Prevalence and incidence of hepatitis C virus infection in men who have sex with men: a systematic review and meta-analysis


Summary

Background WHO has set targets for hepatitis C virus (HCV) elimination by 2030. We did a global systematic review of HCV prevalence and incidence in men who have sex with men (MSM) to provide updated estimates that can guide community education and public health policy.

Methods We did a systematic review and meta-analysis of studies published and listed on MEDLINE or Embase between Jan 1, 2000, and Oct 31, 2019, including conference proceedings. Studies were eligible if they reported measures of HCV prevalence or HCV incidence (or both) among MSM. Studies that relied on participants’ self-reported HCV status with no laboratory confirmation were excluded. Pooled HCV estimates in MSM were stratified by HIV status and by injecting drug use, then by WHO region and by income level. Random-effects meta-analysis was done to account for between-study heterogeneity and examined using the I² statistic. Pooled HCV prevalence was also compared with HCV estimates in the general population and presented as prevalence ratios (PRs). In HIV-negative MSM, incidence estimates were stratified by use of HIV pre-exposure prophylaxis (PrEP). The systematic review was registered with PROSPERO, number CRD42020156262.

Findings Of 1221 publications identified, 194 were deemed to be eligible and included in the systematic review and meta-analysis. Overall, the pooled HCV prevalence in MSM was 3·4% (95% CI 2·8–4·0; P=0·98·0%) and was highest in Africa (5·8%, 2·5–10·4) and South-East Asia (5·0%, 0·0–16·6). Globally, HCV prevalence was 1·5% (1·0–2·1) in HIV-negative MSM and 6·3% (5·3–7·5) in HIV-positive MSM. Compared with the general population, HCV prevalence was slightly higher in HIV-negative MSM (PR 1·56, 95% CI 1·14–2·01) and markedly higher (6·22, 5·14–7·29) in HIV-positive MSM. Pooled HCV prevalence was substantially higher in MSM who had ever injected drugs (30·2%, 22·0–39·0) or currently injected drugs (45·6%, 21·6–70·7) than in those who never injected drugs (2·7%, 2·0–3·6). In HIV-negative MSM, the pooled HCV incidence was 0·12 per 1000 person-years (95% CI 0·00–0·72) in individuals not on PrEP and 14·80 per 1000 person-years (9·65–20·95) in individuals on PrEP. HCV incidence in HIV-positive MSM was 8·46 per 1000 person-years (6·78–10·32).

Interpretation HIV-positive MSM are at substantially increased risk of HCV. Overall, HIV-negative MSM had a slightly higher prevalence of HCV than the general population but had a lower prevalence than HIV-positive MSM. High HCV incidence in HIV-negative MSM is likely to be associated with variation in the prevalence of injecting drug use and HIV.

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Introduction

In 2015, WHO estimated that 1·75 million new hepatitis C virus (HCV) infections occurred annually worldwide and about 71 million people were living with chronic HCV infection.1 Parenteral transmission, mainly through injecting drug use and unsafe injection in health-care settings, is the dominant mode of HCV transmission.1 In response, improvements to safe injection practices inside and harm reduction interventions for people who inject drugs (PWID), improving health-care-related injection safety, screening of blood products, and massive upscaling of HCV screening and linkage to care. For people diagnosed with HCV, the strategy targets treatment for 80% of eligible patients. Overall, the strategy aims for a 65% reduction in HCV deaths and a 90% reduction in new infections by 2030 compared with 2015.1
Research in context

Evidence before this study
We did a systematic review of publications in English and listed on MEDLINE or Embase between Jan 1, 2000, and Oct 31, 2019, using search terms for hepatitis C virus (HCV) or hepatitis C, prevalence or incidence, and men who have sex with men (MSM). Studies were eligible if they reported measures of HCV prevalence or HCV incidence (or both) among MSM. Only studies that reported laboratory-confirmed HCV status and those that were based on medical record review were included. Previous systematic reviews on HCV in MSM have so far been focused on men living in high-income countries and have not considered the status of HIV pre-exposure prophylaxis (PrEP) use in HIV-negative MSM.

Added value of this study
Results from this meta-analysis highlight the higher burden of HCV infection in MSM than in the general population globally, particularly in those who inject drugs, those living with HIV, and those living in some low-income and lower-middle-income countries. Our results also show large variation between regions and countries of different income levels, relating to variation in the rates of injecting drug use and prevalence of HIV. Among HIV-negative MSM, we found a notably high incidence of HCV infection in those who were using PrEP for HIV infection, whereas incidence was low in those who were not on PrEP.

Implications of all the available evidence
High rates of injecting drug use appear to be the main driver of the HCV epidemic in MSM. Poor control of HIV infection and other sexually transmitted infections and high-risk sexual practices in specific subgroups of MSM could further facilitate HCV transmission. The findings of this study highlight the need for integrated health services for HCV prevention and for testing and treatment to be offered to MSM populations, particularly MSM who live with HIV, who use PrEP, or who report injecting and non-injecting drug use.

Methods

Search strategy and selection criteria
This systematic review and meta-analysis included studies that were published in English between Jan 1, 2000, and Oct 31, 2019. The literature review was done in December, 2019, by a search of studies listed on MEDLINE or Embase, including conference proceedings. Reference lists of review articles that were published in the same period were also searched. The following key words were used for the search: (gay OR “homosexuality, male” OR “men who have sex with men” OR ”men having sex with men”) AND (HCV OR “hepatitis C”) AND (prevalence OR incidence OR “risk factors”). Studies were eligible if they reported quantitative measures of HCV prevalence, HCV incidence, or both, among MSM only or MSM and other populations. Study populations could include HIV-positive or HIV-negative men who were described as homosexual, bisexual, or MSM. We included only studies that reported laboratory-confirmed HCV status, including HCV serological testing or HCV RNA testing (or both), and those that were based on medical record review. Studies that relied on participants’ self-reported HCV status with no laboratory confirmation were excluded. Studies that did not specify the MSM-specific results in their study population were also excluded.

Article titles and abstracts were reviewed for inclusion based on the inclusion and exclusion criteria. All abstracts were screened by two authors (FJ and SB). Full text articles were then retrieved and assessed for...
eligibility by the same two investigators. A consensus was reached based on the eligibility criteria. For articles that reported results from the same cohort but at different follow-up timepoints, only the article with the most complete results was included. This systematic review was done according to the PRISMA\textsuperscript{19} and MOOSE\textsuperscript{20} guidelines.

Data analysis
Studies were rated according to their study design and HCV testing methods (appendix p 1). Studies that recruited participants from communities with larger sample sizes were scored higher, and those that recruited participants from clinics with smaller sample sizes were scored lower. HCV testing methods were rated higher if a third-generation HCV antibody assay was used with additional confirmatory testing.

Data were extracted from eligible studies and entered into preformatted Microsoft Excel spreadsheets. For studies that published results on HCV prevalence, datapoints included sample size of eligible participants, and the number testing positive using either HCV serology (seroprevalence) or HCV RNA test (viraemia prevalence). Pooled prevalence estimates were grouped separately for seroprevalence and viraemia prevalence. These outcomes were then stratified by HIV status (negative vs positive) in studies in which HCV prevalence by participants’ HIV status was available, and by injecting drug use status (never, previous use, current use [defined as within the previous 6–12 months], or injecting drug use status not presented).

For studies that published results on HCV incidence, datapoints included sample size of eligible participants, total person-years of follow-up, and the number of participants with incident HCV infection. A case of incident HCV infection was defined as a participant who had a negative HCV antibody test at study entry, who later seroconverted to HCV antibody-positive or had a positive HCV RNA test during study follow-up (or both). These outcomes were then stratified by HIV status and by injecting drug use status. HCV re-infection was not considered in this review.

For all eligible studies, extra datapoints included country of origin, year of publication, and HCV testing method used, as well as HIV PrEP use among men who were HIV-negative. Men whose follow-up finished before 2012, the year of the first regulatory approval of PrEP, were assumed not to be taking PrEP.\textsuperscript{21} The four cohort studies in HIV-negative MSM whose study follow-up finished after 2012 were all in men taking PrEP. In HIV-negative MSM, pooled HCV incidence was further stratified by status of HIV PrEP use.

All statistical analyses were done using Stata version 16.1. Meta-analyses were done to calculate pooled prevalence and incidence estimates and corresponding 95% CIs of HCV infection in MSM populations globally. Random-effects meta-analysis was applied to account for between-study heterogeneity and examined using the $I^2$ statistic.\textsuperscript{21}

For HCV prevalence studies, pooled HCV prevalence was presented as the percentage of participants who tested positive for HCV among the total number tested. For HCV incidence studies, pooled HCV incidence was presented as the number of participants who had acquired HCV infection per 1000 person-years of follow-up.

Meta-analytic estimates of HCV prevalence and incidence were reported by HIV status and by WHO region (African region, region of the Americas, South-East Asia region, European region, Eastern Mediterranean region, and Western Pacific region), and by income level as defined by the World Bank (low-income, lower-middle-income, upper-middle-income, and high-income economies).\textsuperscript{22} Pooled HCV prevalence was compared between HIV-negative and HIV-positive MSM by country, by WHO region, and by income level, using meta-regression, and the differences were presented as prevalence ratios (PRs) and their corresponding 95% CIs. Meta-analytic estimates of HCV prevalence and incidence were also stratified by a history of any injecting drug use and current injecting drug use status, and by WHO region. Time trends in pooled HCV prevalence and incidence according to the year of study publication were examined using meta-regression. This analysis was done separately by HIV status and by injecting drug use, then further stratified by WHO region and by income level.

In five studies, 70% or more of the participants were PWID, and thus the studies reported very high HCV prevalence. Due to the strong association between injecting drug use and HCV infection, these studies were treated as outliers and excluded from overall pooled estimates, except for estimates stratified by injecting drug use.

To investigate the burden of HCV infection in MSM populations compared with the general population, PRs were calculated comparing the pooled HCV seroprevalence in the MSM population with the corresponding HCV prevalence in the general population of the same country or WHO region. PRs and corresponding 95% CIs were calculated by country and then by WHO region by pooling country-specific PRs in the same WHO region. General population estimates on HCV prevalence were drawn from published data from the Polaris Observatory HCV Collaborators,\textsuperscript{23} except for Tanzania,\textsuperscript{24} Singapore,\textsuperscript{25} Myanmar,\textsuperscript{26} and South Korea,\textsuperscript{27} for which the estimates of HCV prevalence in the general population were not available in the Polaris Observatory publication and alternative sources were used. Because gender-specific HCV prevalence is not available in the Polaris Observatory publication, a comparison of pooled HCV prevalence in MSM with the general male population could not be done. There were no HCV estimates from the general population in Liberia and Moldova, so no comparison was possible in those two countries.
The systematic review was registered with PROSPERO, CRD42020156262.

Role of the funding source
This study was commissioned and paid for by WHO. As a global systematic review on HCV infection in MSM, the Global HIV, Hepatitis and Sexually Transmitted Infections Programmes at WHO had an active role in the design, conduct, and analysis of the study, interpretation of the data, and writing of the report. Some staff members were included as study coauthors (NL, VM, RB, BM, and AV). 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
Our search of MEDLINE and Embase identified 1221 publications (including conference proceedings), among which 386 duplicates were removed. The remaining 835 publications underwent abstract screening, resulting in the exclusion of a further 424 publications. 411 publications underwent full-text review, of which 223 studies were excluded (72 no MSM denominator, 72 no relevant data, 56 duplicate study, 12 HCV testing self-reported, 11 HCV re-infection only). Six studies were identified through cross-referencing. Resulting in 194 studies for data extraction (figure 1).

For estimates of seroprevalence, 162 studies were used, most of which were done in the Europe region (n=60), and region of the Americas (n=46), and the Western Pacific region (n=39; appendix pp 2–5). Nine studies were from the African region, five were from the South-East Asia region, and two were from the Eastern Mediterranean region. The one remaining study was done in countries from multiple regions.

In five studies, 70% or more of the participants were PWID, and thus the studies reported very high HCV prevalence. These studies were from Thailand (70% of participants PWID), South Africa (88%), Mexico (100%), Vietnam (100%), and the UK (100%). The remaining studies that presented status of injecting drug use recruited less than 20% of PWID among MSM participants.

There was substantial heterogeneity between studies on the estimates of HCV prevalence in MSM across different regions (I²=98·0%) and economies (I²=98·0%). Overall, the pooled estimate for HCV seroprevalence in MSM across all studies (excluding those recruiting ≥70% PWID) was 3·4% (95% CI 2·8–4·0). By WHO region, the highest pooled HCV prevalence was 5·8% (2·5–10·4) in Africa, followed by 5·0% (0·0–16·6) in South-East Asia, 4·5% (2·4–7·1) in the Eastern Mediterranean, 4·1% (3·1–5·2) in the Americas, 3·1% (2·3–4·0) in Europe, and 2·5% (1·6–3·7) in the Western Pacific (table 1). According to income level, the highest pooled HCV prevalence was 10·3% (3·0–21·0) in low-middle income economies, followed by 5·8% (1·1–13·4) in low-income economies, 3·7% (3·4–4·0) in high-income economies, and 1·6% (1·1–2·1) in upper-middle-income economies (appendix p 6).

In estimates of HCV prevalence stratified by HIV status (60 studies in HIV-negative MSM and 101 studies in HIV-positive MSM), the overall pooled prevalence was 1·5% (95% CI 1·0–2·1) in HIV-negative MSM and 6·3% (5·3–7·5) in HIV-positive MSM (table 1). The difference in pooled HCV prevalence between HIV-positive and HIV-negative MSM was highest in Europe (PR 8·66, 95% CI 5·37–13·98), followed by the Western Pacific (5·29, 2·44–11·44) and the Americas (5·21, 2·77–9·80; table 1).

For both HIV-negative and HIV-positive MSM, the pooled prevalence was highest in low-income and lower-middle-income economies (appendix p 6). The difference in pooled HCV prevalence by HIV status was highest in high-income economies (6·74, 4·66–9·74), followed by upper-middle-income economies (6–12, 2·63–14·26). The PR was 1·80 (0·08–38·24) in low-income economies and 1·18 (0·06–21·70) in lower-middle-income economies.

Few studies examined HCV prevalence in MSM stratified by history of injecting drug use (n=40). These were mostly in the Americas (n=16), and in Europe (n=15). Five more studies were done in the Western Pacific, and one in South-East Asia, and one in mixed regions. Overall, the pooled HCV prevalence was 2·7% (95% CI 2·0–3·6) in MSM who reported never having used injecting drugs, 30·2% (22·0–39·0) in those who...
In studies in which data on injecting drug use status were not presented (n=119), the pooled HCV prevalence was 3.5% (95% CI 2.7–4.3), and varied between 2.4% (1.4–3.6) in the Western Pacific and 9.7% (0.0–30.9) in South-East Asia (appendix pp 11–12).

We found no significant time trends in pooled HCV prevalence in either HIV-negative (p=0.66) or HIV-positive (p=0.44) participants.

### Table 1: Prevalence of HCV in PWID

<table>
<thead>
<tr>
<th>Region of the Americas</th>
<th>Overall</th>
<th>HIV-negative</th>
<th>HIV-positive</th>
<th>PR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of studies</td>
<td>n/N</td>
<td>Pooled prevalence, % (95% CI)</td>
<td>Number of studies</td>
</tr>
<tr>
<td><strong>South-East Asia</strong></td>
<td>45</td>
<td>3048/54375</td>
<td>4.1% (3.1–5.2)</td>
<td>17</td>
</tr>
<tr>
<td><strong>Mixed countries</strong></td>
<td>1</td>
<td>111/7426</td>
<td>1.5% (1.2–1.8)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Region of the Americas</strong></td>
<td>45</td>
<td>3048/54375</td>
<td>4.1% (3.1–5.2)</td>
<td>17</td>
</tr>
<tr>
<td><strong>Asian region</strong></td>
<td>45</td>
<td>3048/54375</td>
<td>4.1% (3.1–5.2)</td>
<td>17</td>
</tr>
<tr>
<td><strong>Europe</strong></td>
<td>55</td>
<td>5097/85145</td>
<td>3.5% (2.7–4.4)</td>
<td>26</td>
</tr>
<tr>
<td><strong>Latin America</strong></td>
<td>45</td>
<td>3048/54375</td>
<td>4.1% (3.1–5.2)</td>
<td>17</td>
</tr>
<tr>
<td><strong>Mixed countries</strong></td>
<td>1</td>
<td>111/7426</td>
<td>1.5% (1.2–1.8)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Region of the Americas</strong></td>
<td>45</td>
<td>3048/54375</td>
<td>4.1% (3.1–5.2)</td>
<td>17</td>
</tr>
<tr>
<td><strong>Mixed countries</strong></td>
<td>1</td>
<td>111/7426</td>
<td>1.5% (1.2–1.8)</td>
<td>1</td>
</tr>
</tbody>
</table>

*PR (95% CI): Prevalence ratio (95% confidence interval) for PWID with any history of injecting drug use compared to PWID without any history of injecting drug use.
### Table 1: Pooled estimates of HCV seroprevalence among men who have sex with men by HIV status and WHO region

<table>
<thead>
<tr>
<th>Region</th>
<th>Overall</th>
<th>HIV-negative</th>
<th>HIV-positive</th>
<th>PR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of studies</td>
<td>Pooled prevalence, % (95% CI)</td>
<td>Number of studies</td>
<td>Pooled prevalence, % (95% CI)</td>
</tr>
<tr>
<td>Western Pacific region</td>
<td>30</td>
<td>2% (1-3)</td>
<td>21% (17-26)</td>
<td>22% (18-26)</td>
</tr>
<tr>
<td>Australia</td>
<td>3</td>
<td>2% (1-3)</td>
<td>1% (0-3)</td>
<td>1% (0-3)</td>
</tr>
<tr>
<td>China</td>
<td>10</td>
<td>1% (0-3)</td>
<td>1% (0-3)</td>
<td>1% (0-3)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>10</td>
<td>4% (3-6)</td>
<td>0% (0-1)</td>
<td>0% (0-1)</td>
</tr>
<tr>
<td>Japan</td>
<td>12</td>
<td>2% (1-3)</td>
<td>0% (0-1)</td>
<td>0% (0-1)</td>
</tr>
<tr>
<td>Mongolia</td>
<td>1</td>
<td>3% (2-5)</td>
<td>0% (0-1)</td>
<td>0% (0-1)</td>
</tr>
<tr>
<td>Singapore</td>
<td>1</td>
<td>0% (0-1)</td>
<td>0% (0-1)</td>
<td>0% (0-1)</td>
</tr>
<tr>
<td>South Korea</td>
<td>1</td>
<td>2% (1-3)</td>
<td>0% (0-1)</td>
<td>0% (0-1)</td>
</tr>
<tr>
<td>Vietnam</td>
<td>2</td>
<td>2% (1-3)</td>
<td>0% (0-1)</td>
<td>0% (0-1)</td>
</tr>
</tbody>
</table>

**Notes:**
- *Mixed regions includes one study that was done in Australia, Canada, Europe, and South Africa.
- HCV=hepatitis C virus.
- PR=prediction ratio. *PR of HIV-positive to HIV-negative participants. 95% CI could not be calculated.

### Table 2: Pooled estimates of HCV seroprevalence among men who have sex with men by injecting drug use and WHO region

<table>
<thead>
<tr>
<th>History of injecting drug use</th>
<th>Current injecting drug use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>Ever</td>
</tr>
<tr>
<td>Number of studies</td>
<td>Pooled prevalence, % (95% CI)</td>
</tr>
</tbody>
</table>

**Notes:**
- *Mixed regions includes one study that was done in Australia, Canada, Europe, and South Africa. HCV=hepatitis C virus.
HIV-positive (p=0·64) MSM, nor in MSM who had never injected (p=0·81), had ever injected (p=0·21), or currently injected (p=0·28) drugs. A comparison of HCV prevalence in MSM with the general population was made after excluding the five studies in which at least 70% of participants were PWID.39–42 Overall, the PR of HCV in MSM compared with the general population was 3·04 (95% CI 2·55–3·53; Table 3). In regions with more than five studies available, PRs ranged from 1·29 (0·91–1·67) in the Western Pacific

![Table 3](https://www.thelancet.com/gastrohep)
to 4·20 (95% CI 3·06–5·34) in Europe. Among HIV-negative MSM, the overall PR of HCV compared with the general population was 1·58 (95% CI 1·14–2·01). Nevertheless, the pooled HCV prevalence was no higher, or was even lower, than the general population in the majority of countries with available data. We did find, however, that HCV prevalence among HIV-negative MSM was significantly higher than the general population for eight countries: Burkina Faso, Tanzania, Libya, the Netherlands, Canada, the USA, Indonesia, and Vietnam. The PRs in these countries ranged from 1·55 (1·33–1·80) in the USA to 34·62 (24·24–47·92) in Indonesia.

Among HIV-positive MSM, HCV prevalence was significantly higher than the general population with an overall PR of 6·22 (95% CI 5·14–7·29). By region, the highest PR was in the Eastern Mediterranean (69·2, 58·2–81·4) followed by the Americas (7·80, 2·97–12·62) and the Netherlands (4·0%, 0·2–8·5). Overall prevalence in MSM was analysed in 46 studies (appendix pp 8–9). All of these studies except three (two in China145,146 and one in Thailand147) were done in high-income economies. There was substantial heterogeneity between studies on the estimates of HCV incidence in MSM across different regions (P=98·0%). 11 studies examined HCV incidence in HIV-negative MSM, including seven that focused on HIV-negative MSM not on PrEP. HCV incidence in these HIV-negative MSM not on PrEP ranged from 0 per 1000 person-years to 2·0 per 1000 person-years (figure 2, table 4).

Prevalence of HCV viraemia in MSM populations was examined in 23 studies,19,30,34,40–42,45,47,50,51,53,57,62,66,67,71,77,85,101,119,121,130,162,164,166,168,171–173,197–219 most of which were done in Europe (n=18) and in high-income economies (n=21; appendix p 7). There was substantial heterogeneity between studies in estimates of the prevalence of HCV viraemia in MSM across different regions (I²=94·3%). Overall, the pooled prevalence of HCV viraemia was 1·6% (95% CI 0·8–2·8). It was 0·5% (0·1–1·1) in HIV-negative and 2·4% (1·4–3·6) in HIV-positive MSM (appendix p 14). Among 11 studies that reported HCV viraemia prevalence in HIV-negative MSM, two studies of PrEP trial participants in the UK (3·1%)148 and the Netherlands (4·0%)111 reported the highest prevalence.

Two studies reported HCV viraemia prevalence among MSM who were current users of injecting drugs. A US study that recruited individuals with recent HIV seroconversion reported a prevalence of 8·3% in 12 men,196 and a Swiss study reported a prevalence of 25·2% in 202 participants who were HIV-positive.197 We found no significant time trends in pooled prevalence of HCV viraemia in either HIV-negative (p=0·94) or HIV-positive (p=0·11) MSM.

HCV incidence in MSM was analysed in 46 studies (appendix pp 8–9). Since 2018, four studies in Belgium,198 France,199 the Netherlands,200 and Canada (recruiting participants from France and Canada)201 reported substantially higher HCV incidence rates in HIV-negative MSM on PrEP, ranging from 10·0 per 1000 person-years to 29·3 per 1000 person-years, with a pooled incidence of 0·12 per 1000 person-years (95% CI 0·00–0·72; table 4). 11 studies examined HCV incidence in HIV-negative MSM not on PrEP. HCV incidence in these HIV-negative MSM not on PrEP ranged from 0 per 1000 person-years to 2·0 per 1000 person-years (figure 2, table 2).

HCV incidence in HIV-positive MSM was examined in 39 studies, mostly done in Europe (n=19) and the Western Pacific (n=11; appendix pp 8–9). The pooled HCV incidence was 8·46 per 1000 person-years (95% CI 6·78–10·32). The HCV incidence reported in HIV-positive MSM varied considerably across the studies, ranging from 0 per 1000 person-years to 23·49 per 1000 person-years. In II studies that excluded PWID,19,34,40–42,45,47,50,51,53,57,62,66,67,71,77,85,101,119,121,130,162,164,166,168,171–173,197–219 the pooled HCV incidence was 5·84 per 1000 person-years.

Table 3: HCV prevalence ratios in MSM compared with the general population

<table>
<thead>
<tr>
<th>Prevalence in general population, %</th>
<th>Overall prevalence in MSM</th>
<th>HIV-negative</th>
<th>HIV-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pooled prevalence, %</td>
<td>PR (95% CI)</td>
<td>Pooled prevalence, %</td>
</tr>
<tr>
<td>Western Pacific region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>2·7%</td>
<td>1·29 (0·91–1·67)</td>
<td>1·4%</td>
</tr>
<tr>
<td>Australia</td>
<td>1·30%</td>
<td>2·8%</td>
<td>2·61 (1·78–2·51)</td>
</tr>
<tr>
<td>China</td>
<td>1·21%</td>
<td>1·0%</td>
<td>0·83 (0·76–0·89)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>3·28%</td>
<td>3·5%</td>
<td>1·07 (0·97–1·18)</td>
</tr>
<tr>
<td>Japan</td>
<td>0·98%</td>
<td>2·1%</td>
<td>2·10 (1·23–3·18)</td>
</tr>
<tr>
<td>Mongolia</td>
<td>9·80%</td>
<td>18·0%</td>
<td>1·84 (0·84–3·49)</td>
</tr>
<tr>
<td>Singapore</td>
<td>1·70%</td>
<td>0·0%</td>
<td>0·00 (0·00–0·83)</td>
</tr>
<tr>
<td>South Korea</td>
<td>1·30%</td>
<td>4·1%</td>
<td>3·12 (1·66–5·34)</td>
</tr>
<tr>
<td>Vietnam</td>
<td>1·49%</td>
<td>24·6%</td>
<td>16·52 (14·97–28·20)</td>
</tr>
<tr>
<td>Overall</td>
<td>NA</td>
<td>3·3%</td>
<td>3·04 (2·55–3·53)</td>
</tr>
</tbody>
</table>

Pooled estimates excluded studies that recruited a majority of participants (>70%) who reported injecting drug use. HCV=hepatitis C virus. MSM=men who have sex with men. PR=prevalence ratio. NA=not available.
Figure 2: Pooled incidence of HCV infection in men who have sex with men by HIV status

In another 11 studies in which data on injecting drug use were not presented, the pooled HCV incidence was 11.55 per 1000 person-years (10.11–13.08). In the remaining 17 studies that specified that some of the participants were PWID, the pooled HCV incidence was 8.46 per 1000 person-years (5.43–12.09; appendix p 15).

Only four studies reported HCV incidence in MSM who reported a history of injecting drug use. The incidence in these studies ranged from 23.3 per 1000 person-years to 48.4 per 1000 person-years.

Pooled HCV incidence in HIV-positive MSM appeared to increase over time, with an estimated annual increase of 10.9% (95% CI –2.13 to 15.5), but these trends were not statistically significant (p=0·10). The increase in incidence was more pronounced in 11 studies done in the Western Pacific (p=0·050), with an estimated annual increase of 59.4% (0 to 154.0).

**Discussion**

Globally, the pooled seroprevalence for HCV infection in MSM was 3.4% (95% CI 2.8–4.0), with variation across regions. Based on a small number of studies, the prevalence was estimated to be highest in Africa and South-East Asia. The pooled HCV prevalence in HIV-negative MSM was slightly higher than the general population (PR 1.58, 95% CI 1.14–2.01), whereas the pooled HCV prevalence in HIV-positive MSM was substantially higher than the general population (6.22, 5.14–7.29). HCV prevalence in MSM was strongly associated with injecting drug use. The pooled HCV prevalence was highest in MSM who currently used injecting drugs, followed by those who had ever used injecting drugs. Pooled HCV incidence was low in HIV-negative MSM who were not on PrEP, whereas the pooled HCV incidence in four recent studies of HIV-negative MSM on PrEP was much higher, and was even higher than the pooled HCV incidence in HIV-positive MSM.

The overall pooled HCV prevalence of 3.4% in the current review is lower than the 4.7% reported in a 2017 systematic review and meta-analysis focusing on studies done in industrialised countries and published between January, 2000, and December, 2015. This previous

<table>
<thead>
<tr>
<th>HIV-negative MSM not on PrEP</th>
<th>HIV-positive MSM</th>
<th>HIV-negative MSM on PrEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies</td>
<td>Pooled incidence per 1000 person-years (95% CI)</td>
<td>Number of studies</td>
</tr>
<tr>
<td>African region</td>
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</tr>
<tr>
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</tr>
<tr>
<td>European region</td>
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<td>0.09 (0.00–0.37)</td>
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</tr>
<tr>
<td>Denmark</td>
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<td>France</td>
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<td>Germany</td>
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<td>0</td>
</tr>
<tr>
<td>Netherlands</td>
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</tr>
<tr>
<td>Spain</td>
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<td>0</td>
</tr>
<tr>
<td>Switzerland</td>
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</tr>
<tr>
<td>UK</td>
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</tr>
<tr>
<td>Region of the Americas</td>
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</tr>
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<td>Canada</td>
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</tr>
<tr>
<td>USA</td>
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<td>South-East Asia region</td>
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<td>Thailand</td>
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</tr>
<tr>
<td>Western Pacific region</td>
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</tr>
<tr>
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<tr>
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<tr>
<td>South Korea</td>
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<tr>
<td>Mixed regions*</td>
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</tr>
<tr>
<td>Overall</td>
<td>7</td>
<td>0.12 (0.00–0.72)</td>
</tr>
</tbody>
</table>


Table 4: Pooled estimates of HCV incidence among MSM by HIV status and WHO region

(3.32–9.04). In another 11 studies in which data on injecting drug use were not presented, the pooled HCV incidence was 11.55 per 1000 person-years (10.11–13.08). In the remaining 17 studies that specified that some of the participants were PWID, the pooled HCV incidence was 8.46 per 1000 person-years (5.43–12.09; appendix p 15).

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review reported a similar pooled prevalence of 1.5% in HIV-negative MSM to the current review (also 1.3%), but a higher prevalence of 8.3% in HIV-positive MSM (compared with 6.3% in the current study). The additional studies that we included were largely from upper-middle-income economies with a low HCV prevalence in the general population, which might have contributed to the lower pooled HCV prevalence. The current pooled HCV prevalence of 6.3% in HIV-positive MSM was very similar to that reported in a 2016 global systematic review and meta-analysis of HCV burden in HIV-positive people, which included studies published between January, 2002, and January, 2015. This previous review reported a pooled prevalence of 6.4% (95% CI 3.2–10.0) in HIV-positive MSM populations globally. With recent studies published since 2015 included in the current review, the pooled HCV incidence is slightly lower in HIV-negative MSM (0.12 per 1000 person-years vs 0.44 per 1000 person-years), and higher in HIV-positive MSM (8.46 per 1000 person-years vs 6.35 per 1000 person-years) than the aforementioned 2017 review.

Another 2017 systematic review focusing on studies of HCV incidence in MSM published between January, 2000, and September, 2016, reported a pooled incidence of 0.4 per 1000 person-years in HIV-negative MSM and 7.8 per 1000 person-years in HIV-positive MSM.

Injecting drug use is a predominant driver for the burden of HCV infection in MSM. The higher pooled HCV prevalence in Africa and South-East Asia could be influenced by the small number of studies available, and the fact that a few studies included a high proportion of participants who were PWID, including in Tanzania (13–2%) and Indonesia (11–9%). The higher HCV prevalence in MSM in South-East Asia could also be influenced by the higher HCV prevalence in PWID overall in some countries in that region, including Thailand and Indonesia. The variations in HCV prevalence could also reflect the availability of needle and syringe programmes and opioid agonist therapy in the region, because these harm reduction programmes reduce the risk of HCV infection. Harm reduction coverage for PWID is higher in high-income countries in western Europe, Australasia, and Canada, and could have contributed towards the lower HCV prevalence of MSM who used injecting drugs in these countries than elsewhere.

To a lesser extent than injecting drug use history, the burden of HCV infection in MSM was also associated with HIV infection, with the pooled HCV prevalence higher in HIV-positive MSM than in HIV-negative MSM. The higher prevalence in HIV-positive MSM is not fully explained by higher rates of injecting drug use, although under-reporting of injecting behaviour is possible. Other potential reasons for higher HCV prevalence in HIV-positive MSM include behavioural factors, such as higher levels of sexual contact with higher numbers of sexual partners, and biological factors, such as higher HCV viral load in semen in addition to lower immunity compared with HIV-negative MSM.

The high prevalence of HCV in MSM living with HIV in lower-income and lower-middle-income economies is also noteworthy. Whereas nine high-income countries have reached the UNAIDS 90/90/90 targets to eliminate HIV transmission by 2018, HIV treatment coverage is lower in some low-income and lower-middle income economies where HIV prevalence is high and HIV treatment coverage in these settings is even lower for MSM. Impaired immune function associated with HIV infection in the MSM population in these countries might facilitate HCV transmission in both HIV-positive and HIV-negative MSM by means of increased transmissibility of HCV. Further evaluation of HCV treatment coverage and associated immune function and HCV risk is warranted.

In HIV-negative MSM in most countries, HCV prevalence was no higher or was even lower than the general population. However, eight countries (Burkina Faso, Tanzania, Libya, Indonesia, Vietnam, the Netherlands, Canada, and the USA) had significantly higher HCV prevalence in HIV-negative MSM than in the general population. Oversampling of participants with a history of injecting drug use might have contributed to the high prevalence of HCV in HIV-negative MSM in these countries, even though we excluded studies with 70% or more MSM who were PWID in the analyses. Some studies done in high-income countries specifically included MSM who used drugs, often but not necessarily by injection, to enhance sex. The co-occurrence of sexual and injecting drug use risk might have contributed to a higher HCV prevalence in HIV-negative MSM in these settings.

HCV incidence in HIV-positive MSM varied considerably by region. Regional variations in sexual behaviour might have contributed to this diversity. Longitudinal evidence from some cohort studies of HIV-positive MSM in Europe identified an increasing trend in HCV incidence since the late 1990s. This increase in HCV incidence coincided with increasing sexual practices associated with HCV transmission, such as fisting and group sex, between HIV-positive partners in the context of serosorting, aiming to minimise the risk of onward HIV transmission. This also coincided with a resurgence of ulcerative STIs, including syphilis and lymphogranuloma venereum, in the communities of HIV-positive MSM in the same region.

High HCV incidence has recently been reported in four studies in northern Europe and Canada in which HCV-negative MSM were taking PrEP for HIV prevention, with a pooled incidence of 14.8 per 1000 person-years (95% CI 9.6–20.9). This high incidence could be due to increased sexual mixing of HIV-negative men, after taking PrEP, with HIV-positive MSM. Because PrEP is used by MSM at high risk of HIV infection, it is not surprising that PrEP study participants have a high
incidence of other STIs, including gonorrhoea, chlamydia, and syphilis.\textsuperscript{12} Evidence from the same studies also indicates that these HIV-negative MSM at high risk of HIV infection had a relatively high prevalence of HCV viraemia before PrEP initiation.\textsuperscript{73,190} This evidence suggests that the high risk for HCV and other STIs pre-existing in at least some of the HIV-negative men who were at high risk of HIV infection, and was not necessarily related to changes in sexual behaviour or condom use after PrEP. Given the high HCV incidence rates observed in HIV-negative MSM in these PrEP studies, PrEP programmes could be an effective way to reach, test, and treat MSM who potentially have high rates of STIs, including HCV.

In this systematic review, data for HCV in MSM in low-income and lower-middle-income countries were scarce. In particular, few data were available for HCV viraemia prevalence and HCV incidence, which are crucial for prevention efforts and health planning. HCV viraemia estimates require HCV RNA testing and incidence estimates rely on longitudinal studies, both of which are costly, which could have hindered the conduct of similar studies in these countries. Also, the current systematic review considered articles written only in English, which might have led to fewer studies from non-English-speaking countries being included. In areas including north Africa, the Middle East, South-East Asia, and eastern Europe, where few studies were eligible for inclusion, the pooled results will be more sensitive to new study results in future should they have been missed in this review due to this language limitation. The direction of the bias that might have been introduced as a result is difficult to predict. Across the 113 countries included in the Polaris Observatory review of HCV prevalence in the general population, population-based studies were available in 20 (18%) countries.\textsuperscript{21} Population-based studies are unavailable in MSM. We used broad study inclusion criteria to maximise the sample size from a large variety of recruitment sources. Only studies that recruited 70% or more of MSM participants among PWID were excluded from the overall estimates. Imbalances also existed across regions, which meant that some countries contributed much more to the regional estimates than others. Countries with a small number of studies are likely to have been under-represented in regional estimates, but these estimates should be broadly representative of countries of a similar MSM community in the same region.

Substantial heterogeneity existed between studies on the estimates of HCV prevalence and incidence in MSM across different regions and economies. In addition to variations in injecting drug use, HIV status, and regional differences that have been considered in the analyses, other factors might have also contributed to the variation in the rates observed. Variation could arise because of different HCV testing methods and age structures of the participants. Injecting drug use history was based on participant self-reporting. Injecting drug use is a highly stigmatised behaviour in most settings, and in many jurisdictions is punishable by substantial terms of imprisonment; therefore, it was likely to have been under-reported.\textsuperscript{12} This under-reporting might have led to an underestimation of injecting drug use-associated HCV risk. We did not consider modes of administering drugs other than injecting. The type of drug injected was not considered in this systematic review, and was not reported in most studies. The association of drug use with HCV risk could differ between users of opioids and users of synthetic stimulants that are often used during sex to enhance sexual pleasure.\textsuperscript{22} Aside from injecting drug use, nasal drug use has also been identified as a potential risk factor for HCV transmission,\textsuperscript{218,219} but the evidence is still too scarce to be included in this review.

MSM populations globally have a higher burden of HCV infection than the general population, and the difference is more pronounced in MSM living with HIV. Higher rates of injecting drug use are likely to be the main driver of the HCV epidemic in MSM populations. Poor control of HIV infection and other STIs and high-risk sexual practices in specific subgroups of MSM communities might further facilitate HCV transmission. The WHO HCV elimination targets are on the way to being achieved for several indicators, such as for the prevention of mother-to-child transmission, and blood and medical injection safety in clinical settings. Reaching PWID and people in prisons will be critical to achieving the HCV elimination targets. This systematic review highlights the higher burden of HCV infection in MSM than in the general population.

More effort is required to offer adapted, evidence-based, and integrated prevention, testing, and treatment services to MSM, notably those most at risk of HCV, including HIV-positive MSM, MSM who use PrEP, and MSM who report injecting and non-injecting drug use. As has been achieved in the field of HIV prevention, integrated funding mechanisms and differentiated service delivery models are required for MSM.

Contributors
FJ, GJD, GM, and AEG conceptualised the review project and developed the study protocol. NL, VM, RB, and AV reviewed the study protocol before it was finalised. FJ did the literature review. FJ and SB screened and reviewed all the published literature, including title, abstract, and full text. FJ did the data extraction and meta-analysis and drafted the manuscript. All authors contributed to the interpretation of study results, reviewed the draft manuscript, and approved the final version of manuscript before its submission.

Declaration of interests
FJ and AEG report grants from WHO during the conduct of the study. GJD reports grants from Gilead, AbbVie, Merck, and Bristol-Myers Squibb, personal fees from Gilead, AbbVie, and Merck, and non-financial support from Gilead, AbbVie, and Merck, outside of the submitted work. GM reports grants from Gilead and grants from AbbVie, outside of the submitted work. AEG reports personal fees and non-financial support from Gilead, outside of the submitted work. All other authors declare no competing interests.

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