Methods and indicators to validate country reductions in incidence of hepatitis C virus infection to elimination levels set by the World Health Organization

Declaration of interests

I have no conflicts of interest to declare.
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Global Health Sector Strategy (GHSS) on viral hepatitis 2016-2021
Elimination of hepatitis C virus infection (HCV) as a public health problem by 2030

Key issues regarding validation of the HCV incidence target:

- Can be difficult to measure using the gold-standard method (i.e., prospective follow-up and re-testing of people at risk)
- Few countries have collected 2015 "baseline" incidence
- Substantial country-level variation in the level of HCV burden, epidemic dynamics, populations affected and availability of resources calls for having a choice of options to validate the HCV targets
Objectives

1. Review methods by which HCV incidence can be monitored and discuss their applicability in different contexts

2. Assess the extent to which certain HCV-specific indicators track HCV incidence using mathematical modelling

3. Discuss the advantages and disadvantages of an absolute HCV incidence target compared to the current relative target, and suggest a suitable threshold

Recommend several options that countries could use to validate the HCV incidence target

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Methods to validate country responses for decreasing incidence of hepatitis C virus infection (HCV)

<table>
<thead>
<tr>
<th>METHOD</th>
<th>1. PROSPECTIVE HCV RE-TESTING OF PEOPLE AT RISK (GOLD STANDARD)</th>
<th>2. RETROSPECTIVELY-COLLECTED HCV RE-TESTING DATA</th>
<th>3. LINKED REPEATED CROSS-SECTIONAL STUDY</th>
<th>4. TESTS FOR RECENT INFECTION:</th>
<th>5. HCV ANTIBODY PREVALENCE AND DURATION OF RISK BEHAVIOIR</th>
<th>6. SERIAL MEASUREMENTS OF HCV ANTIBODY PREVALENCE (DEMOGRAPHIC METHOD)</th>
<th>7. SURVEILLANCE OF ACUTE HCV INFECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAIN ADVANTAGE(S)</td>
<td>• Systematic data collection procedures can be adopted to maximise data quality and participant follow-up</td>
<td>Easy and inexpensive (can use routine HCV testing data)</td>
<td>Easier and less resource intensive (based on X-sectional surveys, which may be already ongoing or are generally easier to implement than cohorts)</td>
<td>Faster because a single sample derived from one X-sectional survey is needed</td>
<td>Lower cost and faster because a single sample derived from one X-sectional survey is needed</td>
<td>Faster because can capitalise on population-based cross-sectional surveys, which may be already ongoing (e.g., for HIV surveillance)</td>
<td>Easy and inexpensive (use routine notification by clinicians, laboratories or sentinel surveillance)</td>
</tr>
<tr>
<td>MAIN DISADVANTAGE(S)</td>
<td>• Resource intensive</td>
<td>Limited application, since routine HCV testing is uncommon</td>
<td>Can require large sample sizes</td>
<td>Can require large sample sizes</td>
<td>Can overestimate incidence</td>
<td>Unclear how reliable/valid the incidence estimates are compared to the gold-standard</td>
<td>Can considerable underestimate incidence and mis-estimate trends over time because few participants seek testing, and case definitions, testing patterns or the reporting system have changed over time</td>
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<tr>
<td>PREVIOUS APPLICATIONS</td>
<td>• Population: mostly PWID and MSM; rarely nationwide and in the general population</td>
<td>• Population: mostly HIV-positive MSM</td>
<td>• Population: mostly PWID</td>
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<tr>
<td></td>
<td>• Setting: widely used, mostly large urban cities of high-income countries</td>
<td>• Setting: mostly high-income countries</td>
<td>• Setting: a few countries like Canada, Australia, Greece</td>
<td>• Setting: limited application, mostly proof of concept studies</td>
<td>• Setting: several countries</td>
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<td>POTENTIAL FOR VALIDATING THE HCV INCIDENCE TARGET</td>
<td>✔ Can capitalise on community-based test-and-treat efforts by re-testing those identified as being HCV-negative (as done in Egypt)</td>
<td>✔ Dependent on availability of regular routine testing and data collection in defined cohorts (currently, primarily for MSM)</td>
<td>✔ Primarily for populations with high risk of HCV infection (e.g., PWID, MSM)</td>
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<td>✔ Primarily for PWID but potentially for other groups like MSM</td>
<td>✔ Feasibility and reliability in estimating HCV incidence needs to be examined</td>
<td>❔ Limited application on its own but could complement findings derived through other methods</td>
</tr>
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Methods to validate country responses for decreasing incidence of hepatitis C virus infection (HCV)

Direct methods
- Measure new or recent HCV infections
  - Prospective cohort study
  - Retrospective cohort study
  - Linked X-sectional study
  - Tests for recent infection

Indirect methods
- Estimate HCV incidence based on HCV antibody prevalence
  - Linked HCV antibody prevalence with duration of risk behavior
  - Linked HCV antibody prevalence with HCV-related mortality in multiple surveys

Other
- No estimate of HCV incidence but can infer HCV incidence trends over time
  - Surveillance of reported cases of acute HCV infection
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Alternative indicators for validating the HCV incidence target

1. Trends in chronic HCV prevalence
2. Scale-up levels of HCV treatment +/- preventative interventions
3. Trends in antibody HCV prevalence
4. Trends in HCV testing

METHODOLOGY

• Extended analyses of up to 17 dynamic HCV transmission models previously developed for various global settings and populations\(^1\)-\(^{14}\)

• Models originally developed to project future trends in chronic HCV prevalence and incidence following the scale-up of HCV treatment +/- HCV preventative measures

• Modelled populations:
  - PWID (n=9)
  - MSM (n=1)
  - General population (n=7)

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\(^1\) Ayoub et al. BMJ Open 2019
\(^2\) Ayoub et al. J Viral Hepat 2017
\(^3\) Fraser et al. Addiction 2018
\(^4\) Fraser et al. Am J Epidemiol 2019
\(^5\) Lim et al. Lancet Glob Health 2020
\(^6\) Lim et al. Int J Epidemiol 2018
\(^7\) Macgregor et al. EClinicalMed 2020
\(^8\) Marquez et al. Int J Drug Policy 2021
\(^9\) Stone et al. medRxiv 2021
\(^10\) Trickey et al. Liver Int 2020
\(^11\) Trickey et al. J Viral Hepat 2019
\(^12\) Trickey et al. Lancet Gastroenterol Hepatol 2019
\(^13\) Walker et al. Lancet Glob Health 2020
\(^14\) Ward et al. Addiction 2018
## Alternative indicators for monitoring decreases in hepatitis C virus (HCV) incidence

<table>
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<tr>
<th>ALTERNATIVE INDICATOR</th>
<th>RELATIONSHIP WITH HCV INCIDENCE</th>
<th>FACTORS THAT CAN AFFECT RELATIONSHIP WITH HCV INCIDENCE</th>
<th>MINIMUM COUNTRY-LEVEL DATA NEEDED</th>
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<td>1. Trends in chronic HCV prevalence ✅</td>
<td>Tracks trends in HCV incidence well in different settings and populations</td>
<td>• Few and the impact seems low</td>
<td>• Trends in chronic HCV prevalence at baseline and endpoint of HCV elimination initiative</td>
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| 2. Scale-up levels of HCV interventions ✅ | Variable in different settings and populations and so no universal target can be set; however, country-specific modelling can be used to determine if level of scale-up would have reduced incidence | • Prevention intervention scale-up  
• Population growth  
• Underlying epidemic dynamics  
• Elimination time frame  
• Population heterogeneity in risk and targeting of HCV treatment | • Scale-up levels of HCV treatment and HCV preventative interventions  
• Baseline chronic or antibody HCV prevalence and historic trends in prevalence |
| 3. Trends in HCV antibody prevalence ❌ | Does not track HCV incidence well: relationship is highly variable across settings and populations | • Prevention intervention scale-up  
• Population turnover  
• Population heterogeneity in risk and targeting of HCV treatment | • N/A |
| 4. Scale-up levels of HCV testing ❌ | Does not track HCV incidence well: relationship is highly variable across settings and populations | • Prevention intervention scale-up  
• Population sub-groups that are tested and retested  
• Downstream cascade of care (e.g., referral for care, uptake of HCV treatment) | • N/A |
Correlation between projected relative decrease in HCV incidence and chronic HCV prevalence over the course of the HCV elimination initiative for different scale-up levels in HCV treatment

Overall: relative decrease in chronic HCV prevalence tracks well relative decrease in HCV incidence

Relationship holds well if HCV preventative interventions are also scaled-up
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<th>Minimum country-level data needed</th>
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Absolute HCV incidence target

**WHAT THRESHOLDS TO USE?**

- Empirical data on HCV incidence are scarce, and so targets can only be derived from modelled estimates
- General population:
  - 80% reduction relative to the WHO 2015 global estimate\(^1\) = 5 per 100,000 person-years
- People who inject drugs
  - 80% reduction relative to the single global estimate\(^2\) = 2 per 100 person-years

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<td>Obviates the need to collect HCV incidence data at baseline</td>
<td>Penalises countries with high baseline HCV incidence, as these would need to achieve greater reductions than if a relative target was used</td>
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<tr>
<td>Benefits countries which already have low baseline HCV incidence, as it prevents need for further reduction</td>
<td>Does not provide information on the past trajectory of HCV incidence</td>
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<tr>
<td>Directs global efforts towards countries with high baseline HCV incidence, and thus, higher need for intervention</td>
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<tr>
<td>Sets a universal threshold below which the rate of HCV transmission can be considered negligible, independent of setting</td>
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1WHO. Global health sector strategy on viral hepatitis 2016-2021
2Trickey A et al. Lancet Gastroenterol Hepatol 2019
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Inform WHO guidance for country validation of viral hepatitis elimination.
Proposed process to validate the hepatitis C virus (HCV) incidence target

STEP 1: Determine populations needing to be monitored to validate HCV incidence target

- What proportion* of new HCV cases occur among high-risk populations relative to the general population?
  - small
  - moderate
  - large

Validate HCV incidence target in the general population only
Validate HCV incidence target among high-risk populations and in the general population
Validate HCV incidence target among high-risk populations only

Can HCV incidence be estimated at baseline and endpoint of HCV elimination initiative?
- Yes
  - Validate HCV elimination using either the absolute or the relative HCV incidence target
- No
  - Validate HCV elimination using the absolute HCV incidence target

Can chronic HCV prevalence be estimated at baseline and endpoint of HCV elimination initiative?
- Yes
  - Validate HCV elimination by documenting an 80% decrease in chronic HCV prevalence
- No
  - Unlikely to be able to validate the HCV incidence target

Are data available on the scale-up level of HCV interventions over the course of the HCV elimination initiative and on the general characteristics of the local epidemic?
- Yes
  - Validate by documenting an 80% decrease in incidence using country-specific mathematical modelling
- No
  - Unlikely to be able to validate the HCV incidence target

*Proportion refers to the percentage of new HCV cases occurring among high-risk populations relative to the general population.
Proposed process to validate the hepatitis C virus (HCV) incidence target

STEP 1: Determine populations needing to be monitored to validate HCV incidence target

- What proportion* of new HCV cases occur among high-risk populations relative to the general population?
  - small
  - moderate
  - large

  - Validate HCV incidence target in the general population only
  - Validate HCV incidence target among high-risk populations and in the general population
  - Validate HCV incidence target among high-risk populations only

STEP 2: Determine option for validating the HCV incidence target in each of the populations needing to be monitored

- Can HCV incidence be estimated at baseline and endpoint of HCV elimination initiative?
- Validate HCV elimination using either the absolute or the relative HCV incidence target

- Can HCV incidence be estimated only at the endpoint of HCV elimination initiative?
- Validate HCV elimination using the absolute HCV incidence target

- Can chronic HCV prevalence be estimated at baseline and endpoint of HCV elimination initiative?
- Validate HCV elimination by documenting an 80% decrease in chronic HCV prevalence

- Are data available on the scale-up level of HCV interventions over the course of the HCV elimination initiative and on the general characteristics of the local epidemic?
- Validate by documenting an 80% decrease in incidence using country-specific mathematical modelling

- Unlikely to be able to validate the HCV incidence target
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Inform WHO guidance for country validation of viral hepatitis elimination
New WHO guidance provides options with respect to the methods and indicators that countries can use to validate the HCV incidence target.
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