University of BRISTOL

Bristol Medical School

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

Adelina Artenie, Niklas Luhmann, Aaron G. Lim, Hannah Fraser, Zoe Ward, Jack Stone, Louis MacGregor, Josephine G. Walker, Adam Trickey, Lara K. Marquez, Laith J. Abu-Raddad, Houssein Ayoub, Nick Walsh, Matthew Hickman, Natasha K. Martin, Philippa Easterbrook, Peter Vickerman

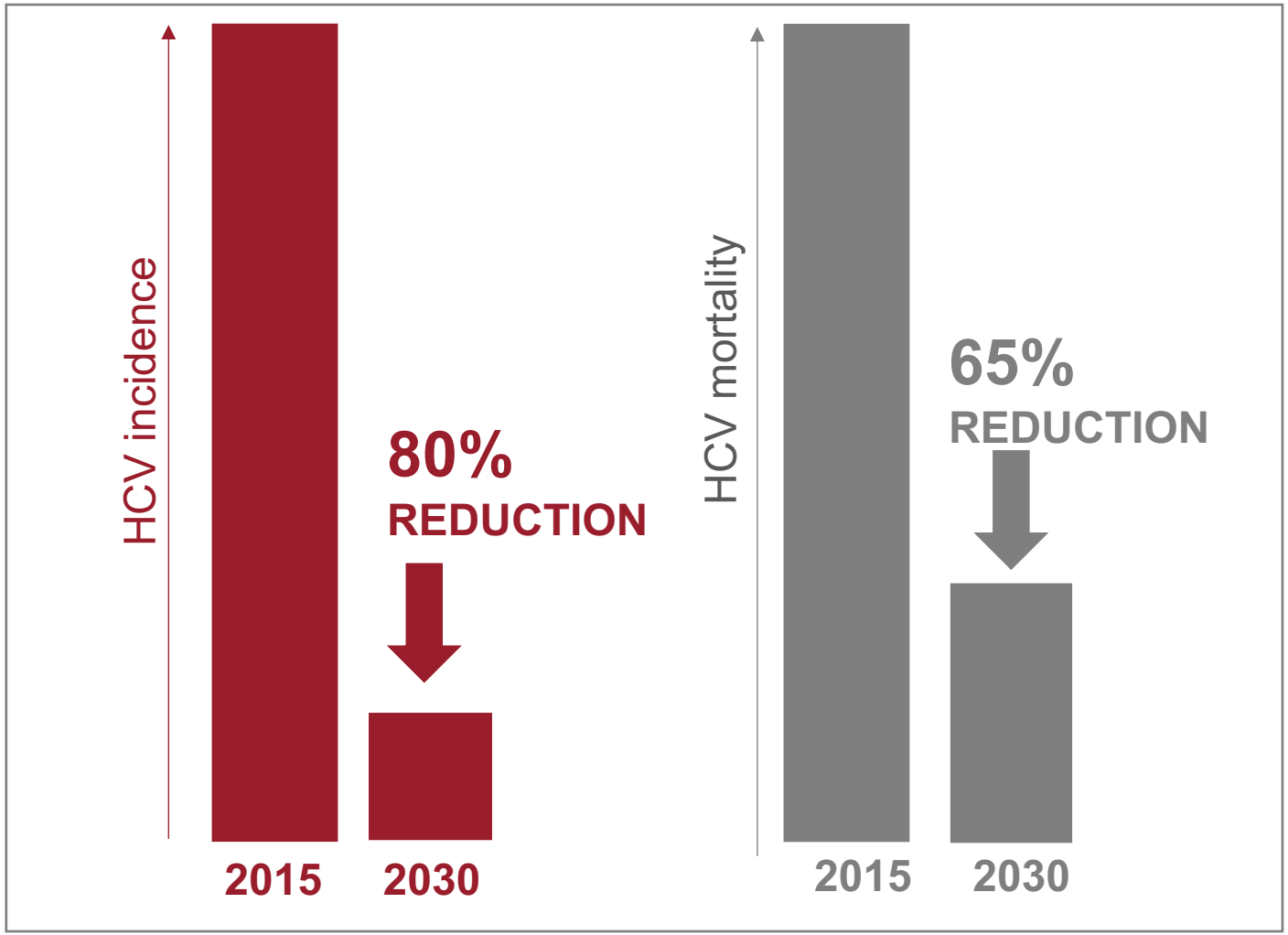
Declaration of interests

I have no conflicts of interest to declare.

The work presented has been accepted for publication on August 17, 2021:

Artenie A, Luhmann, N., Lim, A.G. et al. Methods and indicators to validate country reductions in incidence of hepatitis C virus infection to elimination levels set by the World Health Organization. *The Lancet Gastroenterology & Hepatology* 2021 [In Press].

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 (ie, 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

Inform WHO guidance for country validation of viral hepatitis elimination

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

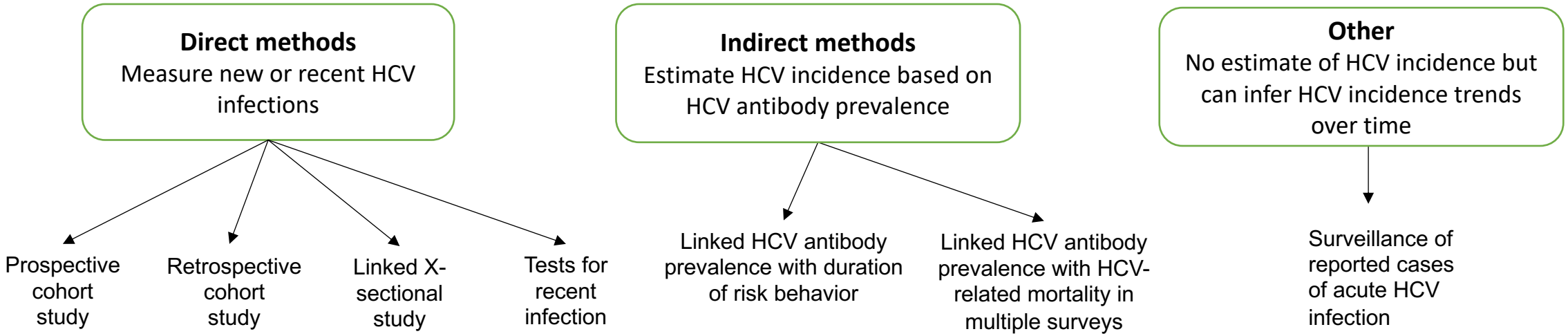
Recommend several options that countries could use to validate the HCV incidence target

Inform WHO guidance for country validation of viral hepatitis elimination

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

METHOD	1. PROSPECTIVE HCV RE-TESTING OF PEOPLE AT RISK (GOLD STANDARD)	2. RETROSPECTIVELY-COLLECTED HCV RE-TESTING DATA	3. LINKED REPEATED CROSS-SECTIONAL STUDY	4. TESTS FOR RECENT INFECTION: • HCV RNA+ and Ab- • HCV Ab avidity index	5. HCV ANTIBODY PREVALENCE AND DURATION OF RISK BEHAVIOUR	6. SERIAL MEASUREMENTS OF HCV ANTIBODY PREVALENCE (DEMOGRAPHIC METHOD)	7. SURVEILLANCE OF ACUTE HCV INFECTION
MAIN ADVANTAGE(S)	• Systematic data collection procedures can be adopted to maximise data quality and participant follow-up	Easy and inexpensive (can use routine HCV testing data)	Easier and less resource intensive (based on X-sectional surveys, which may be already ongoing or are generally easier to implement than cohorts)	Faster because a single sample derived from one X-sectional survey is needed	Lower cost and faster because a single sample derived from one X-sectional survey is needed	Faster because can capitalise on population-based cross-sectional surveys, which may be already ongoing (e.g., for HIV surveillance)	Easy and inexpensive (use routine notification by clinicians, laboratories or sentinel surveillance)
MAIN DISADVANTAGE(S)	• Resource intensive • Can require large sample sizes	Limited application, since routine HCV testing is uncommon	Can require large sample sizes	• Can require large sample sizes • Can overestimate incidence • Does not capture reinfection	• Unclear how reliable/valid the incidence estimates are compared to the gold-standard	• Unclear how reliable/valid the incidence estimates are compared to the gold-standard • Requires additional demographic data • Does not capture reinfection	Can considerable under-estimate 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
PREVIOUS APPLICATIONS	• Population: mostly PWID and MSM; rarely nationwide and in the general population • Setting: widely used, mostly large urban cities of high-income countries	• Population: mostly HIV-positive MSM • Setting: mostly high-income countries	• Population: mostly PWID • Setting: a few countries like Canada, Australia, Greece	• Population: mostly PWID • Setting: limited application, mostly proof of concept studies	• Population: mostly PWID • Setting: several countries	• Population: general population • Setting: not yet implemented, but used in the HIV field	• Population: general population • Setting: several countries in Europe and across the European Union, US, Egypt, Taiwan
POTENTIAL FOR VALIDATING THE HCV INCIDENCE TARGET	✅ Can capitalise on community-based test-and-treat efforts by re-testing those identified as being HCV-negative (as done in Egypt)	✅ Dependent on availability of regular routine testing and data collection in defined cohorts (currently, primarily for MSM)	✅ Primarily for populations with high risk of HCV infection (e.g., PWID, MSM)	✅ Primarily for populations with high risk of HCV infection (e.g., PWID, MSM)	✅ Primarily for PWID but potentially for other groups like MSM	? • Feasibility and reliability in estimating HCV incidence needs to be examined	✗ Limited application on its own but could complement findings derived through other methods

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



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

Inform WHO guidance for country validation of viral hepatitis elimination

Objectives

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

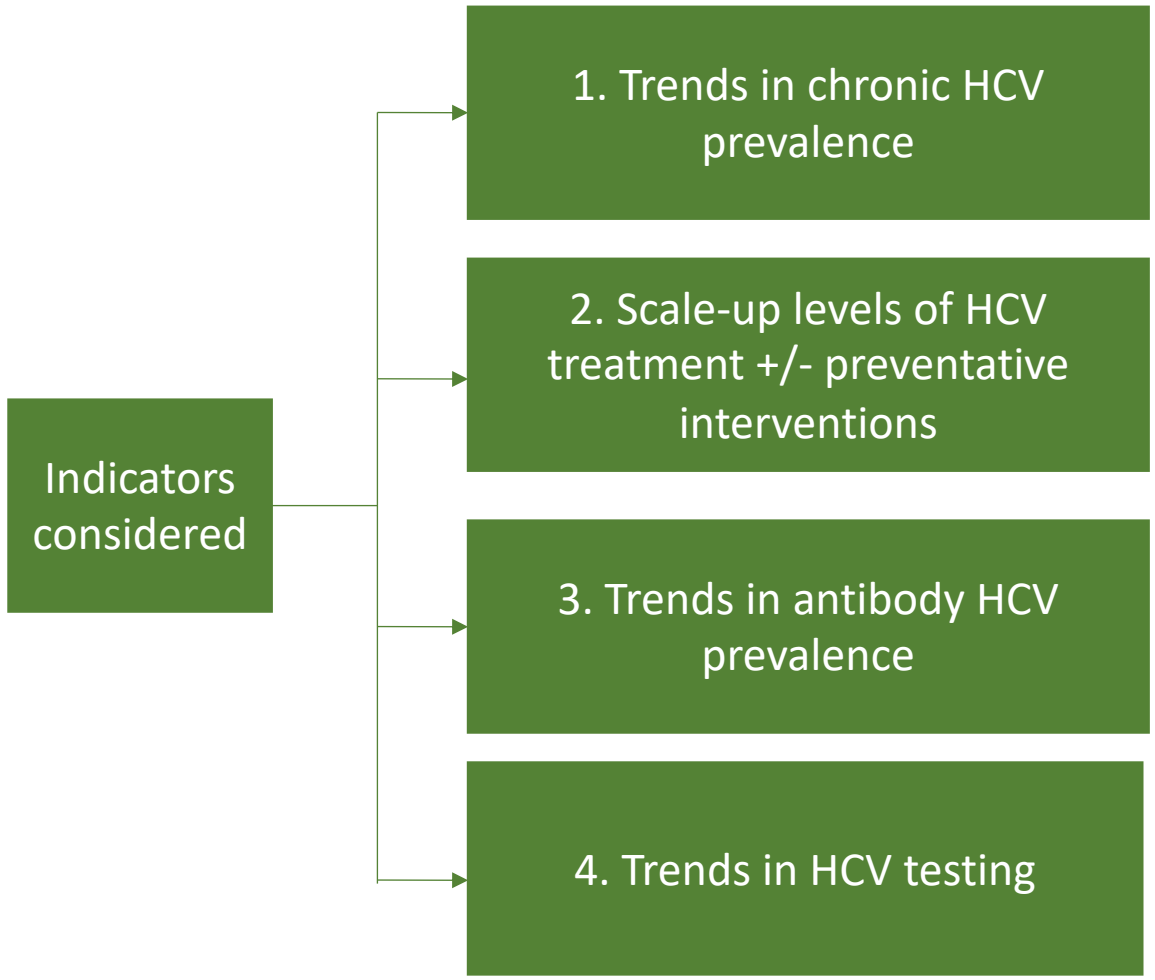
2. Assess the extent to which certain HCV-specific indicators track HCV incidence using mathematical modelling

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

Inform WHO guidance for country validation of viral hepatitis elimination

Alternative indicators for validating the HCV incidence target



METHODOLOGY

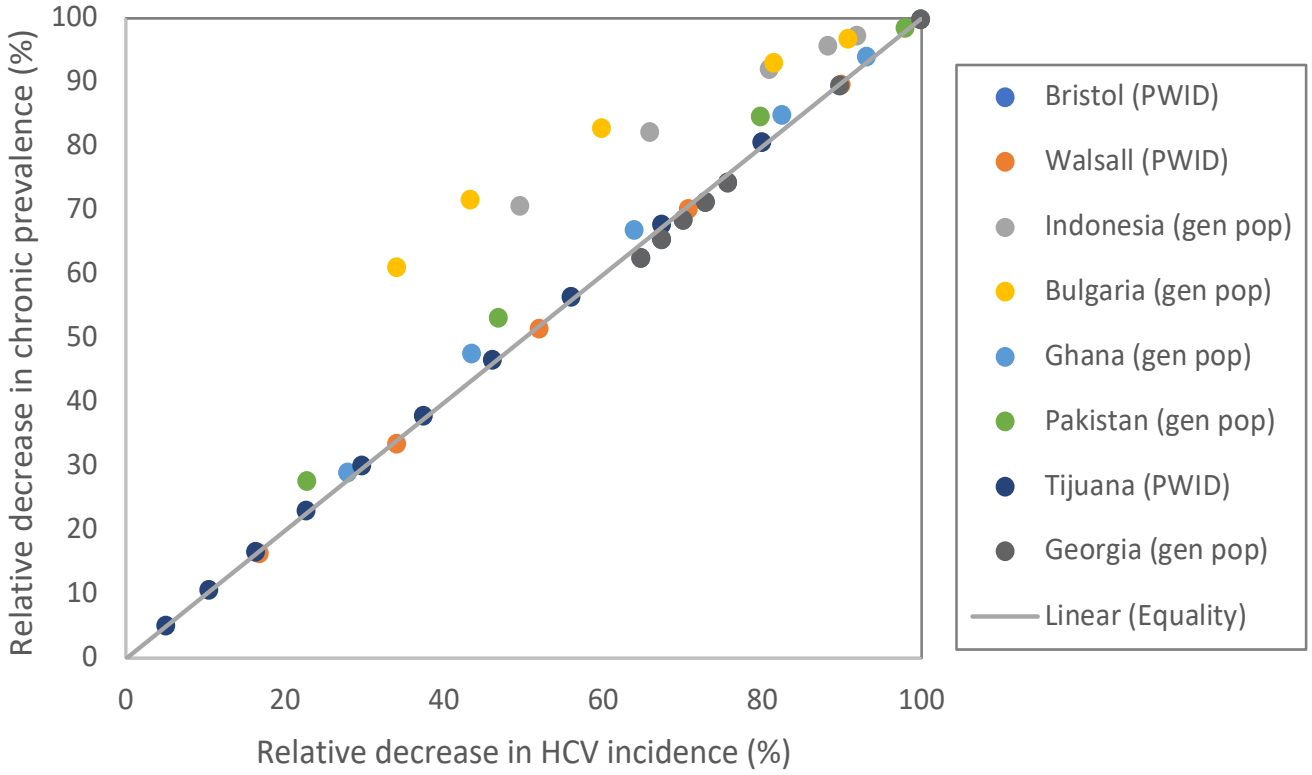
- Extended analyses of up to 17 dynamic HCV transmission models previously developed for various global settings and populations[1-14]
- Models originally developed to project future trends in chronic HCV prevalence and incidence following the scale-up of HCV treatment +/- HCV preventative measures
- Modelled populations:
  - PWID (n=9)
  - MSM (n=1)
  - General population (n=7)

[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

ALTERNATIVE INDICATOR	RELATIONSHIP WITH HCV INCIDENCE	FACTORS THAT CAN AFFECT RELATIONSHIP WITH HCV INCIDENCE	MINIMUM COUNTRY-LEVEL DATA NEEDED
1. Trends in chronic HCV prevalence ✅	Tracks trends in HCV incidence well in different settings and populations	• Few and the impact seems low	• Trends in chronic HCV prevalence at baseline and endpoint of HCV elimination initiative
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

Alternative indicator #1: Trends in chronic HCV prevalence



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

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

Alternative indicators for monitoring decreases in hepatitis C virus (HCV) incidence

ALTERNATIVE INDICATOR	RELATIONSHIP WITH HCV INCIDENCE	FACTORS THAT CAN AFFECT RELATIONSHIP WITH HCV INCIDENCE	MINIMUM COUNTRY-LEVEL DATA NEEDED
1. Trends in chronic HCV prevalence ✅	Tracks trends in HCV incidence well in different settings and populations	• Few and the impact seems low	• Trends in chronic HCV prevalence at baseline and endpoint of HCV elimination initiative
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

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

Inform WHO guidance for country validation of viral hepatitis elimination

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

Inform WHO guidance for country validation of viral hepatitis elimination

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

[1]WHO. Global health sector strategy on viral hepatitis 2016-2021
[2]Trickey A et al. Lancet Gastroenterol Hepatol 2019

ADVANTAGES AND DISADVANTAGES COMPARED TO A RELATIVE TARGET

ADVANTAGES	DISADVANTAGES
• **Obviates the need to collect HCV incidence data at baseline**	• **Penalises countries with high baseline HCV incidence, as these would need to achieve greater reductions than if a relative target was used**
• **Benefits countries which already have low baseline HCV incidence, as it prevents need for further reduction**	• Does not provide information on the past trajectory of HCV incidence
• Directs global efforts towards countries with high baseline HCV incidence, and thus, higher need for intervention	
• Sets a universal threshold below which the rate of HCV transmission can be considered negligible, independent of setting	

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

Inform WHO guidance for country validation of viral hepatitis elimination

Objectives

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

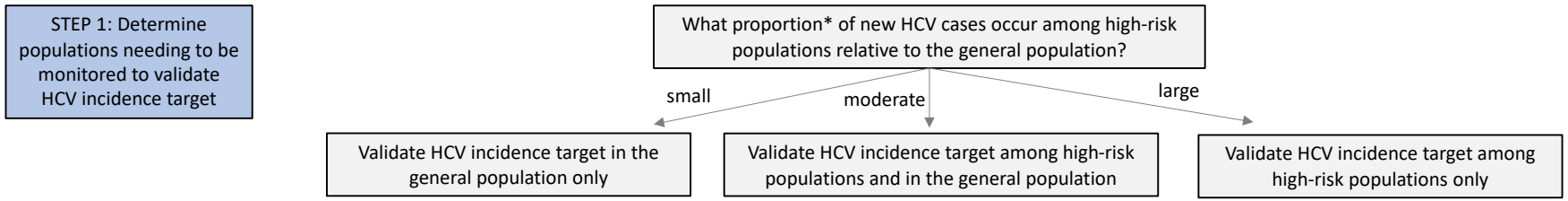
2. Assess the extent to which certain HCV-specific indicators track HCV incidence using mathematical modelling

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

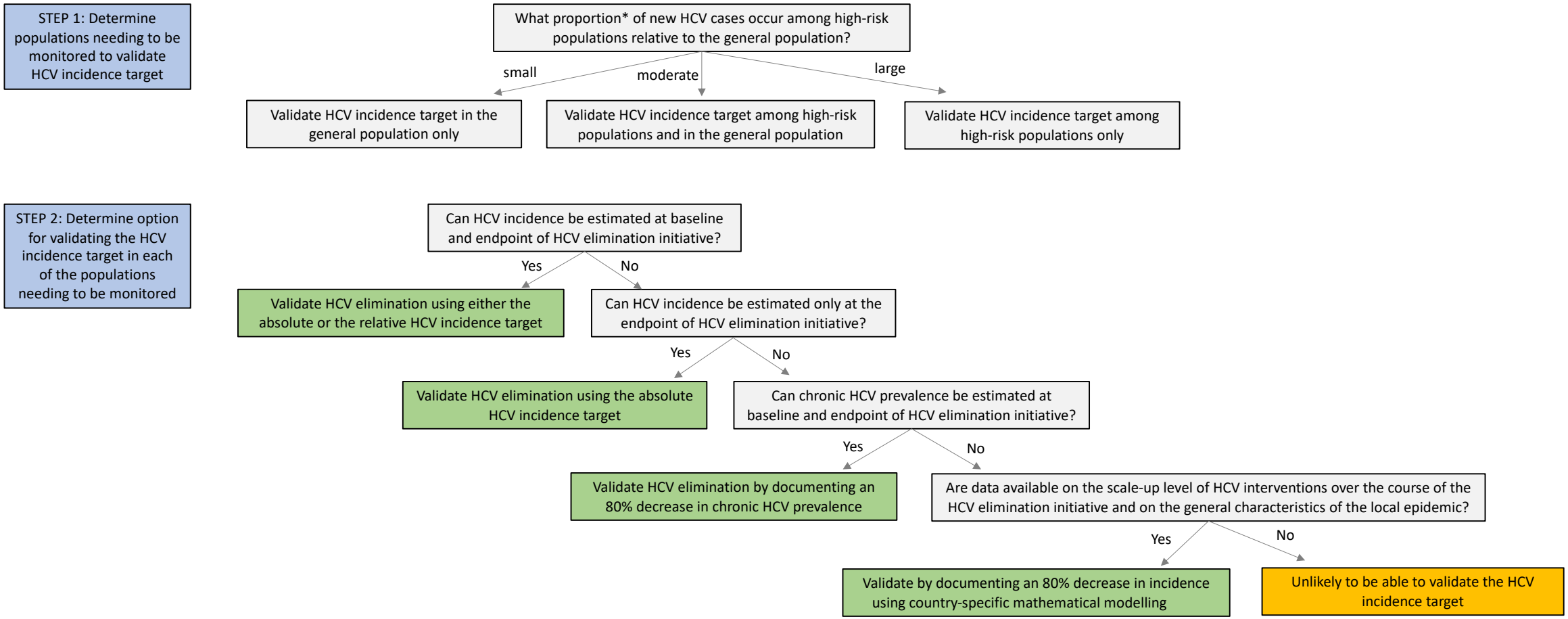
Recommend several options that countries could use to validate the HCV incidence target

Inform WHO guidance for country validation of viral hepatitis elimination

Proposed process to validate the hepatitis C virus (HCV) incidence target



Proposed process to validate the hepatitis C virus (HCV) incidence target



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

Inform WHO guidance for country validation of viral hepatitis elimination

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

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

World Health Organization

INTERIM GUIDANCE FOR COUNTRY VALIDATION OF VIRAL HEPATITIS ELIMINATION

JUNE 2021

TECHNICAL REPORT

BOX 4.5 Measuring indicators for validation of elimination of HCV transmission

A. Preferred approaches

Measuring incidence in the general adult population

Method of choice: direct estimation based on a prospective cohort design (HCV antibody [Ab] retesting of persons who initially tested negative)
Suitable only if: (i) HCV incidence is sufficiently high to balance sample size requirements (suggested threshold: ≥0.1 per 100 person-years), and (ii) financial and logistical resources are available to conduct nationwide surveillance among a representative cohort

Alternative
infection.
Applicable if
infection; and

BOX 4.1 Impact targets for validation of HCV transmission

Countries should have achieved the following impact targets for validation of HCV transmission:

- **≤5 new annual HCV infections/100 000 persons**

*This HCV incidence should be **representative** of the adult population at country level.*

AND

- **≤2 new annual HCV infections/100 PWID**

*This HCV incidence should be **representative** of the adult PWID population at country level.*

BOX 4.5 Measuring indicators for validation of elimination of HCV transmission *(continued)*

Measuring incidence in specific populations with ongoing risk behaviour and HCV exposure

Method of choice: direct estimation through a prospective cohort design (HCVAb or RNA retesting of persons who initially tested negative for HCVAb or RNA).
Suitable only if: financial and logistical resources are available to conduct surveillance among a representative cohort (no threshold on baseline incidence because it is generally high).

ed on tests for recent HCV infection
is sufficiently high to balance sample size
100 person-years); (ii) nationwide repeated
l/or RNA can be conducted.

d on a retrospective cohort design (HCVAb or
egative for HCVAb or RNA).
e data collected through medical records are
ation targeted remained consistent over time.

uction in HCV viraemic prevalence over time
idence

nstraints and limited strategic information
e above methods to measure HCV incidence
-income countries (LMICs), where the majority
ddition, incomplete surveillance may produce
any LMICs may not have sufficiently robust
ates.

directly through relevant representative
in HCV viraemic prevalence can be
tive measurement approach assesses a
r an absolute incidence target. Further
establish whether an absolute measure

ement of >80% reduction in viraemic
pared to baseline) *and* among people
n in HCV incidence and is an alternate
impact targets (≤5 new annual HCV
ections/100 PWID).

uction in viraemic prevalence over time
PWID at country level.

mented through repeat cross-sectional
population groups. These include
o have sex with men (MSM) (if RNA
ehold surveys.

Acknowledgements

- Peter Vickerman
- Niklas Luhmann
- Aaron G. Lim
- Hannah Fraser
- Zoe Ward
- Jack Stone
- Louis MacGregor
- Josephine G. Walker
- Adam Trickey
- Lara Marquez
- Laith J. Abu-Raddad
- Houssein H. Ayoub
- Nick Walsh
- Matthew Hickman
- Natasha K. Martin
- Philippa Easterbrook

Postdoctoral fellowships

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

CanHepC Canadian Network on Hepatitis C / Réseau Canadien sur l'Hépatite C

Fonds de recherche Santé Québec

Funding for this work: World Health Organization, Health Protection Unit for Evaluation of Interventions and Behavioural Science funded by the UK National Institute for Health Research

University of BRISTOL