in specific sites and among specific groups (drug treatment/harm reduction sites, pregnant women, blood donors, prison/jail entrants or military recruits).

- Trends in intervention provision. This is likely to include changes in HCV treatment uptake with or without parallel changes in the coverage of other prevention interventions. This could just be trends in the numbers that have been treated, overall and preferably in specific groups or those in contact with a specific intervention, or possibly some form of treatment and prevention cascade which can then be used to better understand the coverage of interventions, including what proportion of infections have been treated, and in what ways people are being lost to care. Ideally, the number of people treated for HCV would also be expressed as a rate within specific risk groups. Similarly, other intervention data could also be numbers in recent contact with an intervention (e.g. number of PWID in recent contact with needle or syringe programs (NSP)), or preferably trends in the coverage (% of PWID in recent contact with NSP) of interventions.

Unfortunately, it is not possible to directly use either of these data measures to determine if a country has reached the WHO elimination target for decreasing incidence; this can only be ascertained by using modelling to translate observed changes in HCV prevalence or increases in the coverage of treatment and prevention interventions into likely decreases in HCV incidence. The likely relationship between these markers and underlying HCV incidence could depend on several factors, such as the on-going HCV epidemic in a particular setting, its population dynamics, and who is accessing treatment and prevention interventions. In this analysis, we use modelling undertaken in various settings through existing projects by our groups to show how changes in these metrics (HCV prevalence or intervention provision) could be used to determine changes in HCV incidence. Most of these modelling analyses have already been published with each analysis evaluating what is needed to achieve HCV elimination on HCV incidence, either in terms of levels of testing and/or treatment with or without concurrent scale-up of prevention interventions. The studies are summarised in Supplementary Table 1, with included analyses either considering HCV epidemics focussed among PWID or MSM, or more generalised epidemics among the whole population.

2.0 Methods

We used 17 previously undertaken modelling analyses from 12 studies (1-12) that evaluated what levels of testing and/or treatment are needed to achieve HCV elimination (see Supplementary Table 1) with 10 analyses also considering the impact of concurrent increases in prevention interventions. This included nine analyses among PWID (1-4), one among MSM (5) and seven among the general population (6-12), with eight in high income countries (HIC) and nine in lower or middle income countries (LMICs). All studies modelled HCV transmission dynamically using compartmental differential equation models, with 17 considering an elimination target of decreasing HCV incidence by 90% and seven assessing a target of decreasing incidence by 80% (Supplementary Table 1). In all models, successful HCV treatment resulted in individuals becoming susceptible to infection again. We did not consider models of just prison or HIV-positive MSM because we consider these to be part of broader epidemics among all MSM or PWID.

PWID HCV transmission models were available for UK (Dundee, Bristol and Walsall), USA (Perry County in Kentucky, San Francisco, and Scott County in Indiana), Tanzania (Dar es Salaam), Kenya (Nairobi) and Mexico (Tijuana). All these models assumed HCV transmission risk was proportional to the prevalence of infection with all models incorporating reduced HCV acquisition risk due to opioid substitution therapy (OST) and NSP based on a recent Cochrane systematic review (13). Some models contained included stratification relevant to each context: injecting duration (Perry County, UK sites), age (San Francisco), sex (Tanzania and Kenya), and a high-risk behaviour (sharing works in last 6 months for Perry County and San Francisco; recent

crack injecting and/or homelessness for UK models), with the risk of HCV transmission and acquisition varying across these strata. The Tanzania and Kenya models also stratified by HIV infection and HIV treatment and included transmission of HIV. All models incorporated inflows of new HCV uninfected injectors and outflows due to cessation of injecting, drug-related and other death. In each setting, the models were calibrated to site specific HCV prevalence data, possibly over time and by age or duration of injecting. HCV prevalence trends were increasing in some settings and decreasing in others (see Supplementary Table 1). Some models were also calibrated to changes in the coverage of OST and NSP (overall or by age) in that setting over time. All models considered the effect of scaling up NSP and OST on achieving HCV elimination.

The MSM HCV transmission model was calibrated to the UK and included transmission of HIV and HCV with the transmission risk for both HIV and HCV being elevated amongst high-risk MSM (defined as having >15 anal sex partners in the last year) and by the effect of chemsex (5). The model also included sero-adaptive mixing with HIV-positive men being more likely to mix with other HIV-positive men and to have reduced condom use. HIV infection was also assumed to increase the infectivity of HCV, reduce spontaneous clearance and increase disease progression. Coverage of HIV treatment was modelled as increasing over time, and HIV pre-exposure prophylaxis (PrEP) was included in recent years. HCV screening and treatment could occur at different rates in HIV-infected MSM and HIV-negative MSM on or off PrEP. The MSM model was calibrated to data on the HIV prevalence among MSM, and prevalence of HCV among HIV-positive and HIV-negative MSM. We also modelled changes in the coverage of HIV treatment and HCV screening and treatment over time. Important inputs included the proportion of MSM that are high risk, their level of sexual activity, levels of sexual mixing by high and low risk and HIV status, and condom use depending on whether their partner is HIV sero-concordant or not. Data generally came from two surveys undertaken in the UK (14, 15).

General population HCV transmission models were available for Pakistan (3 models), Georgia, Egypt, Indonesia, Bulgaria and Ghana (7-12, 16). Each model assumed individuals entered at birth and were tracked until death. The models generally included stratification by sex, age and injecting drug use status (never, currently and previously) or general high-risk behaviour. Individuals could initiate injecting drug use when they become a young adult and then cease injecting drug use after an average duration. All models included vertical HCV transmission, and all except 2 included transmission due to IDU. In these other two models, HCV transmission was modelled with a range of generic risk categories, but not specifically PWID. The models were calibrated to country-specific data on HCV prevalence in the general population (sometimes by age and sex) and among PWID (if modelled), sometimes over time if data was available (Georgia, Egypt and Pakistan). Other important inputs included the estimated size of the PWID population (over time in Georgia), the average age of individuals when they start and stop injecting, levels of population growth, and the age distribution of the population. All models were also calibrated to data on historical levels of HCV treatment, while the Georgia model was also calibrated to changes in PWID intervention coverage. Most data for each model came from that specific country, with the models for Bulgaria, Ghana and Indonesia utilising data from recent systematic reviews (17, 18), whereas the models for Pakistan, Egypt and Georgia utilised more detailed local data obtained through in-country collaborators (7, 11, 12, 16).

All models were calibrated using Bayesian sampling approaches that produced multiple model fits incorporating uncertainty in the model parameters and calibration data. More details on the models, their parameterisation and calibration can be found in the source studies given in Supplementary Table 1.

2.1 Model analyses

The models were used to undertake four analyses to consider whether the following alternative indicators could be used for determining whether an 80 or 90% decrease in HCV incidence has been achieved by 2030 in a specific modelled population, in line with WHO HCV elimination targets.

1. Reduction in HCV chronic prevalence. The models were used to determine what reduction in HCV chronic prevalence occurs when the model predicts that HCV incidence in the modelled population has decreased by 80 or 90% by 2030. Where possible, we considered the concurrent scale-up of HCV prevention and treatment interventions and determined the decrease in HCV chronic prevalence that occurs with and without the effects of prevention interventions. To evaluate the role of the prevention interventions, we also estimate how their effect is related to the modelled relative decrease in HCV transmission risk (incidence) resulting from these interventions. This is only possible for Pakistan in general population settings (assumed a generic 30 or 50% decrease) and the PWID modelled epidemics, where the modelled decrease in transmission risk was estimated as the product of the efficacy of OST (risk ratio (RR) 0.50 95% CI 0.40-0.63) and NSP (RR 0.44, 95% CI 0.24-0.80), both from a recent Cochrane systematic review(13), and the increase in coverage modelled in each setting.
2. Reduction in HCV antibody prevalence. The models were used to estimate the reduction in HCV antibody prevalence that occurs when the model predicts that HCV incidence in the modelled population has decreased by 80 or 90% by 2030. This is done in the same way as for analysis 1, but we

also consider how decreases in antibody prevalence among young individuals or new PWID also relate to the overall changes in HCV incidence in the modelled populations.

3. Increase in coverage of prevention and treatment interventions. The models were used to estimate the increase in coverage of treatment and prevention interventions needed to achieve an 80 or 90% decrease incidence in the modelled population. In all settings, we determine the number of infected individuals that need to be treated to achieve the incidence target, and where possible consider this with and without the effects of the scale-up in prevention interventions. The number of people needing treatment is presented as a coverage (%) of the baseline number of individuals infected in the population, with 150% meaning that the number treated needs to be 150% of the baseline number infected. Similarly to analysis 1, we evaluate the role of the scale-up in prevention interventions by estimating how its effect on the treatment target is related to the modelled decrease in HCV transmission risk resulting from these interventions.
4. Increase in testing interventions. The models were used to estimate the increase in HCV testing needed to achieve an 80 or 90% decrease incidence in the modelled population. This is done in the same way as for analysis 3.

Lastly, we also considered whether an absolute chronic prevalence target could be used as an alternative indicator for an absolute incidence target. Because this involved additional modelling (it was not considered in the original model analyses), this was only undertaken by the models for Kenya, Pakistan, Georgia, Tijuana, Bristol and Walsall.

3.0 Results

3.1 Reductions in chronic prevalence as a marker of reductions in incidence

All 17 model analyses could provide estimates for the relative decrease in chronic prevalence that occurs when the model projected an 80 or 90% decrease in HCV incidence by 2030 as a result of HCV treatment with and without prevention intervention scale-up. In each scenario, we considered the overall decrease in prevalence and incidence in the modelled population, not decreases among specific sub-groups (such as PWID in a general population model or among high-risk or HIV-positive MSM in a model of all MSM). If possible, each model also provided projections with or without the scale-up in prevention interventions if this was included in their model scenarios (details in Supplementary Table 1). The projections are summarised in Figure 1b in the main text, which shows that the estimated percentage decrease in chronic prevalence was generally very similar (generally <10% deviation) to the modelled decrease in incidence if there is no scale-up in prevention interventions. This result generally held across all settings and scenarios modelled, including for PWID, MSM or the general population, increasing or decreasing epidemics, and settings with changing or stable population sizes.

The main factor that leads to a deviation between the reduction in chronic HCV prevalence and incidence is if prevention interventions scale-up at the same time as HCV treatment. This results in a deviation that is related to the degree to which prevention interventions are scaled up and decrease HCV transmission risk, and so directly decrease HCV incidence. However, even when prevention interventions make a large contribution to decreasing HCV transmission and incidence, the prevalence target does not decrease too much (Figure 1b) despite there being a large effect on the required treatment target (see following section). Indeed, our modelling data suggests that for every 10% relative decrease in transmission risk due to prevention interventions, the prevalence target decreases by a relative amount of about 4.1% (Supplementary Figure 1). This small effect is because the prevention interventions are also indirectly decreasing chronic prevalence over time and so the degree to which chronic prevalence decreases when incidence decreases by 80 or 90% is not affected too much. For instance, among PWID in Dar es Salaam, reaching the 90% incidence reduction target with only HCV treatment results in an 88.4% (95% credibility interval 87.6-89.7) reduction in chronic prevalence, whereas if the incidence target is achieved through a combined scale-up of harm reduction interventions (from 16 to 75% coverage for NSP and 23 to 50% for OST, resulting in an estimated 45% decrease in transmission risk) and treatment then the chronic prevalence reduction is less, at 74.9% (95% credibility interval 71.7-82.4). We found the same deviation between the reduction in chronic HCV prevalence and incidence when prevention interventions were scaled up in combination with HCV treatment in the generalised HCV epidemic in Pakistan. The target of an 80% incidence reduction was associated with a chronic prevalence reduction of 85.0% (95% credibility interval 82.8-87.9) with treatment only, but this reduced to a 65.0% (95% credibility interval 62.7-68.9) reduction in chronic prevalence when we also included the impact of a generic intervention that reduced HCV transmission risk by half.

Otherwise, we found evidence that the decreases in HCV chronic prevalence may be greater than the corresponding decreases in HCV incidence in general population epidemics where a large contribution of

transmission is due to injecting drug use. For example, in Bulgaria and Indonesia, where injecting drug use is estimated to contribute majorly to HCV transmission (9), the decrease in overall chronic HCV prevalence was 96-99% when HCV incidence decreased by 90% (due to treatment scale-up), whereas in Ghana, where the contribution of injecting drug use is small, decreases in prevalence tracked reductions in incidence very closely. This effect is due to most HCV transmission being concentrated among the small population of PWID in Bulgaria and Indonesia, but the models assumed an even distribution of treatment across the population (ie, PWID and non-PWID). To achieve a 90% decrease in country-level incidence in these settings, higher rates of treatment are needed in PWID than in non-PWID. This higher overall level of treatment results in a greater overall reduction in prevalence across all groups. This raises the possibility that the required decrease in HCV prevalence may be greater in general population settings where there is considerable heterogeneity in HCV risk, unless treatment is preferentially targeted to those at higher risk of HCV transmission. If this targeting of treatment to high-risk groups occurs, it is then safe to assume that changes in prevalence in these high-risk groups will track their changes in incidence (as shown for PWID and MSM HCV epidemics in Figure 1b in main text), and so if the overall prevalence and prevalence in the high-risk groups decrease by 80/90% then incidence will have decreased similarly in both groups.

3.2 Reductions in antibody prevalence as a marker of reductions in incidence

We could use eight modelling analyses to look at whether decreases in antibody prevalence could be used as a marker of decreases in HCV incidence, five among PWID and three among the general population with five from LMICs and three from HICs. As expected, and shown in Supplementary Figure 2, antibody prevalence is not a good marker of decreases in incidence, with the decrease in antibody prevalence being variable and consistently much smaller than the corresponding decrease in HCV incidence. Unfortunately, the variability in these initial projections does not suggest that a specific percentage reduction in HCV antibody prevalence could reliably translate to achieving an 80 or 90% decrease in HCV incidence. In addition, although the decrease in antibody prevalence (that corresponds to an 80 or 90% decrease in incidence) tends to be larger among young or recently initiated injectors, it still does not track decreases in incidence well. Unexpectantly, the decrease in antibody prevalence is also larger with greater NSP and OST scale-up.

3.3 Treatment and prevention targets as a marker of reductions in incidence

All modelling analyses could be used to look at whether increases in treatment scale-up could be used as a marker of decreases in HCV incidence (Supplementary Table 1), with 10 analyses also looking at the impact of increases in prevention scale-up (with Pakistan and Tijuana considering multiple levels of scale-up). In each modelled scenario, estimates were made of the proportion of the initial infection burden that needed treatment (treatment coverage) to achieve the WHO elimination target for incidence in that setting (80 or 90% decrease depending on analysis), with and without the concurrent scale-up of prevention interventions. None solely considered whether the scale-up of prevention interventions could achieve this target because earlier modelling suggests this is unlikely to be possible (19). The projections in Supplementary Figure 3 suggest that the overall number of treatments needed to eliminate is generally greater (aside from a few exceptions) than the overall initial burden of infection (i.e. treatment coverage is >100%) in all population groups modelled (PWID, MSM and general population), but is variable and dependent on the following factors.

a. Prevention intervention scale-up: The required treatment coverage can reduce considerably if prevention interventions are scaled up, with greater scale-up in prevention interventions causing larger reductions. Indeed, as can be seen in Supplementary Figure 4, the relative decrease in the treatment coverage target closely correlates with the relative decrease in transmission risk resulting from the scale-up in prevention interventions, with each 10% relative decrease in transmission risk due to prevention interventions decreasing the treatment coverage target relatively by about 12%.
b. Increasing epidemics: The required treatment coverage is heightened in settings with increasing epidemics (e.g. Perry County, Scott County and Dundee). For example, 310% and 170% of the initial HCV burden in these PWID populations need to be treated to achieve elimination in the increasing HCV epidemics among PWID in Scott County and Perry County, respectively, whereas it is 120-131% in Tijuana, San Francisco, Bristol and Walsall (UK) where the HCV epidemics among PWID are relatively stable. This effect is also seen in the general population settings, where the treatment ratio is 117-136% in Pakistan when we assume it has an increasing epidemic, but 90-100% in Pakistan, Georgia and Egypt when we assume their epidemics are decreasing.
c. Population growth: The required treatment coverage is similarly heightened in settings with growing populations and reduced in settings without population growth. For example, for the increasing populations in Ghana (2.2% growth per year) and Pakistan (1.3-2.1% per year), over 130% of the initial disease burden needs to be treated to eliminate HCV in those countries, whereas in Bulgaria and Georgia, where the populations are not growing, 98% and 91% of the initial disease burden needs treating, respectively.

d. Elimination time frame: The required treatment coverage may reduce moderately if elimination is achieved over a shorter time frame. This is only based on modelling from one setting, with the required treatment coverage for Pakistan reducing from 136% to 117% when the elimination time frame is reduced by 2 years from 2016-2030 to 2018-2030.

3.4 Testing targets as a marker of reductions in incidence

Not many models have considered what testing is needed to achieve HCV elimination, and so there is little model data to aid in the development of testing targets. Overall, we used two models to consider what HCV testing was needed to achieve HCV elimination, including one model for MSM (UK) and one for the general population (Pakistan). Although very limited, these models suggested it would not be easy to use testing targets for determining whether a country has achieved elimination. For instance, in Pakistan our modelling showed that to achieve elimination we needed to first time screen 140% of the population over 2018-2030 (with 90% referral), with rescreening also being needed (every year for PWID and every 5 years otherwise) such that 238% of the population are screened overall by 2030. This reduced to 90% (with 80% referral) if transmission risk is halved through the scale-up of hypothetical prevention interventions. In the UK MSM model, 470% of the MSM population needed screening over 2020-2030 to achieve elimination if PrEP is at 12.5% coverage, reducing to 417% if PrEP is at 25% coverage. For 12.5% PrEP coverage, this translated to HIV-diagnosed MSM and MSM on PrEP being screened every 6 months with other HIV-negative MSM being screened every 4-5 years, while if PrEP is at 25% coverage (25%) no screening of HIV-negative MSM not on PrEP is needed.

3.5 Absolute prevalence target as a marker of an absolute incidence target

Results were only available for six settings for this analysis. For the two general population epidemic models, the model projected that the chronic prevalence would be about 0.03% and 0.2% in Pakistan and Georgia, respectively, when the HCV incidence in these settings had been reduced to approximately 4-5 per 100,000 pyrs. Conversely, among PWID, the chronic prevalence of infection was estimated to have decreased to 4.3%, 10.3%, 12.4% and 15.1% when incidence had been reduced to 2 per 100 pyrs in Kenya, Tijuana, Walsall and Bristol, respectively. Although these projections are for limited settings, they suggest there may not be an absolute prevalence target for general population or PWID epidemics that corresponds to these absolute HCV incidence targets. However, it is recommended that further modelling is done to confirm this.

4.0 Discussion

Findings from this modelling suggest there are two main ways in which indirect 'non-incidence' data could be used to assess whether a country has achieved HCV elimination in terms of decreasing HCV incidence.

The best option is to track changes in overall chronic prevalence, including among sub-groups that drive transmission, which our modelling suggests will closely track changes in HCV incidence unless there is considerable scale-up in effective HCV prevention interventions. Conservatively, irrespective of whether prevention interventions have scaled up, if chronic prevalence has reduced by at least 80% overall and among high-risk subgroups, then we can safely assume that incidence has probably decreased by approximately 80%. Alternatively, if prevention interventions have scaled up and thought to have decreased transmission risk, then for every 10% relative decrease in transmission risk/incidence resulting from these interventions the required prevalence target is estimated to decrease relatively by about 4%. Importantly, though, because most elimination initiatives are generally focussed on scaling up treatment, with the scale-up of prevention interventions being more modest in most cases, it is likely that the effect of prevention interventions will be small. Also, because the impact of prevention interventions is likely to be uncertain, in most cases it will be safer to still require an 80% decrease in prevalence to ensure incidence has decreased by 80%. It is also important to understand if anything has increased incidence, maybe due to new risk behaviours or an expansion of injecting drug use – this would lead to an increase in the prevalence target.

Alternatively, the other option is to track changes in the uptake of treatment and prevention interventions. However, there is no 'one size fits all' treatment target for determining whether a country has reached the HCV elimination target for decreasing incidence. As a minimum, we can say that if less than 100% of the baseline infected population has been treated then it is unlikely that a 80 or 90% reduction in incidence has been achieved unless prevention interventions have scaled up significantly or there is a decreasing epidemic. However, if they have scaled up, then every 10% relative decrease in transmission risk/incidence due to prevention interventions decreases the required number of treatments needed for achieving elimination by 12% in relative terms. Unfortunately, our modelling also suggests that the required amount of treatment for achieving elimination is also sensitive to a number of other factors, making its translation into decreases in HCV incidence a non-trivial task that requires setting specific modelling. Specifically, the treatment targets will be heightened in settings with greater population growth or increasing HCV epidemics, and possibly decreased if elimination is being achieved over a shorter time period. Because of these dependences, treatment numbers by themselves

cannot be used to assess elimination unless other epidemiological data is available, specifically on the population demographics, baseline chronic HCV prevalence and its likely trends. For settings with these data, it is possible that modelling can be used to determine the treatment targets needed for achieving elimination.

Other than these two markers, it will not be easy to use testing data to estimate progress towards achieving elimination, because it will require data on the subsequent cascade of care, and reliable data on the likely coverage of testing and retesting in the overall population and important high-risk subgroups. Also, we do not recommend the use of antibody prevalence data to monitor changes in incidence, even among new injectors or young individuals where their trends in prevalence do not track incidence closely. Lastly, our modelling suggests it is unlikely that an absolute prevalence target can be used as an alternative indicator for reaching an absolute incidence target.

Importantly, our findings highlight the importance of tracking the scale-up in prevention interventions and to understand their likely impact on HCV transmission risk. For interventions focussed on the prevention of HCV transmission among PWID, a recent Cochrane systematic review(13, 20) provides sufficient data for estimating their impact, with data suggesting that OST reduces the risk of HCV acquisition by 50% (risk ratio (RR) 0.50 95% CI 0.40-0.63), NSP by 56% (RR=0.44, 95% CI 0.24-0.80), and combined by 76% (RR=0.24 95% CI=0.07-0.89). These estimates can be used with data on changes in coverage of these interventions over time to estimate the resulting average decrease in transmission risk at the population level, which can then be used to understand how they change the prevalence target. For other interventions, data is less clear. Other than transmission among PWID, unsafe injections and medical procedures are thought to be important routes of HCV transmission in many LMICs (21). Modelling data suggests that unsafe injections have contributed significantly to global HCV transmission(21, 22), with improvements in injecting safety (23, 24) dramatically reducing global levels of blood borne viruses (25). Data on the risk of HCV transmission through needle stick injury (26) has and could be used to estimate how changes in unsafe injections can reduce HCV transmission risk. Lastly, improvements in blood safety have also probably reduced the level of HCV transmission(27), while reductions in other community risk behaviours may also have benefit, but unfortunately data on their importance for HCV transmission is limited (28) and the effectiveness of interventions for tackling these risks is sparse. More evidence is needed to determine the likely impact of scaling up these interventions for reducing HCV transmission and achieving elimination.

Our modelling suggests that tracking changes in chronic HCV prevalence at the population level and in specific risk groups may be the most reliable alternative indicator for documenting changes in incidence if incidence data is not available. This leads to the question of how this should be done. For higher risk groups, many LMICs already undertake intermittent rounds of national bio-behavioural surveys (BBS) among PWID and MSM for monitoring changes in HIV prevalence and risk behaviours. These are generally funded through international organisations. Some of these surveys already test for HCV antibody prevalence, so it should be possible to also undertake HCV RNA testing to monitor changes in chronic HCV prevalence if funding is available. Importantly, these surveys also monitor changes in the coverage of prevention interventions, something that is important for monitoring HCV elimination, although questions on HCV treatment uptake need to be included more widely. In settings that do not undertake BBSs among PWID and MSM, then data for these high-risk groups could come from routine testing linked to interventions or services that these risk groups are in contact with, including such things as harm reduction interventions, STI clinics, emergency departments or prisons. Unfortunately, there is a greater likelihood that the sampling of individuals in these settings is not representative of the whole MSM or PWID population, while the frequent linkage of this testing to treatment initiatives may further bias the data. It is therefore crucial to critique the likely biases in any of these routine data sources before deciding whether they can reliably document trends in HCV chronic prevalence and prevention and treatment uptake.

For other ‘lower risk’ groups and the general population, national population surveys are the gold standard for documenting changes in chronic prevalence. These have been done in some LMIC and HIC settings, but their global coverage is patchy because of their high expense, with only 3 to 4 countries having undertaken multiple HCV surveys (18). Alternatively, HCV testing could be added to on-going national surveys, as has been done in some demographic health surveys in Africa (Egypt(29), Cameroon(30) and Democratic Republic of the Congo (31)) or the Population-based HIV Impact Assessment (PHIA) surveys (Rwanda, Tanzania). If national surveys are not available or possible then sentinel surveillance testing would have to be used. This testing would have to sample individuals not based on their risk profile or whether they have been tested before and would need to minimise the degree to which people are attending services to access testing and treatment for HCV. This could include routine testing of antenatal women or blood donors, but again care would need to be taken in critiquing whether the testing in these settings is likely to give a fair representation of population prevalence. For example, in Georgia, the vast majority of HCV infections are among males(32), so testing of antenatal women would severely underestimate the prevalence of HCV in that setting. Despite this, data from such sources have been used to monitor trends in HIV prevalence in different

settings for UNAIDS, and so similar correction methods may be useable for HCV as have been developed for HIV (33).

Similarly, for using treatment targets to monitor elimination, we need to have reliable estimates for the size of the infected population, which are generally uncertain and so affect our estimates of how many individuals need treating. This imprecision is either due to uncertainty around size estimates for risk groups such as PWID, which are hard to enumerate, or possible biases in estimates of HCV prevalence due to surveys not capturing all risk groups, such as imprisoned populations, homeless or PWID. This last issue has been highlighted in recent discussions around estimates of the burden of HCV infection in the USA using the national NHANES household survey (34-36).

Crucially, all possible alternative indicators for assessing impact on HCV incidence require some understanding of the on-going epidemic in a country. Minimally, the use of chronic HCV prevalence to monitor incidence requires data on the scale-up in prevention interventions and knowledge of what risk groups drive HCV transmission to ensure that they are sampled adequately in any assessment of how prevalence is decreasing. For using data on the uptake of treatment and prevention interventions, we still need to know what the baseline HCV prevalence was and have some idea of how prevalence has been changing over time, preferably also in the main risk groups. This will need to be sufficient to enable modelling to estimate the treatment numbers needed, which our existing modelling has shown can be highly variable depending on this and other factors. There are also likely to be different treatment scenarios that could achieve elimination of incidence depending on how treatment is targeted to high-risk subgroups. For instance, if injecting drug use is the main driver of HCV transmission, but only makes up a small proportion of the HCV burden in a particular setting, then in these settings' elimination of incidence may be possible through just focussing treatment on the small proportion of infections among PWID, so reducing the number of treatments needed to achieve elimination. These points highlight the importance of understanding your epidemic and having data on who is being treated to have any hope of reliably documenting how a country is progressing to elimination. If sufficient data is available, modelling can help with this as has been done previously for Pakistan(6, 7, 12), Georgia(16), Australia(37, 38), Scotland(39, 40), Kenya, Tanzania(41), Iceland(42) and Egypt (11), with these models then being useful for helping plan ongoing elimination strategies and for evaluating progress towards achieving elimination. However, to do this it is crucial that transmission is modelled mechanistically including the main processes that drive HCV transmission; this is needed to reliably model the effect of treatment on incidence in these groups.

4.1 Strengths and limitations

The strengths of our analyses are the use of multiple models for different risk groups and settings with varied HCV epidemics to investigate the possible utility of different proxy measures for assessing decreases in HCV incidence. Most of these model analyses have been peer reviewed and published, so providing re-assurance as to their validity. However, limitations still exist.

We were largely limited to using sub-analyses of existing analyses, with different models considering different elimination targets over different time frames. Models were also developed and calibrated in different ways depending on the setting and data that was available. While this may have affected some of the model projections in ways that we could not foresee, it also strengthens our confidence with regards to the use of chronic HCV prevalence as an alternative indicator. We also had difficulty in utilising models from other teams, especially at this time, because many modellers were busy undertaking Covid-19 related modelling. Some analyses were limited by the small number of models that were able to look at that proxy measure, such as for testing targets. Although it may be useful to undertake further modelling to consider whether testing targets can be used to document progress towards elimination, initial modelling suggests this may be complex so limiting its utility.

We were also limited in understanding the degree to which routine surveillance prevalence measures could be used to document trends in HCV prevalence. Further work, possibly involving multi-parameter evidence synthesis is needed to better understand how routine measures can be combined to estimate the HCV prevalence in a country(43, 44) (while accounting for their biases) and documenting how it changes over time. Similar methods have been utilised successfully for HIV(33), giving hope for their use with HCV.

A large proportion of the model projections came from HICs, many just considered PWID focussed HCV epidemics and few considered MSM or the impact of prevention interventions in general population epidemics. Further analyses are needed in LMICs that account for the drivers of transmission, and more modelling is needed to assess the impact of prevention interventions in general population epidemics. Although additional analyses have considered the HCV epidemic in HIV-positive MSM, and requirements for HCV elimination in this group, these do not answer the question of what is needed to reach HCV elimination in all MSM, which is what was needed here.

4.2 Validation of prediction models and interpretation of observational trends

There is also an urgent need for comparison and validation of these model projections against observed data, particularly if service coverage changes are used to assess impact on incidence. This validation is essential for determining whether the mechanistic models and assumptions linking intervention scale-up to changes in prevalence/incidence are accurate. Importantly, a recent comparison of one of our models with data on the reduction in HCV incidence following the scale-up in HCV treatment in a prison setting suggests they are in agreement (45), giving some validation to our model projections. Similar comparisons of models with data on the impact of treatment on HCV incidence are needed in other settings and populations.

Importantly, even in settings where incidence is directly measured, modelling is useful for disentangling intervention impact from other epidemiological changes. Numerous factors other than scale-up of HCV treatment can contribute to observed changes in HCV incidence such as changes in: harm reduction coverage, risk behaviour, or injecting drug use initiation or cessation patterns. In this context, models can incorporate these changing factors alongside scale-up of HCV treatment and harm reduction interventions, and can then be validated against observed incidence. For example, a modelling study, incorporating observed HCV treatment and prevention intervention coverage expansion as part of the National Hepatitis C Action Plan in Scotland, projected what declines in HCV incidence should occur with this level of intervention scale-up (39). The study found that observed HCV incidence declines among PWID were consistent with model predictions given the level of intervention scale-up and changes in background risk, providing further validation that the model simulation of intervention impact on transmission is consistent with what occurs in reality. This type of analysis is particularly important because countries may mistakenly attribute decreases in incidence to increases in treatment even if risk behaviour declines, and therefore could remain vulnerable to viral resurgence if risk increases again. As such, even in settings where incidence is directly measured, modelling can be required for interpretation and deeper mechanistic insights into what factors generated the observed outcome.

4.3 Conclusions and implications

Our modelling suggests that changes in chronic prevalence can be reliably used to estimate changes in HCV incidence. Uptake in treatment and prevention interventions in different sub-groups may also be used if data on baseline prevalence trends are available, and modelling is used to produce country specific treatment targets. Routine testing data may help with estimating these baseline epidemic characteristics (6), although biases will have to be critiqued and accounted for. Although this gives a possible pathway by which country level elimination initiatives can be evaluated and validated without the use of incidence data, further work is needed to estimate treatment and prevention targets for each country and to validate our modelling projections in specific settings that collect treatment, prevalence and incidence data. Through doing this, we should be able to produce different ‘non-incidence’ targets that countries can aim towards for achieving HCV elimination.

Supplementary Tables

Supplementary Table 1: Summary of modelling studies

Risk group modelled	Country	Setting/ city	Chronic HCV prevalence*	Epidemic dynamics £	Population dynamics £	Elimination target for decreasing HCV incidence	Baseline coverage prevention interventions	Scenarios modelled Effect** of prevention interventions	Chronic prevalence target	Antibody prevalence target	Treatment target	Testing target	
PWID	UK	Bristol	45.0%	decreasing	decreasing	80/90% decrease	NSP 56%; OST 81%	Yes,	Yes	No	Yes	No	(1)
	UK	Walsall	19.0%	decreasing	decreasing	80/90% decrease	NSP 28%; OST 72%	NSP 80%; OST 80%	Yes	No	Yes	No	
	UK	Dundee	26.0%	decreasing	Stable	80/90% decrease	NSP 48%; OST 72%		Yes	No	Yes	No	
	USA	Scott County	61.3%	increasing	increasing	90% decrease	NSP 38%; OST 0%	Yes, NSP and OST 50%	Yes	Yes	Yes	No	(2)
	USA	Perry County	58.8%	increasing	increasing	90% decrease	NSP 0%; OST 5%	Yes, NSP 83%; OST 50%	Yes	Yes	Yes	No	(3)
	USA	San Francisco	76.0%	decreasing	decreasing	90% decrease	NSP 83%; OST 13%		Yes	Yes	Yes	No	
	Tanzania	Dar es Salaam	33.7%	increasing	decreasing	90% decrease	NSP 16%; OST 23%	Yes, NSP 50%; OST 75%	Yes	Yes	Yes	No	NA
	Mexico	Tijuana	67.1%	Stable	Stable	80/90% decrease	NSP 0%; OST 0%	Yes, NSP and OST 50%	Yes	Yes	Yes	No	(4)
	Kenya	Nairobi	11.8%	Uncertain	Increasing	80/90% decrease	NSP 60%; OST 8%	Yes, NSP 75%; OST 40%	Yes	No	Yes	No	NA
MSM	UK	Not specific	1.6%	decreasing	stable	90% decrease	PrEP 0%	Yes, PrEP 12.5%	Yes	No	Yes	Yes	(5)
General population	Pakistan A	National	3.9%	increasing	increasing	80/90% decrease	None modelled	Yes, all risk halved	Yes	No	Yes	No	(6)
	Pakistan B	National	3.7%	increasing	increasing	80% decrease	None modelled	Yes, all risk halved	Yes	Yes	Yes	Yes	(7)
	Pakistan C	National	3.2%	decreasing	increasing	90% decrease	None modelled	No	Yes	Yes	Yes	No	(12)
	Egypt	National	6.9%	decreasing	increasing	90% decrease	None modelled	No	Yes	Yes	Yes	No	(11)
	Indonesia	National	0.6%	decreasing	increasing	90% decrease	None modelled	No	Yes	No	Yes	No	(8)
	Bulgaria	National	1.1%	decreasing	decreasing	90% decrease	None modelled	No	Yes	No	Yes	No	(9, 10)
	Ghana	National	1.5%	decreasing	increasing	90% decrease	None modelled	No	Yes	No	Yes	No	
	Georgia	National	5.4%	decreasing	decreasing	80/90% decrease	NSP %; OST %	No	Yes	No	Yes	No	

*Chronic prevalence is for the overall risk group modelled and estimated at the point when the elimination initiative begins; **Prevention interventions include scale up of opioid substitution therapy (OST) and needle and syringe programs (NSP) for PWID models, HIV pre-exposure prophylaxis (PrEP) for MSM, and a hypothetical intervention that halves acquisition risk for Pakistan. £ This gives details of how HCV prevalence is changing in the modelled epidemic over time (in absence of the elimination initiative) and how the size of the modelled population is changing over time. Pakistan A is Pakistan Lim et al. in figures 1b and supplementary figure 3, Pakistan C is Pakistan Ayoub et al in figures and Pakistan B is used in the testing analysis and supplementary figure 2.

Supplementary Table 2: Summary of using different indicators for monitoring decreases in incidence

Outcome measure	Useable as indicator of elimination	Factors effecting target	Country level data needed to estimate elimination target
Chronic prevalence	Yes, tracks incidence well	Prevention intervention scale-up, population heterogeneity in risk	Trends in chronic prevalence in overall population and high-risk groups over elimination initiative, scale-up in prevention interventions
Antibody prevalence	Not reliable measure even in young or new injectors	Prevention intervention scale-up, probably other factors	N/A
Uptake of treatment and prevention interventions	Yes, but not trivial. Country specific modelling needed	Population growth, epidemic dynamics and drivers, how treatment is targeted	Baseline chronic prevalence and historic trends, number of treatments in different sub-groups over time, scale-up in prevention interventions
Screening rate	Not recommended – too complex	Prevention intervention scale-up, resulting cascade of care, population sub-groups that are screened and rescreened	NA

Supplementary Table 3: Country-specific HCV incidence estimates for PWID and overall, with percentage reductions in incidence needed to reach global incidence targets (WHO estimates used for overall and Trickey estimates used for PWID (9))*

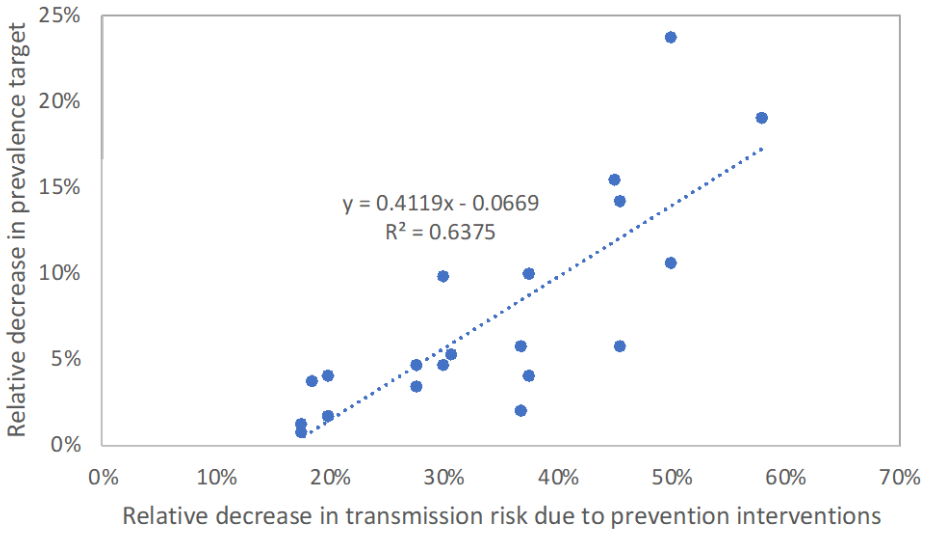
Country	Region	PAF of IDU 2018-2030	Epidemic type	HCV incidence estimates from Trickey et al.		% decrease needed to reach global incidence target	
				Overall 100,000pyr	PWID 100pyr	Overall	Among PWID
Ghana	AFRO	3%	Generalised	67.03	7.13	93%	72%
Kenya	AFRO	31%	Mixed	15.86	6.24	68%	68%
Madagascar	AFRO	6%	Generalised	25.86	0.98	81%	0%
Mauritius	AFRO	90%	Concentrated	63.26	26.45	92%	92%
Mozambique	AFRO	21%	Mixed	63.33	18.52	92%	89%
Nigeria	AFRO	2%	Generalised	58.26	0.50	91%	0%
Senegal	AFRO	10%	Generalised	45.59	10.37	89%	81%
Tanzania	AFRO	37%	Mixed	116.27	6.36	96%	69%
AFRO		14%		59.74	4.30		
Afghanistan	EMRO	58%	Mixed	62.10	9.67	92%	79%
Egypt	EMRO	5%	Generalised	153.67	5.33	97%	62%
Iran	EMRO	85%	Mixed	15.59	9.41	68%	79%
Lebanon	EMRO	46%	Mixed	9.07	4.22	45%	53%
Libya	EMRO	42%	Mixed	14.61	40.48	66%	95%
Morocco	EMRO	37%	Mixed	16.82	8.89	70%	77%
Pakistan	EMRO	18%	Mixed	106.38	7.97	95%	75%
Saudi Arabia	EMRO	92%	Concentrated	17.75	23.32	72%	91%
Syria	EMRO	15%	Mixed	34.46	17.04	85%	88%
Tunisia	EMRO	84%	Mixed	12.38	8.63	60%	77%
EMRO		16%		78.64	8.91		
Albania	EURO	60%	Mixed	17.15	4.02	71%	50%
Armenia	EURO	73%	Mixed	46.44	8.24	89%	76%
Austria	EURO	100%	Concentrated	10.25	6.21	51%	68%
Azerbaijan	EURO	52%	Mixed	73.64	14.67	93%	86%
Belarus	EURO	96%	Concentrated	38.20	15.05	87%	87%
Belgium	EURO	100%	Concentrated	13.51	6.84	63%	71%
Bosnia	EURO	100%	Concentrated	7.79	9.89	36%	80%
Bulgaria	EURO	100%	Concentrated	25.11	14.76	80%	86%
Croatia	EURO	71%	Mixed	9.11	3.90	45%	49%
Cyprus	EURO	35%	Mixed	10.24	7.36	51%	73%
Czech Republic	EURO	88%	Mixed	15.98	2.97	69%	33%
Denmark	EURO	92%	Concentrated	10.00	3.43	50%	42%
Estonia	EURO	100%	Concentrated	62.23	13.57	92%	85%
FYROM	EURO	98%	Concentrated	7.54	9.85	34%	80%
Finland	EURO	100%	Concentrated	20.60	9.66	76%	79%
France	EURO	93%	Concentrated	7.93	6.51	37%	69%
Georgia	EURO	100%	Concentrated	176.78	8.36	97%	76%
Germany	EURO	89%	Mixed	10.48	7.94	52%	75%
Greece	EURO	23%	Mixed	15.85	10.08	68%	80%
Hungary	EURO	30%	Mixed	10.77	8.55	54%	77%
Iceland	EURO	100%	Concentrated	11.28	7.75	56%	74%
Ireland	EURO	79%	Mixed	18.39	11.93	73%	83%
Israel	EURO	37%	Mixed	30.40	4.57	84%	56%
Italy	EURO	100%	Concentrated	31.86	6.52	84%	69%
Kazakhstan	EURO	99%	Concentrated	41.35	7.81	88%	74%
Kyrgyzstan	EURO	50%	Mixed	46.95	4.93	89%	59%
Latvia	EURO	100%	Concentrated	57.64	16.36	91%	88%
Lithuania	EURO	76%	Mixed	14.45	7.61	65%	74%
Luxembourg	EURO	94%	Concentrated	32.73	12.81	85%	84%
Malta	EURO	79%	Mixed	5.95	2.48	16%	19%
Moldova	EURO	52%	Mixed	39.58	9.35	87%	79%
Montenegro	EURO	100%	Concentrated	16.80	7.46	70%	73%
Netherlands	EURO	52%	Mixed	2.03	5.52	0%	64%
Norway	EURO	83%	Mixed	11.90	7.95	58%	75%
Poland	EURO	86%	Mixed	17.76	12.24	72%	84%
Portugal	EURO	100%	Concentrated	13.83	15.65	64%	87%
Romania	EURO	100%	Concentrated	46.48	23.61	89%	92%
Russia	EURO	100%	Concentrated	104.99	14.43	95%	86%
Serbia	EURO	100%	Concentrated	9.27	2.84	46%	30%
Slovakia	EURO	88%	Mixed	34.25	10.75	85%	81%
Slovenia	EURO	95%	Concentrated	8.90	2.96	44%	32%
Spain	EURO	31%	Mixed	14.12	9.76	65%	80%
Sweden	EURO	85%	Mixed	14.47	11.86	65%	83%
Switerland	EURO	85%	Mixed	14.38	9.68	65%	79%
Tajikstan	EURO	98%	Concentrated	57.15	8.30	91%	76%
Turkey	EURO	91%	Concentrated	26.92	11.37	81%	82%

Country	Region	PAF of IDU 2018-2030	Epidemic type	HCV incidence estimates from Trickey et al.		% decrease needed to reach global incidence target	
				Overall 100,000pyr	PWID 100pyr	Overall	Among PWID
Turkmenistan	EURO	32%	Mixed	56.25	8.23	91%	76%
UK	EURO	98%	Concentrated	25.14	12.44	80%	84%
Ukraine	EURO	100%	Concentrated	38.08	6.31	87%	68%
Uzbekistan	EURO	23%	Mixed	80.74	5.62	94%	64%
EURO		84%		38.15	11.32		
Argentina	PAHO	58%	Mixed	22.25	8.81	78%	77%
Brazil	PAHO	83%	Mixed	36.05	11.08	86%	82%
Canada	PAHO	83%	Mixed	24.33	12.54	79%	84%
Mexico	PAHO	53%	Mixed	21.42	28.75	77%	93%
USA	PAHO	77%	Mixed	36.24	4.27	86%	53%
Uruguay	PAHO	49%	Mixed	12.66	2.11	61%	5%
PAHO		74%		32.10	7.07		
Bangladesh	SEARO	15%	Mixed	21.31	7.42	77%	73%
India	SEARO	6%	Generalised	17.32	7.75	71%	74%
Indonesia	SEARO	67%	Mixed	13.27	22.16	62%	91%
Myanmar	SEARO	75%	Mixed	28.68	6.67	83%	70%
Nepal	SEARO	67%	Mixed	18.44	12.06	73%	83%
Taiwan	SEARO	64%	Mixed	22.72	12.62	78%	84%
Thailand	SEARO	43%	Mixed	18.34	20.58	73%	90%
SEARO		18%		17.55	12.50		
Australia	WPRO	62%	Mixed	25.79	5.09	81%	61%
China	WPRO	56%	Mixed	16.22	6.59	69%	70%
Japan	WPRO	100%	Concentrated	19.36	7.18	74%	72%
Malaysia	WPRO	65%	Mixed	82.33	8.91	94%	78%
New Zealand	WPRO	82%	Mixed	40.39	11.98	88%	83%
Philippines	WPRO	14%	Mixed	11.56	6.97	57%	71%
Viet Nam	WPRO	58%	Mixed	24.11	12.25	79%	84%
WPRO		58%		17.94	7.11		
GLOBAL		43%		30.02	8.61		

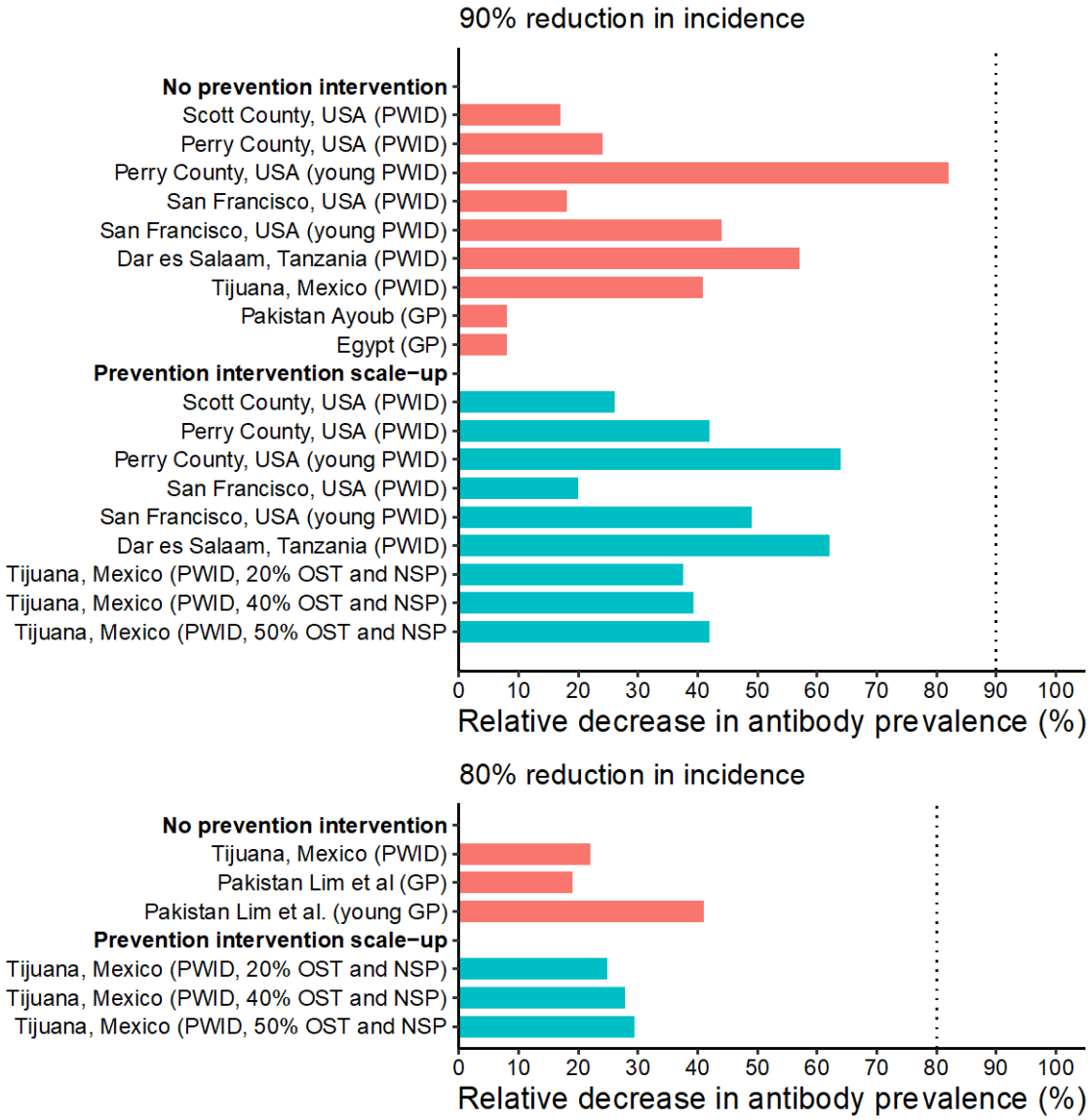
*global incidence target for PWID is 2 per 100 person-years and for the general population is 5 per 100,000 person years

Supplementary Figures

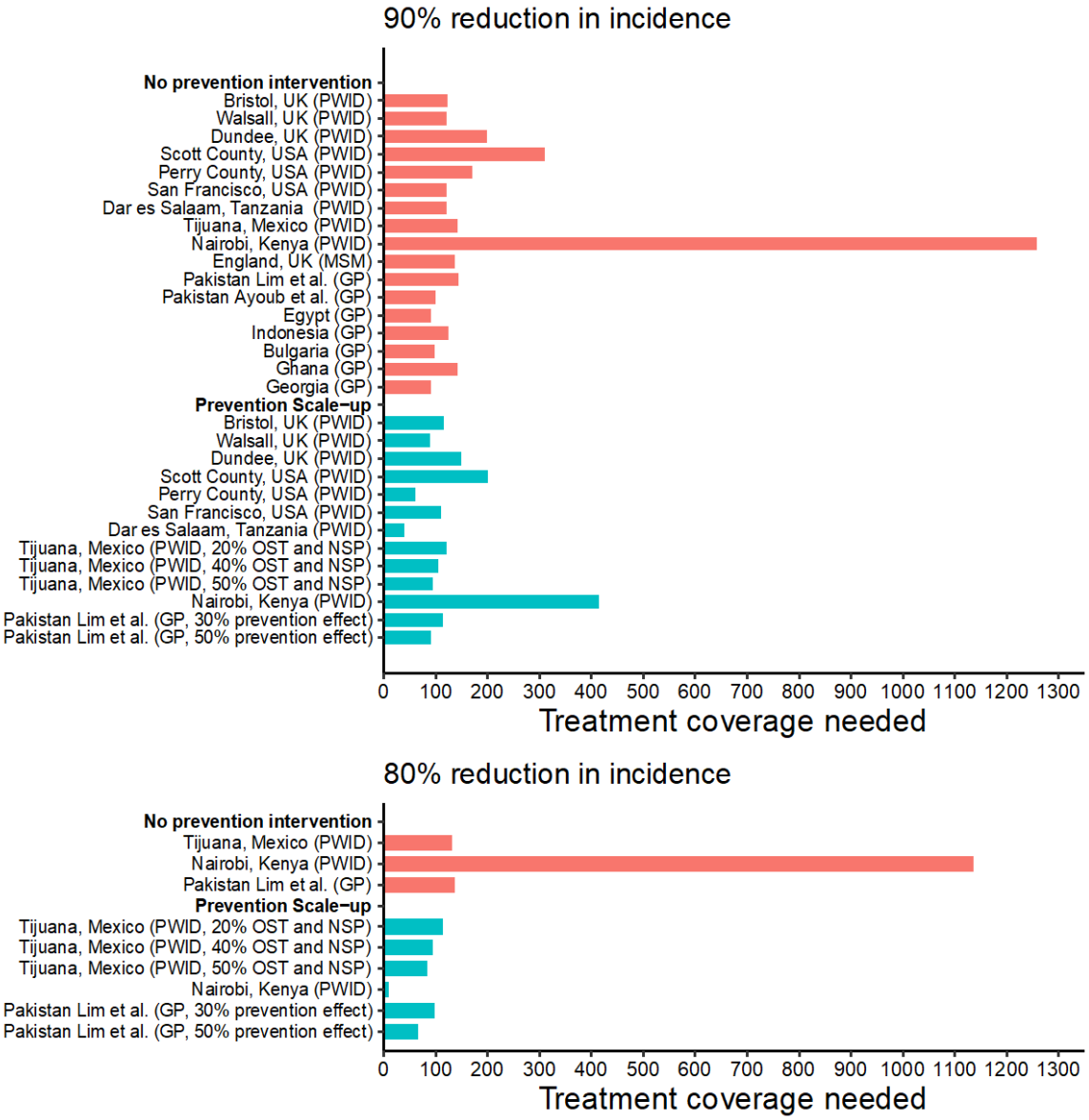
Supplementary Figure 1: Effect of decreases in transmission risk from prevention interventions on the prevalence target for achieving HCV elimination. Model projections consider the impact of a scale-up in prevention interventions over the period to 2030 that results in a relative decrease in transmission risk, and determine the degree to which that reduces the decrease in HCV prevalence that occurs (through HCV treatment) when an 80 or 90% decrease in HCV incidence is achieved by 2030, compared to if the prevention interventions had not scaled up.



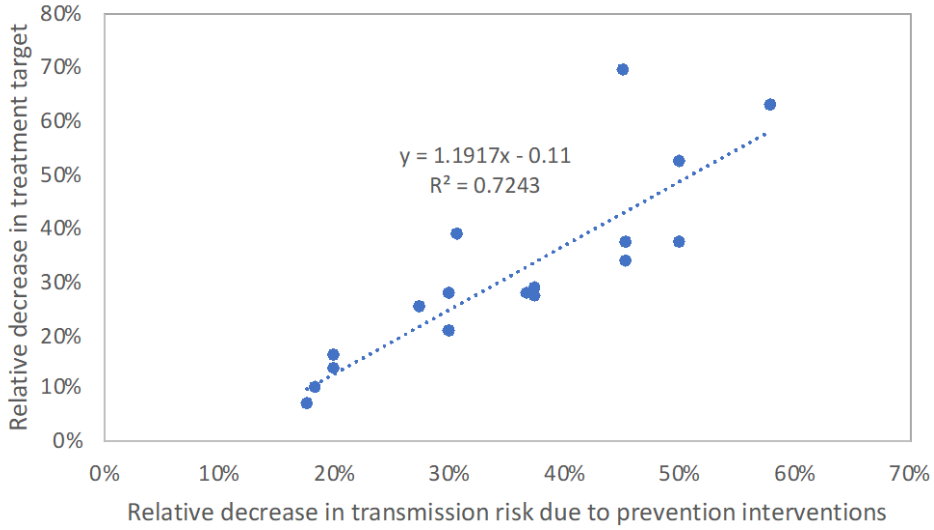
Supplementary Figure 2: Relative decrease in HCV antibody prevalence that occurs when an 80% or 90% decrease in HCV incidence is achieved through scaling up treatment with or without concurrent scale-up in prevention interventions for different risk groups and settings.



Supplementary Figure 3: Coverage of treatments needed compared to baseline number of infections (when elimination initiative started) to achieve an 80% or 90% decrease in HCV incidence with or without concurrent scale-up in prevention interventions for different risk groups and settings.



Supplementary Figure 4: Effect of decreases in transmission risk from prevention interventions on the treatment target needed for achieving HCV elimination. Model projections consider the impact of a scale-up in prevention interventions over the period to 2030 that results in a relative decrease in transmission risk, and determines the degree to which that reduces the coverage of treatment needed to achieve a 80 or 90% decrease in HCV incidence over the period, compared to if the prevention interventions had not scaled up.



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