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A global systematic review of hepatitis C elimination efforts through micro-elimination

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Abstract (150/150)

Micro-elimination targets specific sub-populations and/or geographic settings for hepatitis C virus (HCV) elimination. This review reports on global HCV micro-elimination literature published from 2013-2020. Data were extracted from publications to report a score based on the four key components defining micro-elimination. Sustained virologic response (SVR) and treatment initiation proportions were calculated for each manuscript and grouped means of these estimates were compared depending on micro-elimination score and care setting. 83% of the studies were from high-income settings and mainly included people who use drugs or those incarcerated. Among manuscripts, 18 had 'low' micro-elimination scores, 11 had 'high' scores and the differences in mean proportion who initiated treatment and achieved SVR between low and high score groups were statistically significant. Micro-elimination can be a useful complementary strategy for driving engagement in HCV treatment and cure. Our analysis suggests that adhering to more of the core micro-elimination components can improve outcomes.

Key points

- Hepatitis C virus (HCV) micro-elimination initiatives should strive to include all four key components of the micro-elimination strategy: have a clear plan, be multidisciplinary, have clear targets, and monitor outcomes.
- Adhering to the four key micro-elimination components results in greater proportions of treatment initiation and sustained virologic response (SVR).
- Despite micro-elimination being a strategic approach to national HCV elimination, little has been published to date, particularly in lower and middle-income countries.
- Micro-elimination in people who use drugs and people who are incarcerated was relatively well described in the literature; however, there were notable gaps in the literature on groups for which micro-elimination could be relatively straightforward, such as those with bleeding disorders or HCV/HIV co-infection.
- The outcome variables were heterogenous, and therefore did not allow for pooling and meta-analyses.

Introduction

In 2016, the global burden of hepatitis C virus (HCV) infection coupled with new, curative treatments steered the World Health Organization (WHO) to adopt its first Global Health Sector Strategy on Viral Hepatitis [1]. The strategy aims to realize the Sustainable Development Goal of "combatting" hepatitis by calling for the elimination of hepatitis B virus (HBV) and HCV as public health threats by 2030. This includes a reduction in new HCV infections by 80% and a reduction in HCV mortality by 65%. Only 11 high-income countries (HIC) are on track to eliminate HCV by 2030, with the majority off-track by at least 20 years [2]. Even with the availability of highly effective therapies, 60% of HIC are not on track to meet the elimination targets.

Globally, 58 million people are reportedly living with HCV, and in 2019, an estimated 1.5 million people were newly infected [3]. Only an estimated 21% are diagnosed and only 13% of those requiring treatment globally were treated by the end of 2019. Most countries have not yet started national HCV elimination programs and few are on track to reach the WHO targets for HCV elimination. Further, the covid-19 pandemic has negatively impacted elimination progress [4]. To reach WHO elimination targets for HCV, countries must increase the proportion diagnosed from an estimated 20% [3] [5] to over 90% [1] and provide treatment to all persons infected with HCV through more accessible and affordable health services [6][7]. Achieving these goals will require countries to raise awareness of HCV and its consequences; develop national HCV elimination strategies based on local epidemiology, [8] and scale-up HCV testing and treatment services.

The foundation of HCV elimination is treatment with safe and highly effective direct-acting antivirals (DAAs), which became available in 2014 and have since optimized HCV treatment success across patient cohorts [9]. Despite the availability of DAAs, countries can perceive HCV elimination to be daunting, costly, and complex. Soon after the global targets for HCV elimination were set, the concept of HCV micro-elimination was conceived to elucidate optimal care models for specific populations or sub-national regions in order to guide development of national programs. HCV micro-elimination projects can help reveal strategies for streamlining treatment and prevention efforts to help reach WHO elimination targets [10]. The micro-elimination approach encourages stakeholders and policymakers to establish pragmatic sub-national targets. This can enhance collaboration among key stakeholders to generate solutions to obstacles, such as implementing tailored interventions and new models of care to reach key population groups in innovative ways [11][12].

A successful micro-elimination strategy follows defined criteria, which should be adapted to unique epidemiological profiles and settings [9][10]. First, a micro-elimination strategy should have a plan on how to tailor health resources and services to overcome known barriers and achieve high levels of HCV diagnosis and treatment in one or more well-defined populations of interest. Second, the plan should set forth achievable time-bound targets, based on mathematical modelling when relevant, to determine the levels of diagnosis and treatment required to progress to the plan's ultimate targets. Third, these targets should then be implemented through a multi-stakeholder process, with essential participants including government officials, health service providers, and civil society representatives. Finally, progress and outcomes should be monitored and publicly reported using indicators selected at the outset of the process [9].

The introduction of curative DAAs and global ambitions to reach the 2030 viral hepatitis elimination targets resulted in multiple micro-elimination initiatives worldwide. This review article aims to examine, for the first time, the available global evidence on the utility of the micro-elimination approach. We examined which patient cohorts were targeted most frequently by micro-elimination initiatives, evaluated to what extent the initiatives reported following the criteria proposed for a successful micro-elimination approach to HCV, and analysed quantitatively, for the first time, the

effect of adhering to these criteria upon treatment initiation and SVR, as well as the usefulness of the approach across care contexts.

Materials and Methods

Registration

This systematic review is registered with Prospero, registration identification: CRD42020175211.

Search strategy and selection criteria

Eligibility criteria

Inclusion and exclusion criteria (**supplementary file 1**) for studies were determined a priori by JVL and CAP. Inclusion criteria included studies published after 2013 with measurable outcomes that were published in English or Spanish, where the main objective of the study was micro-elimination in a specific sub-population. Reviews and mathematical modelling studies were excluded. Full information on the inclusion and exclusion criteria are included in supplementary file 1. Micro-elimination was defined as research that tackled HCV in a defined population or subnational region and had the goal of eliminating in said population.

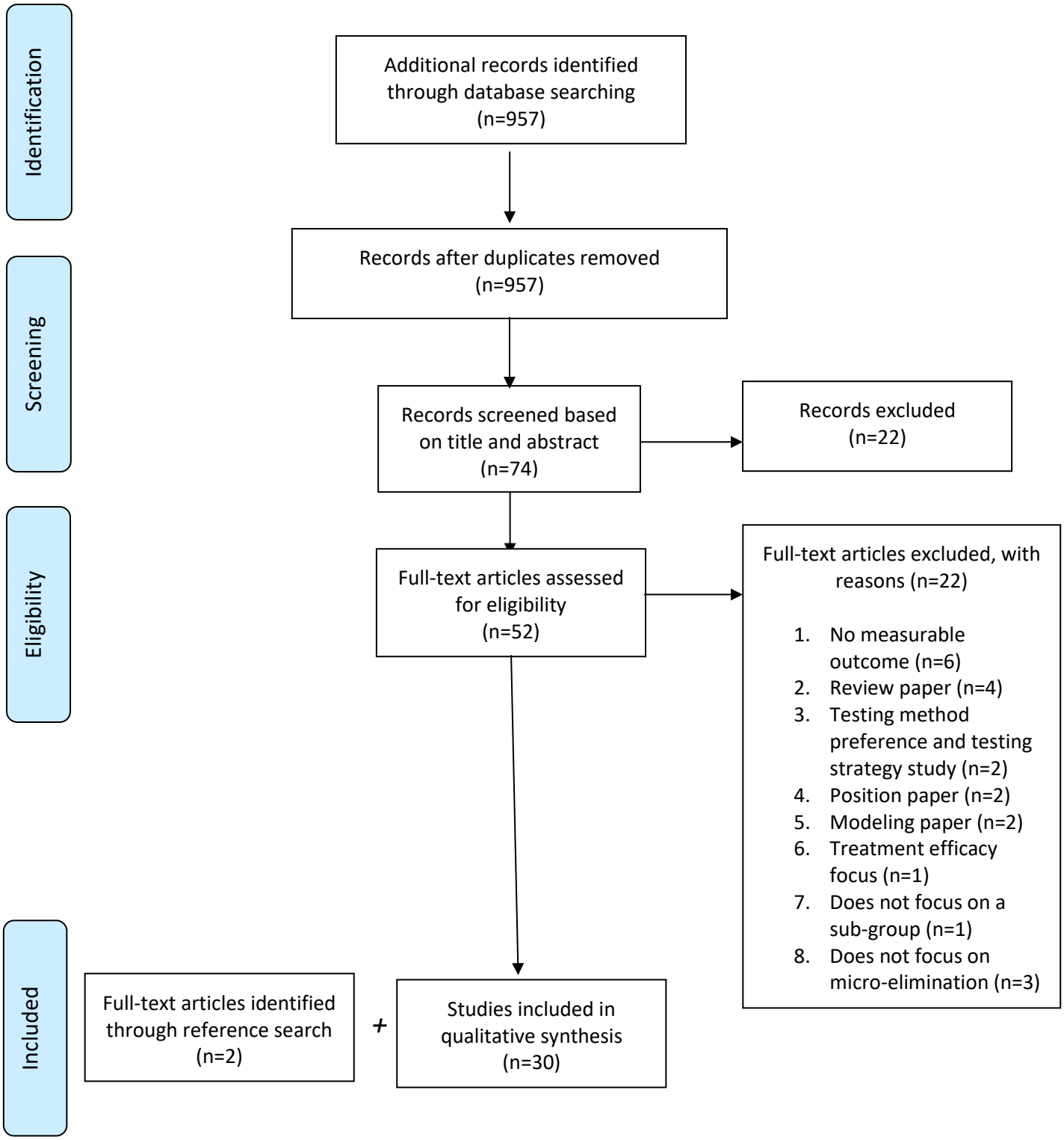
Information sources

PubMed/MEDLINE was searched using terms relating to HCV micro-elimination like “hepatitis C virus”, “micro-elimination” or “microelimination”, “treatment” or “cure”. The search string can be found in supplementary file 2. Abstracts from relevant scientific conferences (The EASL International Liver Conference, American Association for the Study of the Liver [AASLD] The Liver Meeting®, The Asian Pacific Association for the Study of the Liver [APASL] annual meeting, International Network on Hepatitis in Substance Users [INHSU] annual meeting, and the International Viral Hepatitis Elimination Meeting [IVHEM] annual meeting) from the years 2017-2019 inclusive were reviewed. Grey literature was searched using Google Scholar.

Search

A comprehensive list of search terms was established by each researcher prior to searching in PubMed/Medline. Keywords and MeSH terms were associated with hepatitis C, micro-elimination, and treatment (**supplementary file 2**). The search was run from 1 January 2013 to 31 December 2020. The reference lists of selected articles retrieved during the initial search were hand-searched and additional citation checks were performed to further identify potentially relevant studies to include (**Figure 1**). The same process used for the literature search was utilized. A grey literature search was conducted in Google Scholar and a call for authors was also sent out to submit their published work (conference abstracts or manuscripts) for consideration via email. This call included inviting all past Conquering Hepatitis via Micro-Elimination (CHIME) program recipients to submit their published micro-elimination project results for consideration.

Figure 1. PRISMA flowchart of included PUBMED manuscripts



Study selection
Data retrieved through the search strategy were imported from PubMed/Medline into a Word document to be screened. Titles and abstracts were screened by two reviewers (CAP and CB) and citations that did not meet inclusion criteria were removed. A separate independent reviewer (JVL) reviewed the citations for eligibility, a final master list of identified manuscripts was compiled, and then the full manuscripts were reviewed. All identified conference abstracts were then assessed independently by two reviewers (CAP and CB) for inclusion. Disagreement between reviewers was resolved by consensus and reasons for exclusion were reported. If a past conference abstract was later described in a published manuscript, the abstract was excluded, and the manuscript was utilized for data extraction into a standardised form. If an abstract was presented at two or more conferences, the most up-to-date abstract was utilized. Articles and conference abstracts submitted via email by CHIME recipient authors were reviewed for inclusion based on the aforementioned procedure.

Data collection
Data from included studies were extracted by two independent reviewers (CAP and CB) into Microsoft Excel 2013. An additional reviewer (JVL) verified extracted data and disagreements were resolved by discussion until consensus was reached. An Excel table with the extracted data was then shared with all remaining co-authors for verification of data extraction. Comments and changes were updated in a master Excel workbook. The following 17 variables were retrieved: year of publication, title, description of a micro-elimination plan, description of micro-elimination targets, multistakeholder process, monitoring criteria, area/country of focus, target population, setting, study period, type of study and reported outcomes, including number of participants included in each study, number of participants who were viraemic, number of participants who initiated treatment, number of participants who completed treatment, and number of participants who achieved a sustained viral response at 12 weeks (SVR12).

Data analysis
Due to the variability in study designs, a meta-analysis was not performed. Tables were used to summarise characteristics and results of included articles and abstracts. Tables summarised an overall rank score according to the four items of interest: 1. Has a clearly defined plan; 2. Has time-bound targets; 3. Includes a multistakeholder process; and 4. Monitors outcomes, that should be included in a micro-elimination initiative (**see supplementary file 3** for criteria needed for each component).

A score of 4 indicated that all four components of the definition of micro-elimination were reported in the manuscript. A score of 0 indicated that none of the components were reported. Micro-elimination criteria scores were reported as proportions (total number of criteria met out of the total available score (n=4) and according to study type (published manuscript or conference abstract), and the overall number of studies included in this review. To assess the utility of adhering to the recommended components of micro-elimination, the proportion of HCV RNA positive cases that initiated treatment (i.e. intention to treat) and proportion of treatment initiators who obtained sustained virologic response (SVR) were calculated where possible by extracting the data reported in the manuscript and rounding to the nearest whole percentage. Studies with a micro-elimination score of 1 or 2 were grouped, and studies with a score of 3 or 4 were grouped. Additionally, differences between populations were explored by categorising treatment environments as community or clinic/hospital based as a proxy for relative stability and continuity of care for the population. Analysis by specific population was not possible due to the low quantity of studies in some groups.

Proportions were explored using the Shapiro-Wilk and Levene's tests. Differences in group means were inspected with treatment initiation and SVR proportions as the dependent variables using the Mann-Whitney U test, due to *t* Test assumption violations. Statistical procedures were performed using IBM SPSS version 25 and the level of significance was set at 0.05.

Results

Sixty studies (32 full manuscripts and 28 conference abstracts) met the inclusion criteria for this review. Of the 32 published manuscripts, 29 were from the peer-reviewed literature search, one from the grey literature search, and two were received from CHIME recipients. Twenty-eight conference abstracts were also included (**supplementary file 4**). The majority (81.3%; 26/32) of manuscripts identified described micro-elimination efforts in HIC, with the remaining reporting data from middle-income countries: Egypt, Georgia, India, and Mexico. Target populations for the elimination of HCV reported in the articles and conference abstracts are listed in **Table 1**. Of the conference abstracts, almost all (26/28, 92.9%) were from HIC, while two (7.1%) were from lower-middle income countries (LMIC): India and Pakistan. A list of country classifications for the manuscripts can be found in **Table 2**.

Table 1. List of identified micro-elimination target populations in published articles from 2013-2020 (n=32) and conference abstracts from 2017-2019 (n=28).

	Manuscripts	Conference abstracts*
Incarcerated persons	9	6
HIV/HCV co-infected	5	2
People with bleeding disorders**	2	1
People experiencing homelessness	2	3
Those lost to follow-up (LTFU)	2	0
People who use drugs (PWUD) or people who inject drugs (PWID)	7	14
General or adult population in a defined region	5	1
Incarcerated persons and PWID	1	0
People with substance use disorders	0	2
Pregnant women	1	0
Migrants and refugees	1	1
MSM living with HIV	1	0
Undocumented individuals^	0	1
Veterans	0	2
American Indians (Cherokee)	0	1

**Some conference abstracts may have more than one target population, so the total reported is more than 28 studies.*

*** Includes those with bleeding disorders and those attending a haemodialysis unit.*

^Undocumented individuals are those without documented migration status in the country of residence.

HCV, hepatitis c virus; MSM, men who have sex with men.

Published manuscripts and conference abstracts had eight and 11 studies receiving rankings of three out of four components, respectively. 46.4% (n=13) of identified conference abstracts scored a two out of four in comparison to 53.1% (n=17) of the manuscripts. No manuscripts or abstracts received a zero ranking (**figure 2**).

Proportion of HCV RNA positive cases who initiated treatment, and proportion of those who obtained SVR (**Table 2**) were calculated. Three manuscripts were excluded due to not reporting SVR (n=29) and one further manuscript was excluded due to not reporting proportion of population level RNA positivity. In total, 28 manuscripts were included for analysis on treatment initiation.

Two analyses were planned with studies grouped by both micro-elimination score and population type. With respect to micro-elimination scoring: 18 manuscripts had a score of 1 or 2 (group 1), while 11 had a score of 3 or 4 (group 2). For population type, pre-planned analyses were not feasible due to low number of studies among certain populations. Therefore, studies were categorised into community (group 3; n=22) and clinical/hospital (group 4; n=7) settings – as a proxy for relative stability and continuity of care for the population. Details on which studies where included in each analysis are in **Supplementary file 5**.

Table 2. Reported cascade of care of included manuscripts, reported by World Bank country income classification and target population (n=32).

First author	Year	Target population	Country class		Cascade of care					
				Enrolled	Viraemic	Initiated treatment	Completed treatment	SVR	ME score	SVR (%) *
Braun	2020	MSM Living with HIV	HIC	3715	177	150	150	149	3	99
Bartlett	2018	Incarcerated persons	HIC	125	125	119	66	64	2	54
Cuadrado	2018	Incarcerated persons	HIC	847	86	69	66	64	3	93
Cuadrado	2020	Incarcerated persons	HIC	75	75	75	75	75	3	89
Doyle	2020	HIV/HCV co-infection	HIC	200	198	186	173	156	2	84
Falade-Nwulia	2019	HIV/HCV co-infected persons	HIC	593	547	426	x	411	3	97
Fiore	2020	PWID/incarcerated persons	HIC	248	101	84	82	77	2	92
Francheville	2017	General or adult population in a defined region	HIC	123	x	93	84	82	3	88
Fransen	2019	People with bleeding disorders	HIC	299	153	127	x	110	2	87
Giuliani	2020	Incarcerated persons	HIC	196	121	106	x	74	4	70
Harney	2019	People experiencing homelessness	HIC	52	39	24	x	13	2	54
Heil	2019	Persons lost to follow-up	HIC	90	19	12	11	x	1	NA
Jimenez-Galan	2019	Incarcerated persons	HIC	x	163	131	x	127	2	97
Kracht	2018	Persons lost to follow-up	HIC	269	42	19	3	3	2	16
Kracht	2019	PWUD	HIC	487	76	26	x	22	2	82

Maduell	2018	People with bleeding disorders	HIC	26	26	20	20	20	3	100
Martinello	2019	HIV/HCV co-infected persons	HIC	402	371	336	2997	289	2	86
Messina	2020	PWUD and PWID	HIC	123	75	63	63	63	3	100
Mostafa	2020	Pregnant women	LMIC	22	19	13	2	2	2	15
Mokkarala	2019	Incarcerated persons	HIC	132	132	132	x	123	2	93
Olafsson	2018	General or adult population in a defined region	HIC	557	x	526	x	x	1	NA
O'Sullivan	2019	PWUD	HIC	573	259	125	122	109	2	87
Overton	2019	Incarcerated persons	HIC	698	698	698	430	396	2	57
Pérez Castaño	2020	PWUD and PWID	HIC	343	212	174	141	137	2	79
Pérez Hernández	2020	General population (chronic HCV patients)	LMIC	136	136	106	106	105	1	99
Pradat	2017	HIV/HCV co-infected persons	HIC	Data not extracted					2	NA
Remy	2019	PWUD	HIC	3,053	651	621	x	611	3	94
Rizk	2019	HIV/HCV co-infected persons	HIC	173	161	122	x	97	2	80
Shiha	2018	General or adult population in a defined region	LMIC	4215	312	312	x	293	4	94
Solomon	2019	HIV/HCV co-infected persons	LMIC	5,263	323	161	x	56	2	35
Stvilia	2018	PWUD	LMIC	2,780	1,370	1,029	892	482	1	47
Waked	2020	General or adult population in a defined region	LMIC	49,630,319	1,149,346	1,056,478	465,992	381,491	1	82

* SVR proportion based off the number who achieved SVR12 (numerator) and the number of those who initiated treatment (denominator).

X = Data not reported.

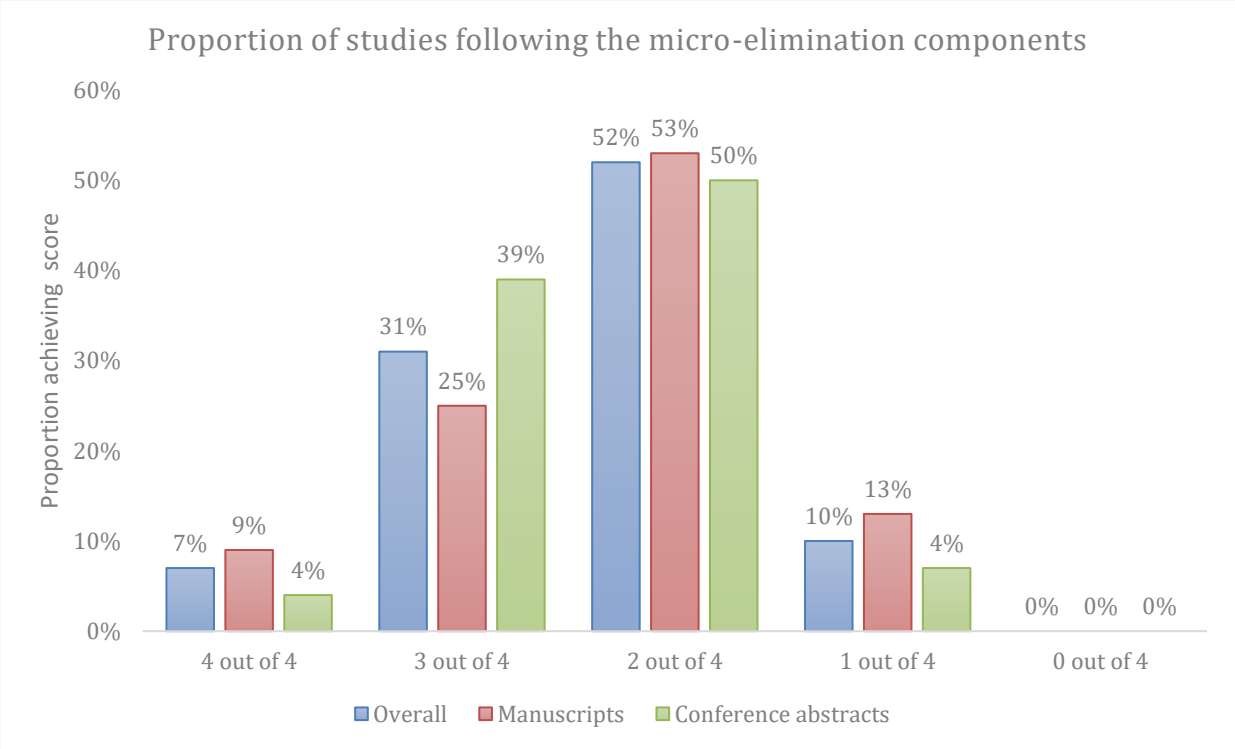
SVR, sustained viral response; ME, micro-elimination; MSM, men who have sex with men; HIV, human immunodeficiency virus; HIC, high-income country; HCV, hepatitis C virus; PWID, people who inject drugs; PWUD, people who use drugs; LMIC, lower-middle income country; SVR12, sustained viral response at 12 weeks; NA, not available.

In exploratory analysis of treatment initiation by micro-elimination score (n=28), the distribution of treatment initiation varied heterogeneously (p=.025) and was normally distributed in groups 1 (p=.073) and 2 (p=.817). Mean rank in group 2 (19.05) was higher than group 1 (11.56), (U = 143.5, p = 0.017). In analysis of SVR by micro-elimination score (n=29), the distribution of SVR varied heterogeneously (p=0.001) and was abnormally distributed in group 1 (p=0.015) but not group 2 (p = 0.051). Mean rank in group 2 (20.73) was higher than group 1 (11.50), (U = 162.0, p = 0.004).

In exploratory analysis of treatment initiation by care setting (n=28), the distribution of treatment initiation was normal for group 3 (p=0.926) and non-normal for group 4 (p=.001). Treatment initiation varied homogenously between groups (p=0.513). There was no difference in mean ranks between group 3 (14.86) and group 4 (13.43), (U = 81, p = 0.717). In SVR analysis (n=29), distribution was non-normal for group 3 (p=0.009) and group 4 (p=0.004). SVR varied heterogeneously between groups (p=0.005). There was also no difference in mean ranks between group 3 (14.84) and group 4 (15.50), for SVR (U = 73.5, p =0.862).

These analyses suggest that studies with a higher micro-elimination score had higher proportions of treatment initiation and SVR relative to those with low scores; whereas, there was no difference in these parameters based on care setting/population.

Figure 2. Description of ranking of published studies following the four key components of micro-elimination.



The four key components of a micro-elimination initiative include: (1) having a plan; (2) having established targets; (3) involving a multistakeholder process; and (4) monitoring outcomes.

Almost all (29/32, 90.6%) manuscripts included an appropriate plan for implementing an HCV elimination program for their target population. However, only 9/32 (28%) reported specific targets. A total of 5/32 (15.6%) plans reported a multi-stakeholder process. 31/32 (96.9%) monitored treatment outcomes (**Table 3**). Details on how each study achieved the micro-elimination components can be found in **supplementary file 6.**

Table 3. Manuscript (n=32) ranking on inclusion of micro-elimination components (n=4).

Author (year)	Micro-elimination criteria					Country	Target population	Setting where the initiative was carried out	Study period	Type of study
	Plan	Targets	Multi SH process	Monitoring	TOTAL (out of 4)					
Bartlett (2018)	✓	×	×	✓	**2**	Australia	Incarcerated persons	A large prison	Mar 2016-Dec 2017	Retrospective case series
Braun (2020)	✓	✓	×	✓	**3**	Switzerland	MSM living with HIV	Swiss HIV Cohort Study (SHCS) clinics	Oct 2015-Nov 2017	Nationwide, multi-centre, interventional study
Cuadrado (2018)	✓	×	✓	✓	**3**	Spain	Incarcerated persons	A prison	May 2016-Jul 2017	Open-label, single-arm, phase-IV clinical trial of low-grade of intervention
Cuadrado (2020)	✓	✓	×	✓	**3**	Spain	Incarcerated persons	A prison	May 2016-Dec 2017	Observational cost-minimization study with retrospective economic evaluation

Doyle (2020)	✓	×	×	✓	**2**	Australia	HIV/ HCV co-infection	GP-led primary care clinics, statewide sexual health service, 2 major academic hospitals	2016-2018	Clinician directed, open-label, non-randomized study
Falade-Nwulia (2019)	✓	✓	×	✓	**3**	USA	HIV/ HCV co-infection	HIV clinic with co-located HCV clinic	Jan 1, 2013- Dec 15, 2018	N/A
Fiore (2020)	✓	×	×	✓	**2**	Italy	PWID/Incarcerated persons	Prison	Jan 2019-June 2019	Prospective cohort study
Franchevill e (2017)	✓	×	✓	✓	**3**	Canada	Entire population	Hospitals	Apr 2015-Apr 2016	Community-based prospective observational study design
Fransen (2019)	✓	×	×	✓	**2**	Belgium	People with bleeding disorders	Hospital	Jul 2018-Apr 2019	Retrospective, monocentric trial
Giuliani (2020)	✓	✓	✓	✓	**4**	Italy	Incarcerated persons	Prison and jail	2017-2018	Cross-sectional study

Harney (2019)	✓	×	×	✓	**2**	Australia	People experiencing homelessness	Services for the homeless	Nov 2016- Jul 2017	Observational cohort study (unclear whether data were prospectively or retrospectively obtained)
Heil (2019)	✓	×	×	×	**1**	The Netherlands	Those lost to follow-up	Medical Centre (tertiary hospital)	2002-2016	Retrospective registry review
Jimenez-Galan (2019)	✓	×	×	✓	**2**	Spain	Incarcerated persons	A large prison	2015-2018	Retrospective observational study (case series) of standard care
Kracht PAM (2019)	✓	×	×	✓	**2**	The Netherlands	PWUD	Addiction care centres	2013-2016	Implementation model
Kracht PAM (2018)	✓	×	×	✓	**2**	The Netherlands	Those lost to follow-up	Outpatient clinic	Retrospective hepatitis C diagnostics from 2001-2015	Intervention

Maduell (2018)	✓	✓	×	✓	**3**	Spain	Individuals attending this haemodialysis unit	A hospital and its associated dialysis centres	Aprr2014-Mar 2017	Prospective, interventional, single-centre study
Martinello (2019)	✓	×	×	✓	**2**	Australia	HIV/HCV co-infection	Health care facility	Jul 2014-Mar 2017 patients were enrolled (ongoing prospective cohort)	Prospective cohort study
Messina (2020)	✓	✓	×	✓	**3**	Italy	PWUD and PWID	Addiction care centres	Jan 2018-Dec 2018	Prospective, interventional, before and after study
Mokkarala (2019)	✓	×	×	✓	**2**	USA	Incarcerated persons	State prison	Dec 2014-Jan 2017	Retrospective registry review
Mostafa (2020)	✓	×	×	✓	**2**	Egypt	Pregnant women	University hospital	Jan 2018-Sep 2019	Retrospective cohort study

Olafsson (2018)	×	×	×	✓	**1**	Iceland	Entire population	Hospitals, prisons, homeless shelters, and other locations	Jan 2016-ongoing	Nationwide elimination programme
Overton (2019)	✓	×	×	✓	**2**	Australia	Incarcerated persons	Prison setting	Apr 2016-Mar 2017	Retrospective cohort study
O'Sullivan (2019)	✓	×	×	✓	**2**	UK	PWUD	Drug and alcohol treatment centre	Dec 2013-Mar 2018	Prospective study
Pérez Castaño (2020)	✓	×	×	✓	**2**	Spain	PWUD and PWID	Methadone treatment centre	June 2018-Feb 2020	Cross-sectional study (descriptive observational)
Pérez Hernández (2020)	×	×	×	✓	**1**	Mexico	General population (chronic HCV patients)	Primary care/telemedicine	Jan 2017-unknown	Prospective cohort study
Pradat (2017)	✓	×	×	✓	**2**	France	HIV/HCV co-infection	Cohort study	2012-2015	Prospective cohort study
Remy AJ (2019)	✓	✓	×	✓	**3**	France	PWUD, migrants, prisoners, homeless	Various community based settings	Jul 2013-Dec 2018	Prospective cohort study
Rizk (2019)	✓	×	×	✓	**2**	USA	HIV/HCV co-infection	Co-located HCV clinic within an HIV clinic	Jan 1, 2014-Aug 2018	Retrospective review of a clinical program aimed at treating persons with HIV/HCV coinfection (case series)

Shiha (2018)	✓	✓	✓	✓	**4**	Egypt	All HCV+ adults (aged 12-80)	Community based settings	Jun 6, 2015-Jun 9, 2016	Prospective interventional study
Solomon (2019)	✓	×	×	✓	**2**	India	PWUD	Integrated care clinic (ICC)	2014-Q2 2017	Cluster randomized trial
Stvilia (2018)	×	×	×	✓	**1**	Georgia	PWUD	NSP	2017-2018	Retrospective cohort study
Waked (2020)	✓	✓	✓	✓	**4**	Egypt	All HCV+ adults aged 18+	Everywhere- MoH hospitals, all primary and rural health clinics, Egyptian Health Insurance Organization, university hospitals, military and police hospitals, all youth centres in the screened areas. Mobile screening teams.	Oct 1, 2018-April 30, 2019	Prospective interventional study

SH, stakeholder; MSM, men who have sex with men; HIV; human immunodeficiency virus; SHCS, Swiss HIV Cohort Study; GP, general practitioner; USA, United States of America; HCV, hepatitis C virus; N/A, not applicable; PWID, people who inject drugs; PWUD, people who use drugs; UK, United Kingdom; NSP, needle and syringe programmes; ICC, integrated care clinic; MoH, ministry of health.

For treatment initiation, 7 of 28 (25%) published studies analysed had treated ≥90% of the infected population. Of studies that treated <90%, most were among PWID (n=6) or prisoners (n=6). Twenty (71%) studies obtained SVR in ≥80% of the infected population (**Table 2**). Of published studies that obtained <80% SVR, most were also among PWID (n=3) and prisoners (n=2).

Discussion

Our data suggest that micro-elimination is a practical complementary strategy to achieve the WHO viral HCV elimination targets. HCV micro-elimination projects can help develop useful HCV testing and treatment strategies for key populations, and these can, in turn, inform national HCV elimination programs. We identified 60 published studies in 21 countries describing micro-elimination initiatives since 2017, revealing high interest in the approach since it was first proposed. The results suggest that micro-elimination is a useful strategy for curing HCV infection, with more than two-thirds (71%) of the reviewed publications reporting SVR greater than 80%. However, only 25% of the analysed studies met or exceeded treating 90% of their infected population. Those that adhered to more of the proposed components (n=4) of a micro-elimination strategy achieved statistically significant higher proportions of treatment initiation and SVR among viraemic individuals; this was not the case when analysed by care environment. The four proposed components of micro-elimination were originally outlined by Lazarus *et al* (2018) on a consensus basis and our study is, to our knowledge, the first to provide a quantitative analysis on their utility. In the low-scoring group, the most commonly unreported components were multi-stakeholder involvement and defined targets. Therefore, future initiatives might make particular efforts to include these in their micro-elimination strategies to increase the likelihood of engagement and cure of viraemic patients.

The most common population in this review was people who use drugs (PWUD). However, many national HCV elimination plans do not target this population [13], which will continue to hinder elimination in those countries where PWUD are over-represented in the HCV epidemic. Another key group studied were people who are incarcerated, who are exposed to multiple HCV risk factors including intravenous drug use; risk of HCV among PWID with recent incarceration is estimated to be 62% higher than those not incarcerated, [14] and globally up to 58% of PWID have reported a history of incarceration [15]. It was more common for analysed studies that targeted PWID and incarcerated persons to have <90% of the viraemic population on treatment and to have obtained <80% SVR in those who initiated treatment. There have been several reported barriers to initiation and follow-up of HCV treatment for PWID and in the prison context [16]. However, in Spain, one model of care to screen and treat all HCV-RNA positive patients through telemedicine has shown promising HCV elimination results, with cure rates of 97%, [17] and another which targeted those serving non-custodial sentences in Spain had good success with a novel micro-elimination approach [18]. In addition, using telemedicine to engage incarcerated persons has been reported as cost-saving [19]. In the United Kingdom, a recent study has reported promising testing and treatment uptake among incarcerated persons using a rapid screening and treatment model [20]. A recent review highlighted the importance of targeting incarcerated persons for HCV testing and treatment, and our results suggest that further work is required to improve outcomes for this population [21]. However, the telemedicine approach appears to be an effective strategy for the prison environment, and future micro-elimination efforts may consider adopting it.

In contrast to PWUD or people who are incarcerated, many of the publications found in this review did not seek out micro-elimination in people with bleeding disorders or transplant patients, who are also at increased risk for HCV. Only three articles (9.4%) included in the review examined people with bleeding disorders and none examined transplant patients, despite them being identified as an important HCV micro-elimination group that should be easy to reach via the health system. Fransen *et al.[22]* described eliminating HCV among patients with bleeding disorders in a single centre in Belgium, with 86% of participants obtaining a cure. This study could be replicated in many other

centres and countries around the world. Similarly, only eight studies reported elimination efforts in people living with HIV (PLHIV) with HCV co-infection, which was surprising given that co-infection prevalence is high and approximately 67% of PLHIV are on antiretroviral therapy globally, offering a viable engagement point for many individuals [23]. One study in Spain which followed a large cohort of PLHIV found an HCV prevalence of 22%, of which 87% achieved SVR at the end of the follow-up period [24]. Identifying patients in this sub-group with the objective of eliminating their HCV infection could potentially improve HIV treatment outcomes. Further, reducing the incidence of HCV among PLHIV can lead to regional HCV micro-elimination among PLHIV [25]. This has led the British HIV Association to release a micro-elimination statement [26] to treat all HIV/HCV co-infected individuals in the UK by 2021, a target that should be emulated around the world and which can help eliminated HCV in other populations as well, such as PWID [27]. Despite HCV treatment in children being a key population for micro-elimination, no included studies reported initiatives among children born to HCV-infected mothers or adolescents who are injecting drugs, for example. *El-Sayed & Indolfi* [28] reflect on this, further elucidating a gap in the literature for other identified key populations for micro-elimination initiatives.

In addition to targeting key populations, micro-elimination efforts reported here have shown that moving testing closer to the patient by using novel testing methods and simplified diagnostic tools like point-of-care rapid tests or dried blood spot (DBS) testing, in addition to reflex testing (Rizk et al, 2019), are important and reliable tools for elimination [29]. Further, a recent review found that decentralization and integration of HCV care into community sites delivered comparable cure rates to specialist care irrespective of population and settings [30]. These innovative methods may further optimize care by minimizing clinic visits and allowing patients to be linked to care more quickly and efficiently [31], and should be considered in regional elimination strategies. Reflex testing, where samples which are positive for HCV antibodies are automatically screened for HCV-RNA, has been shown to increase HCV diagnoses when scaled up nationally at the tertiary level [32]. One study included in our analysis (Martinello *et al*) [33] used DBS to show the feasibility of using this tool to integrate HCV testing in HIV clinics, with >90% of viraemic patients initiating treatment with DAAs and 86% achieving SVR. In comparison, a large non-randomized trial from Iran [34], not included in the review, showed how simplified and people-centred care pathways for key populations can accelerate progress towards HCV elimination. Researchers evaluated on-site rapid HCV antibody testing, venepuncture for HCV RNA testing, liver fibrosis assessment, and linkage to care, to enhance DAA therapy initiation among people with a history of drug use, with promising results. However, in mobile population groups like those experiencing homelessness, despite a documented 100% treatment completion rate, none of those participants (n=22) were able to be followed-up to monitor for SVR12. In contrast, in participants who received care in opioid substitution therapy (OST) clinics (n=44), 89% achieved SVR12. Similar issues with follow-up for homeless persons (Harney *et al*) were encountered in this review.

Notably, the majority of articles included in this review were from HIC (81.3%), which may be interpreted in different ways. It may highlight a disparity between viral hepatitis elimination efforts and research initiatives in HICs and LMICs; competing health challenges in LMICs likely places viral hepatitis elimination lower on a country's list of priorities. However, it may also demonstrate that HIC have disproportionally focused on micro-elimination initiatives and research agendas rather than national elimination strategies as some LMIC countries such as Egypt, which has demonstrated that HCV can be well addressed at the national level, have done [35]. One study in this review from Egypt, Shiha *et al.*, is an excellent example of how successful micro-elimination initiatives can help accelerate national progress toward elimination. There is also an example of geographic micro-elimination from the small rural town O'Brien, in the province of Buenos Aires, Argentina, which reported a chronic prevalence of 5.7% [36] in a study performed in 1999 and later on treated all viremic patients [37]. The majority of LMIC studies undertook subnational initiatives among chronically infected persons in defined regions, whilst in HIC there was a variety of populations with

a preponderance of studies among PWID and incarcerated persons (Table 2). This is illustrative of the wider patterns of infection in HIC and LMIC settings, where historical exposure to HCV may have been consequent to injecting drug use or iatrogenic risk, respectively. LMIC studies in the general population generally had high cure rates; however, those among PWUD, co-infected persons, and pregnant women scored lower, illustrating potential discrete challenges in LMICs for these groups compared to HIC settings, where cure rates were generally higher by comparison. Additional work is warranted to investigate particular hurdles to implementing elimination strategies for these groups in LMICs.

Although the majority of studies reviewed here reported high proportions of SVR, nine studies demonstrated low rates, varying between 15.8 and 79.5%. These initiatives were varied: multiple populations targeted, across high- and low-income settings. Consideration might therefore be given in future micro-elimination projects to resourcing SVR follow-up more intensively, regardless of the setting or the population being targeted. In particular, few studies account for follow-up of re-infection (**Supplementary File 4**; part of the monitor parameter) or DAA adherence. Re-infection is a critical threat to the sustainability of elimination – particularly as the HCV epidemic disproportionately effects those at high risk of re-infection such as PWID – and strategies to monitor and account for re-infection should be integrated when pursuing elimination initiatives [38].

Overall, the key reported components of the micro-elimination initiatives varied, with the majority of studies reporting only two out of four of the proposed core micro-elimination components. More data from LMICs are needed to better understand local epidemiology and relevant target populations. In Tanzania, for example, high rates of HIV, HBV, and HCV have been reported [39] among PWUD, yet, no micro-elimination initiatives were identified there. As the majority of the identified studies were from HIC they must be piloted and adapted to LMIC settings given the different set of challenges faced in resource-constrained settings. However, the data presented here demonstrate that useful metrics are available (micro-elimination score; HCV cascade of care) which can aid program development, particularly for marginalised and high-risk populations. Further, the analyses suggest that those programs which include more of the key components of micro-elimination are likely to engage a higher proportion of the viraemic population and consequently cure their HCV infection.

Limitations

Despite highlighting global HCV micro-elimination initiatives, this review has some limitations that may affect the interpretation of the findings. For example, not all studies included in this review sufficiently reported their data, which hindered data extraction efforts and the outcome variables were heterogenous, and therefore did not allow for pooling and meta-analyses. Further, many studies that were evaluated for inclusion may have been excluded because the main objective of their study was not to eliminate HCV but rather evaluate methods for simplifying diagnoses and treatment initiation, which are also central to reaching the WHO HCV elimination goal. While studies in this review predominantly stated they were employing the micro-elimination strategy, there was a disparity between that claim and adherence to the core components that constitute such an initiative. Regional conference abstracts from Latin America and Africa were not reviewed, given language restrictions and therefore included abstracts are from the larger global meetings. Accordingly, the analysis in this review should be interpreted with relative caution.

The analysis of treatment initiation and SVR relative to micro-elimination score and care setting could not be adjusted for additional variables, due to the previously mentioned variability in study design, so it is possible that variability in SVR could be influenced by alternative unknown factors. Further, we were unable to statistically compare treatment initiation and SVR between population groups due to a paucity of studies in certain groups, therefore the divergent nature of the populations are not directly adjusted for; however, consideration of care setting may have somewhat

ameliorated this. In analysing the micro-elimination scores, it was not possible to determine which components were more central to success than others, and future research might focus on investigating divergences when the literature base is more mature.

We did not identify any studies that targeted psychiatric patients, who are 5-10 times more likely to be infected with HCV than the general population [40-42]. However, sometimes these individuals fall between departments with respect to blood-borne virus care, so some may be captured in other populations in this review, for example PWUD or prisoners. Finally, we identified several studies who targeted lost to follow-up (LTFU) patients. These were included in the review as those LTFU are ostensibly a defined population, however the definition of LTFU may vary depending on the setting, which limits the generalisability of results derived from these studies. Lastly, no identified studies targeted paediatric patients, despite DAA treatment being approved for children age three and up [28].

Conclusions

Micro-elimination is a useful approach for driving engagement in HCV testing and treatment and our analysis suggests that adhering to the proposed core micro-elimination components can result in greater success as measured by proportion of the viraemic population treated and achieving SVR. Care setting, which was used as a proxy for population type in the absence of sufficient studies on different populations, does not appear to influence the proportion of viraemic individuals initiating treatment or obtaining SVR. Globally, there are a variety of successful examples of micro-elimination, highlighting the interest and feasibility of eliminating HCV by employing this strategy. The largest number of studies found in this review addressed eliminating HCV in PWUD and people who are incarcerated, especially in high-income settings. However, there were notable gaps in the literature base, especially in groups for which micro-elimination could be relatively straightforward, such as those with bleeding disorders or HCV and HIV co-infection, who are closely linked with the healthcare system. Good examples of progress in this population are available. Additionally, studies in LMIC settings were particularly lacking. Future efforts should consider these populations and geographical settings. Finally, future studies should pay close attention to all four key components of micro-elimination and consider additional strategies aimed at long-term follow-up for re-infection.

Conflict of interest statement
JVL reports grants, personal fees, and other from AbbVie and Gilead Sciences; personal fees from CEPHEID, GSK, Genfit, Intercept, and Janssen; and grants and personal fees from MSD, outside the submitted work. JC reports grants from Gilead, Abbvie, and Intercept, outside the submitted work. MC reports personal fees from Intercept, Exelyxis, and Target HCC; and other from COST, outside the submitted work. GC 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 the submitted work. JG reports grants and personal fees from Abbvie, Gilead Sciences, Merck, and Cepheid; and grants from Hologic and Indivior, outside the submitted work. JW reports grants from Gilead Sciences, AbbVie, Abbott, Cepheid, Merck, Roche, Siemens, Pharco, Zydus Cadila, non-governmental organizations, professional associations, the United States government, and individuals, outside the submitted work. JFD reports grants and other from Gilead, MSD, Abbvie, and Astra Zeneca; and grants from Cephid, outside the submitted work. CAP, CB, and GJD have nothing to disclose.

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Authors contributions

JVL conceived of the article and developed the preliminary outline. CAP and CB performed the literature and conference abstract review with supervision and input from JVL and JD. Each author (JC, MC, GC, GJD, JG, JW) reviewed a sub-set of data extracted from included articles for verification and doubts were resolved by JVL through consensus with CAP, CB, and JD. CAP wrote the first draft of the manuscript with input from CB. CB undertook statistical analysis. All authors contributed to and reviewed the full draft of the article, subsequent revisions, and approved the final version for submission.

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