Global change in hepatitis C virus prevalence and cascade of care between 2015 and 2020: a modelling study

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Summary

Background Since the release of the first global hepatitis elimination targets in 2016, and until the COVID-19 pandemic started in early 2020, many countries and territories were making progress toward hepatitis C virus (HCV) elimination. This study aims to evaluate HCV burden in 2020, and forecast HCV burden by 2030 given current trends.

Methods This analysis includes a literature review, Delphi process, and mathematical modelling to estimate HCV prevalence (viraemic infection, defined as HCV RNA-positive cases) and the cascade of care among people of all ages (age ≥0 years from birth) for the period between Jan 1, 2015, and Dec 31, 2030. Epidemiological data were collected from published sources and grey literature (including government reports and personal communications) and were validated among country and territory experts. A Markov model was used to forecast disease burden and cascade of care from 1950 to 2050 for countries and territories with data. Model outcomes were extracted from 2015 to 2030 to calculate population-weighted regional averages, which were used for countries or territories without data. Regional and global estimates of HCV prevalence, cascade of care, and disease burden were calculated based on 235 countries and territories.

Findings Models were built for 110 countries or territories: 83 were approved by local experts and 27 were based on published data alone. Using data from these models, plus population-weighted regional averages for countries and territories without models (n=125), we estimated a global prevalence of viraemic HCV infection of 0·7% (95% UI 0·7–0·9), corresponding to 56·8 million (95% UI 55·2–67·8) infections, on Jan 1, 2020. This number represents a decrease of 6·8 million viraemic infections from a 2015 (beginning of year) prevalence estimate of 63·6 million (61·8–75·8) infections (0·9% [0·8–1·0] prevalence). By the end of 2020, an estimated 12·9 million (12·5–15·4) people were living with a diagnosed viraemic infection. In 2020, an estimated 641 000 (623 000–765 000) patients initiated treatment.

Interpretation At the beginning of 2020, there were an estimated 56·8 million viraemic HCV infections globally. Although this number represents a decrease from 2015, our forecasts suggest we are not currently on track to achieve global elimination targets by 2030. As countries recover from COVID-19, these findings can help refocus efforts aimed at HCV elimination.

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Introduction

Hepatitis C virus (HCV) is a bloodborne virus with the potential to cause liver fibrosis, hepatocellular carcinoma, and liver-related deaths. At present, no protective vaccine is available, but since 2014, the first launch of direct-acting antiviral (DAA) therapies that achieve sustained virological response in more than 95% of people has drastically improved HCV management globally. Diagnosis of HCV is also improving with the increased availability of point-of-care diagnostics, including confirmatory tests for HCV RNA. Additionally, strategies to prevent contact with infected blood and blood products and blood-contaminated objects can effectively control the transmission of HCV.[1] In the absence of an approved HCV vaccine regimen,[2] HCV treatment and prevention of new infections remain the key measures for HCV elimination. However, if strategies are developed and implemented to both prevent new infections and effectively treat HCV cases, through efficient diagnosis or early detection of patients and timely linkage to medical care and treatment, then HCV could be eliminated as a public health threat.[3]

In 2016, the 69th World Health Assembly passed a resolution to eliminate viral hepatitis as a public health threat by 2030,[4] and WHO introduced global 2030 targets for the care and management of HCV (65% reduction in mortality, 80% reduction in incidence, ≥90% diagnosed, ≥80% treated).[5] In June, 2021, WHO released interim guidance for country validation of viral hepatitis elimination, with the inclusion of new absolute targets (annual incidence ≤5 per 100 000 and annual mortality ≤2 per 100 000).[6] The Center for Disease Analysis Foundation (CDAF) and the Polaris Observatory have been evaluating the global prevalence of HCV for almost a decade. Our first estimate, published in 2014, quantified viraemic infections globally on the basis of indexed and

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Research in context

Evidence before this study

In the past decade, a number of global estimates of hepatitis C virus (HCV) prevalence have been published by our group, including global prevalence assessments (published in 2014 and 2016), paediatric prevalence (2020), and prevalence among women of childbearing age (2021). WHO has also published reports on global prevalence, incidence, and mortality associated with HCV (2017 and 2021). Global analyses of HCV-related cancer and mortality have been undertaken by the Institute for Health Metrics and Evaluation and the International Agency for Research on Cancer. Finally, estimates of HCV incidence, and incidence among key populations including people who inject drugs, have been published by the University of Bristol (Bristol, UK) and University of New South Wales Sydney (Sydney, NSW, Australia). In addition to searching institutional websites for recent publications from the aforementioned groups, we identified global studies during our country and territory-level literature search of PubMed and grey literature. The search terms ("hepatitis C" AND "prevalence" AND "country/territory") were used to identify articles in all languages published between April 1, 2016, and March 31, 2021, that build on our previous work.

Added value of this study

Building on our 2016 estimate of the global prevalence of HCV, this study provides a progress update for 2020, along with a revised 2015 baseline prevalence estimate incorporating updated serosurvey results from large countries including Egypt, Brazil, Nigeria, and the Democratic Republic of the Congo (among others). Additionally, we report the HCV cascade of care and modelled outcomes and forecasts for the global burden of HCV, including measures of incidence and mortality, for 2015 to 2030. Our results were obtained from a literature search and the use of 110 country and territory-specific disease burden models. To strengthen the analysis, more than 300 experts were consulted to validate the model inputs and outcomes. This consultation led to 83 approved country and territory models, plus another 27 models that were developed on the basis of published data alone. Additionally, we collected 2020 treatment data from 31 countries, allowing for preliminary forecasts of HCV disease burden in the years following the COVID-19 pandemic up to 2030.

Implications of all the available evidence

At the beginning of 2020, 56·8 million viraemic HCV infections were estimated globally. Although this number represents a decrease from 2015, our forecasts suggest we are not currently on track to achieve global elimination targets by 2030. Of the 56·8 million people infected with HCV in 2020, less than a quarter (12·9 million [23%]) had been diagnosed, and only 641 000 were estimated to have initiated treatment in that year. Of the 9·5 million people who initiated direct-acting antiviral therapy between 2015 and the end of 2019, more than a third (3·5 million [36%]) were in Egypt. With less than 10 years remaining to meet the World Health Assembly's target of eliminating viral hepatitis as a public health threat by 2030, substantial effort is needed to eliminate HCV. As decision makers evaluate their HCV elimination efforts and progress following the COVID-19 pandemic, this study provides an updated baseline for future activities.

non-indexed (eg, government report) data published between 2000 and 2013.[7] This analysis was novel in its estimation of viraemic infections (HCV RNA-positive) rather than serological evidence of past or present infection (anti-HCV-positive).[8–10] A second analysis, published in 2016, was expanded and strengthened with the use of disease burden modelling, through which we developed consistent 2015 year-end prevalence estimates on an expanded scope (country and territory, regional, and global levels). The literature search was also extended up to March 31, 2016.[11] Prevalence estimates from this 2015 publication were selected as the baseline for the WHO's global hepatitis report in 2017,[1] and served as a starting point for HCV elimination efforts in many countries and territories. Our group has also published two studies estimating the global prevalence of HCV in the paediatric population (for the year 2018)[12] and in women of childbearing age (for 2019).[13]

The objective of the present analysis was to evaluate progress towards HCV elimination in 2020 at the national, regional, and global levels. This timepoint was selected because it serves as both a milestone for countries and territories that might have deferred their HCV elimination efforts amid the current crisis of the COVID-19 pandemic, and as an assessment of HCV elimination progress 5 years after the broader approval and adoption of DAAs for clinical use in 2015. Furthermore, this analysis evaluates the cascade of care (viraemic infection, diagnosed, treated) at the regional and global level, on the basis of available country and territory data up to the end of 2020; and global forecasts of HCV disease burden from 2015 to 2030.

Methods

Study design

This analysis integrates a literature review, a Delphi process, and mathematical modelling to estimate HCV prevalence and the cascade of HCV care among people of all ages (age ≥0 years [newborn child and older]) for the period between Jan 1, 2015, and Dec 31, 2030. Empirical and programmatic data for the 2020 calendar year (Jan 1 to Dec 31) were retrieved and entered into the models. A Markov model, developed for each country or territory, was used to forecast the HCV prevalence and disease burden between 1950 and 2050, with data extracted for this analysis from 2015 to 2030. Model

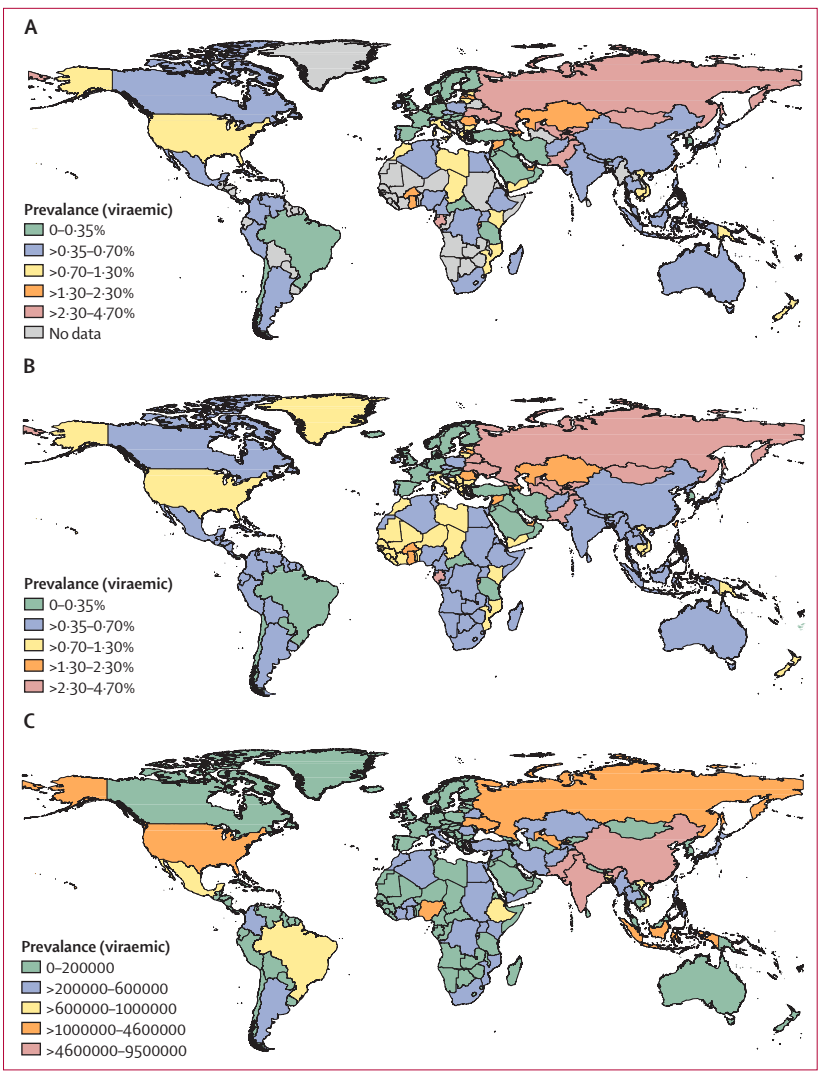

Figure 1: **Country-level and territory-level HCV prevalence estimates (beginning of 2020)**
(A) Viraemic HCV infection prevalence among countries and territories with approved or estimated models. (B) Viraemic HCV infection prevalence for all countries and territories, including those with extrapolated prevalence. (C) Number of viraemic HCV infections for all countries and territories. HCV=hepatitis C virus.

See Online for appendix

stocks (prevalence of HCV, prevalence by stage of disease, and total diagnosed) were summarised as beginning-of-year (Jan 1) outputs, and model flows (incidence of HCV, incidence by stage of disease, annual diagnosed, annual treated, and annual liver-related deaths) were summarised for the calendar year. Data were extracted for 2015 to serve as a revised baseline prevalence estimate for the evaluation of HCV elimination progress, with 2020 data extracted to develop an annual, complete-year cascade of HCV care. Beginning-of-year 2020 data were extracted to generate an updated prevalence estimate for countries and territories. After extracting model data for countries and territories with models, population-weighted regional averages were calculated by Global Burden of Disease Study (GBD) region. These regional averages were then applied for countries and territories without sufficient data to generate a model, to calculate regional and global estimates for 235 countries and territories. Developing a country-level model required (at minimum) data for HCV prevalence by age and sex; thus, we considered 235 countries and territories, as designated by the UN, with population data available by age and sex. Prevalence estimates were described at the national, regional, and global levels, with the cascade of care described regionally and globally. Global disease burden forecasts of new chronic infections (number and rate per 100 000 of the population), annual liver-related deaths (number and rate per 100 000 adults), incident hepatocellular carcinoma (number and rate per 100 000 adults), and incident decompensated cirrhosis (number and rate per 100 000 adults) were described from 2015 to 2030. Details of the data collection, scoring of data sources, Delphi process, and mathematical modelling are described briefly herein and in the appendix (pp 4–20).

Country and territory-level data collection and selection criteria

To evaluate HCV prevalence (including the diagnosed and undiagnosed population), a literature search of PubMed and non-indexed reports was performed to identify studies published between April 1, 2016, and March 31, 2021 (appendix p 15). The outcomes of this search were combined with the outcomes of our previous analyses[7,11] (encompassing studies published from Jan 1, 2000, to March 31, 2016). Non-indexed government reports and personal communications with country and territory experts identified through the Polaris Observatory collaborators network were included when published data were not available (appendix pp 22–33). The analysis included all countries and territories with a population of more than 1·5 million people, with ad-hoc inclusions of nine countries with smaller populations. These nine countries were included following a request from country collaborators, ministries of health, or WHO as part of an ongoing collaboration. Articles were scored with use of a multiobjective decision analysis approach on the basis of how well the prevalence estimate could be extrapolated to the general population (including population sampled, geographic scope, and sampling procedure), the study sample size, and the year of analysis.[7,11]

To estimate the population diagnosed with HCV, data were collected from (in order of priority) national notification or registry data, peer-reviewed literature, or expert opinion. When notification or registry data were used, the case definition was consulted to determine if notifications reflected anti-HCV, HCV RNA, or both. When necessary, the spontaneous clearance rate (based on previous publications surrounding the natural history of HCV) or available data on country-level viraemic proportion was used to adjust notified cases to estimate HCV RNA-positive annual diagnosed cases. In countries

and territories where HCV was a notifiable infection and the number of newly diagnosed cases was reported annually (including deduplication to ensure each patient was only reported once), the total number of diagnosed cases could be calculated by summing annual viraemic diagnosed cases and subtracting the number of deaths and number of cures.

The number of individuals treated annually up to the end of 2020 was estimated from (in order of priority) national databases, audit sales data, government reports, estimates from major treatment centres, or drug suppliers. The completeness of the treated data was analysed to ensure that the final estimate for treatment reflected both the private and public markets. When treatment data were provided for a portion of the market, data were adjusted in discussions with the panel of country or territory experts to capture sales or treatments in channels not reflected in the drug sales data or national databases (appendix pp 28–33).

Similar to our previous analysis, a Delphi process was used to gain country or territory expert consensus and validate collected data to use as model inputs (ie, approved country and territory data; appendix pp 19–20).[11] All experts who contributed to discussions during the study were identified through HCV-related scientific contributions, or through referrals and recommendations from leading researchers or WHO regional offices; overall a total of 324 experts were consulted. In countries or territories where an analysis had not previously been conducted, two or more meetings were held with country or territory experts to achieve consensus regarding input and output variables, and to validate the outputs against available empirical data. Country and territory models that were approved in the previous analysis[11] were revisited for new data from the literature search and discussions were held with country or territory experts to verify the inclusion of any novel prevalence studies.

For countries and territories where meetings with local experts could not be scheduled, published estimates were used (ie, estimated country and territory data). Two epidemiologists (among CE, DMR-S, ElM, or KR-S; and SB) reviewed and scored all published studies according to the multiobjective decision analysis approach, and the highest scored studies were used for modelling. When inputs other than prevalence rate were unavailable for a country or territory, the population-weighted regional average (calculated from countries and territories within the same GBD region) was used.

Country and territory-level HCV disease burden modelling

After reviewing and scoring available studies, a Microsoft Excel-based (version 365) Markov model of HCV infection, described previously,[14–16] was populated with the highest scoring epidemiological data for the country or territory of interest (appendix pp 16–18). The highest scoring prevalence study was selected as the base value

	Viraemic prevalence in 2015*†	Viraemic population (1000s) in 2015*†	Viraemic prevalence in 2020*†	Viraemic population (1000s) in 2020*†
Asia Pacific, high income				
Japan	0·7% (0·6–0·9)	1028 (829–1240)	0·4% (0·4–0·5)	562 (453–678)
South Korea	0·3% (0·2–0·4)	142 (115–190)	0·2% (0·1–0·2)	90 (73–120)
Asia, central				
Armenia	2·4% (2·1–3·5)	72 (62–104)	2·2% (1·9–3·1)	64 (56–93)
Azerbaijan	1·9% (1·2–2·3)	179 (115–223)	1·9% (1·2–2·3)	190 (121–235)
Georgia	3·7% (3·6–4·3)	150 (148–177)	2·4% (2·4–2·8)	96 (95–113)
Kazakhstan	2·1% (1·7–2·3)	366 (310–415)	1·9% (1·6–2·2)	359 (304–407)
Kyrgyzstan	2·7% (2·3–4·3)	160 (137–260)	2·6% (2·2–4·1)	167 (142–270)
Mongolia	6·4% (5·7–10·3)	198 (177–317)	4·2% (3·8–6·8)	139 (124–223)
Tajikistan	2·8% (2·2–3·3)	243 (187–280)	2·7% (2·0–3·1)	254 (195–293)
Uzbekistan	3·1% (2·4–3·7)	959 (767–1150)	3·0% (2·4–3·6)	1004 (804–1205)
Asia, east				
China, mainland	0·7% (0·5–0·9)	10 023 (7692–12 353)	0·7% (0·5–0·8)	9487 (7281–11 693)
Hong Kong	0·3% (0·1–0·4)	18 (5–28)	0·2% (0·1–0·4)	17 (4–27)
Taiwan	1·9% (1·6–5·6)	458 (402–1383)	1·4% (1·2–4·1)	322 (283–974)
Asia, south				
India	0·5% (0·4–1·2)	6427 (5224–15 671)	0·4% (0·4–1·1)	6137 (4988–14 963)
Pakistan	3·6% (2·8–4·9)	7213 (5702–9767)	3·3% (2·6–4·5)	7395 (5846–10 012)
Asia, southeast				
Cambodia	1·3% (0·5–3·3)	207 (82–524)	1·1% (0·5–2·9)	190 (75–482)
Indonesia	0·5% (0·1–1·0)	1302 (186–2595)	0·5% (0·1–1·0)	1364 (195–2721)
Malaysia	0·4% (0·3–1·6)	135 (107–508)	0·4% (0·3–1·5)	127 (100–477)
Philippines	0·4% (0·2–1·3)	451 (223–1350)	0·4% (0·2–1·2)	439 (217–1314)
Thailand	0·6% (0·5–0·8)	381 (346–576)	0·5% (0·5–0·8)	378 (343–571)
Vietnam	1·0% (0·8–1·4)	947 (786–1275)	0·9% (0·8–1·3)	914 (759–1231)
Australasia				
Australia	0·8% (0·7–0·8)	193 (174–207)	0·5% (0·4–0·5)	119 (108–128)
New Zealand	1·1% (0·6–1·5)	50 (27–72)	0·9% (0·5–1·3)	43 (23–62)
Caribbean				
Cuba	0·5% (0·1–1·2)	57 (16–142)	0·5% (0·1–1·2)	55 (15–138)
Dominican Republic	0·7% (0·5–1·6)	70 (49–168)	0·6% (0·4–1·4)	65 (46–157)
Puerto Rico	1·2% (0·7–2·2)	41 (22–72)	1·4% (0·8–2·6)	41 (23–74)
Europe, central				
Bulgaria	1·3% (0·6–2·0)	93 (43–143)	1·2% (0·6–1·9)	86 (40–132)
Croatia	0·5% (0·5–0·8)	21 (20–33)	0·5% (0·4–0·7)	19 (18–29)
Czechia	0·5% (0·2–0·6)	53 (21–67)	0·5% (0·2–0·6)	55 (22–69)
Hungary	0·3% (0·3–0·7)	32 (24–73)	0·3% (0·2–0·7)	29 (22–65)
Poland	0·5% (0·3–0·6)	188 (129–249)	0·4% (0·3–0·5)	157 (108–208)
Romania	2·5% (2·4–3·0)	504 (479–601)	2·3% (2·2–2·7)	437 (415–521)
Slovakia	0·2% (0·2–1·4)	13 (8–78)	0·2% (0·1–1·4)	12 (8–74)
Slovenia	0·2% (0·1–0·2)	4 (3–5)	0·1% (0·1–0·2)	3 (2–4)
Europe, eastern				
Estonia	1·5% (1·1–1·8)	20 (15–24)	1·2% (0·9–1·4)	16 (12–19)
Latvia	2·1% (1·5–2·8)	40 (28–55)	2·0% (1·4–2·8)	38 (27–53)
Lithuania	1·1% (0·7–1·5)	32 (20–45)	1·0% (0·6–1·4)	28 (17–39)
Russia	2·9% (1·8–3·3)	4179 (2568–4828)	2·9% (1·8–3·4)	4255 (2614–4915)
Ukraine	3·2% (2·6–4·2)	1443 (1172–1893)	3·1% (2·5–4·0)	1342 (1089–1760)

(Table 1 continues on next page)

	Viraemic prevalence in 2015*†	Viraemic population (1000s) in 2015*†	Viraemic prevalence in 2020*†	Viraemic population (1000s) in 2020*†
(Continued from previous page)				
Europe, western				
Austria	0·3% (0·1–0·4)	25 (5–39)	0·2% (0·0–0·3)	15 (3–23)
Belgium	0·3% (0·2–0·6)	31 (22–77)	0·2% (0·1–0·5)	24 (17–59)
Denmark	0·2% (0·2–0·3)	11 (10–16)	0·1% (0·1–0·2)	7 (6–10)
Finland	0·4% (0·3–0·5)	22 (17–28)	0·3% (0·3–0·4)	19 (15–25)
France	0·3% (0·2–0·3)	183 (143–234)	0·2% (0·1–0·2)	112 (88–143)
Germany	0·3% (0·2–0·5)	254 (152–457)	0·2% (0·1–0·4)	189 (113–340)
Greece	1·0% (0·7–1·3)	106 (75–136)	0·9% (0·7–1·2)	96 (68–123)
Iceland	0·2% (0·2–0·3)	0·7 (0·6–0·9)	0·1% (0·1–0·1)	0·3 (0·2–0·3)
Ireland	0·6% (0·4–1·1)	30 (20–51)	0·6% (0·4–0·9)	27 (18–46)
Israel	0·9% (0·6–1·3)	73 (47–111)	0·7% (0·5–1·1)	61 (39–91)
Italy	1·4% (0·6–2·0)	888 (388–1298)	1·0% (0·4–1·4)	577 (252–843)
Luxembourg	0·9% (0·5–1·1)	5 (3–6)	0·8% (0·4–0·9)	5 (3–6)
Malta	0·3% (0·2–0·6)	1·2 (1·1–2·6)	0·2% (0·2–0·4)	0·9 (0·8–1·9)
Netherlands	0·1% (0·0–0·2)	20 (8–34)	0·1% (0·0–0·1)	14 (5–24)
Norway	0·3% (0·2–0·5)	14 (9–29)	0·1% (0·1–0·3)	7 (4–14)
Portugal	0·5% (0·5–0·8)	61 (55–92)	0·4% (0·4–0·6)	42 (38–64)
Spain	0·3% (0·2–1·3)	201 (112–742)	0·1% (0·1–0·4)	56 (31–205)
Sweden	0·4% (0·3–0·5)	41 (34–50)	0·3% (0·2–0·3)	26 (22–31)
Switzerland	0·5% (0·5–0·5)	44 (40–47)	0·4% (0·3–0·4)	32 (29–35)
UK	0·3% (0·2–0·4)	177 (132–247)	0·2% (0·1–0·3)	127 (95–177)
Latin America, Andean				
Peru	0·5% (0·3–0·5)	161 (104–167)	0·5% (0·3–0·5)	157 (101–163)
Latin America, central				
Colombia	0·7% (0·6–1·0)	335 (314–492)	0·6% (0·6–0·9)	320 (300–470)
El Salvador	0·3% (0·2–0·3)	17 (13–20)	0·2% (0·2–0·3)	16 (13–19)
Mexico	0·6% (0·6–0·7)	790 (718–862)	0·6% (0·5–0·6)	751 (683–820)
Panama	0·3% (0·3–0·4)	13 (10–17)	0·3% (0·3–0·4)	14 (11–18)
Venezuela	0·6% (0·4–0·7)	169 (134–217)	0·6% (0·5–0·8)	167 (133–215)
Latin America, southern				
Argentina	0·8% (0·3–1·9)	348 (131–819)	0·7% (0·3–1·6)	316 (119–745)
Chile	0·2% (0·0–0·3)	37 (6–52)	0·2% (0·0–0·2)	33 (5–48)
Latin America, tropical				
Brazil	0·3% (0·2–0·4)	724 (391–944)	0·3% (0·2–0·4)	604 (326–787)
North Africa and Middle East				
Afghanistan	0·5% (0·2–0·9)	192 (66–317)	0·5% (0·2–0·9)	203 (70–335)
Algeria	0·7% (0·2–0·9)	288 (80–373)	0·6% (0·2–0·8)	278 (77–360)
Bahrain	1·2% (0·7–1·3)	17 (10–19)	1·0% (0·6–1·1)	17 (10–19)
Egypt	3·3% (2·8–3·9)	3932 (3326–4580)	0·5% (0·4–0·6)	531 (449–619)
Iran	0·3% (0·2–0·3)	201 (135–257)	0·2% (0·2–0·3)	207 (139–265)
Iraq	0·4% (0·2–2·5)	132 (75–905)	0·3% (0·2–2·4)	140 (79–958)
Jordan	0·3% (0·1–0·3)	26 (6–32)	0·3% (0·1–0·3)	27 (6–33)
Lebanon	0·1% (0·0–0·4)	8 (3–27)	0·1% (0·0–0·4)	8 (3–25)
Libya	1·2% (1·1–1·3)	77 (70–83)	1·0% (0·9–1·0)	65 (60–71)
Morocco	0·9% (0·7–1·3)	313 (259–454)	0·8% (0·7–1·1)	292 (241–422)
Oman	0·4% (0·3–0·5)	16 (14–20)	0·3% (0·3–0·4)	17 (14–20)
Qatar	1·3% (1·3–1·6)	35 (33–41)	1·3% (1·3–1·6)	39 (37–45)
Saudi Arabia	0·3% (0·3–0·8)	106 (85–270)	0·3% (0·2–0·7)	97 (78–245)
Syria	1·5% (0·6–3·8)	254 (106–651)	1·6% (0·7–4·0)	276 (116–708)
Tunisia	0·4% (0·3–0·6)	46 (36–63)	0·4% (0·3–0·5)	44 (35–61)

(Table 1 continues on next page)

for modelling, and other studies (including blood donor data and studies from high-risk populations that were excluded from the main point estimate) were used to estimate the high and low values for uncertainty analysis. Subsequently, the model was used to forecast the HCV prevalence (including the undiagnosed population) and disease burden from 1950 to 2050 accounting for annual incidence, mortality, and cure. The model outcomes of new chronic infections (all ages), annual liver-related deaths (adults), incident hepatocellular carcinoma (adults), and incident decompensated cirrhosis (adults) were extracted for 2015–30 to include in global disease burden forecasting.

From a methodological perspective, the biggest difference between the present and previous analysis[11] is the calculation of incidence. First, the incident HCV infections were partitioned into vertically and horizontally acquired infections. Second, both vertically and horizontally acquired infections were calculated as a function of prevalence of chronic HCV infections (among women of childbearing age for vertically acquired infections) in a dynamic model. The change in horizontally acquired infections was calculated dynamically, whereby the annual rate of change in incidence followed the rate of change in prevalence. Previously, HCV incidence was assumed to remain constant after the last year of data. As a result, in the new model a decreasing HCV prevalence due to treatment expansion leads to a reduction in incidence. Additionally, although the model does not consider populations susceptible to HCV infection partitioned by risk group, it implicitly allows for reinfection, whereby a rising HCV prevalence leads to an increased incidence. The changes to incidence forecasting were applied after the last year of available data and are discussed in greater detail in the appendix (p 12).

Within the model, the number of diagnosed viraemic infections was calculated annually for the beginning of the calendar year, accounting for disease progression and mortality within the diagnosed population, as well as cures and newly diagnosed infections in the previous year. For this analysis, the number of people ever diagnosed with HCV was also calculated separately using the number of total viraemic cases diagnosed in 2015, plus all newly diagnosed viraemic cases from the start of 2015 (Jan 1) to the end of 2019 (Dec 31), without accounting for mortality or cure rate.

After the last year of available treatment data (which varied by country; appendix pp 28–33), forecasts for future treatment initiations were developed: the default forecast approximated a logarithmic decrease from the year of peak treatment in each country or territory within the study period (2015–20) to 50% of the peak treatment level over the course of 5 years (appendix pp 5–6). After 5 years, the number of patients treated annually was assumed to stay constant, unless data were available (ie, actual treatment data, country-level plans and estimates for future treatment, or high treatment rates already

documented) to inform forecasts. This forecast was initially developed considering the trajectory of treatment initiations following the launch of pegylated interferon (unpublished data, IMS Health MIDAS database 2013) and was later validated following the launch of DAAs (appendix pp 5–6). When country or territory-specific data were available to inform forecasts, those were used.

Global and regional estimates and sensitivity analysis

GBD regional population-weighted averages from approved and estimated models were calculated and applied for countries and territories with missing data to estimate the global HCV prevalence, cascade of care, and disease burden. The uncertainty in prevalence for approved and estimated models was used to model the prevalence uncertainty at GBD regional level, which was then applied to countries with missing data. Six countries with approved or estimated models (Australia, Egypt, Georgia, India, Mongolia, and Pakistan) were excluded from initial calculations (but were included in final summaries at a regional and global level) because their underlying HCV epidemic or interventions were not representative of those seen in neighbouring countries and territories. Countries and territories without a formal GBD designation were assigned an imputed GBD region (appendix p 21). After applying the GBD regional averages for countries without data, data were summarised for 235 countries and territories by GBD region, WHO region, World Bank income groups, and globally.

The cascade of care was displayed in two formats: as a cumulative cascade (similar to past reporting by WHO[1]) and annual cascade (based on the published consensus cascade of care[17]). The cumulative 2015–19 cascade of care compares ever diagnosed and ever treated cases against a baseline of viraemic prevalence in 2015. The annual cascade for 2020 considered only people who were still HCV viraemic (ie, adding chronic incident cases, and removing cured and mortality from both the prevalent and diagnosed segment).

Crystal Ball (version 11.1.3708.0), an Excel add-in by Oracle was used to calculate 95% uncertainty intervals (UI) by Monte Carlo simulation and to conduct sensitivity analyses. This software allowed us to use customised distributions to capture the uncertainty for any given variable. It then changes one input variable at a time and records the effect of each input variable on the desired forecast (outcome) variable (in this case, the beginning-of-year 2020 global viraemic prevalence). Subsequently, the software ranks inputs by their effect on the forecast variable. Probability distributions[18] used for key inputs have been described previously.[11] To calculate regional and global uncertainty ranges, two sources of uncertainty were considered: country and territory-level uncertainty in prevalence (based on literature search results and expert panel discussions) and the contribution of each country or territory to regional and global prevalence.

	Viraemic prevalence in 2015*†	Viraemic population (1000s) in 2015*†	Viraemic prevalence in 2020*†	Viraemic population (1000s) in 2020*†
(Continued from previous page)				
Turkey	0·3% (0·2–1·3)	282 (162–1029)	0·3% (0·2–1·0)	242 (140–885)
United Arab Emirates	1·3% (0·1–1·8)	118 (7–160)	1·5% (0·1–2·1)	152 (9–206)
Yemen	1·0% (0·6–1·2)	272 (165–329)	0·9% (0·5–1·1)	266 (161–321)
North America, high income				
Canada	0·6% (0·4–0·8)	228 (144–316)	0·4% (0·3–0·6)	156 (99–217)
USA	0·9% (0·7–1·3)	3230 (2307–4337)	0·8% (0·5–1·0)	2494 (1781–3349)
Oceania				
Fiji	0·1% (0·0–0·5)	0·7 (0·1–4·2)	0·1% (0·0–0·5)	0·7 (0·1–4·2)
Papua New Guinea	1·2% (0·7–2·0)	101 (58–162)	1·2% (0·7–1·9)	104 (60–167)
Sub-Saharan Africa, central				
Central African Republic	0·3% (0·3–0·9)	16 (13–41)	0·3% (0·2–0·8)	15 (12–39)
Democratic Republic of the Congo	0·5% (0·2–0·9)	413 (138–735)	0·5% (0·2–0·8)	418 (139–744)
Gabon	5·2% (4·7–5·7)	103 (95–113)	4·7% (4·3–5·2)	104 (96–115)
Sub-Saharan Africa, eastern				
Burundi	4·0% (3·6–30·4)	421 (377–3190)	3·5% (3·1–26·4)	415 (371–3142)
Ethiopia	0·7% (0·4–0·8)	683 (407–814)	0·6% (0·4–0·7)	684 (408–815)
Kenya	0·9% (0·3–1·4)	431 (133–684)	0·9% (0·3–1·4)	482 (149–765)
Madagascar	0·5% (0·3–1·5)	122 (86–376)	0·4% (0·3–1·3)	116 (81–357)
Mozambique	0·9% (0·4–1·2)	249 (124–324)	0·8% (0·4–1·0)	247 (123–321)
Rwanda	1·6% (0·7–2·0)	188 (76–226)	1·4% (0·6–1·7)	183 (74–221)
Tanzania	0·2% (0·2–0·2)	103 (83–124)	0·2% (0·1–0·2)	101 (81–122)
Uganda	0·6% (0·5–0·8)	252 (202–303)	0·6% (0·5–0·7)	260 (208–312)
Sub-Saharan Africa, southern				
South Africa	0·5% (0·4–1·0)	292 (226–572)	0·4% (0·3–0·9)	265 (205–519)
Sub-Saharan Africa, western				
Burkina Faso	1·5% (1·4–1·7)	271 (267–307)	1·4% (1·3–1·5)	285 (281–323)
Cameroon	0·8% (0·6–1·0)	192 (151–242)	0·7% (0·5–0·8)	173 (136–218)
Chad	1·1% (0·9–1·4)	156 (126–204)	0·9% (0·7–1·2)	147 (119–193)
The Gambia	0·8% (0·4–1·6)	18 (8–35)	0·8% (0·3–1·5)	18 (8–35)
Ghana	1·5% (0·8–3·8)	412 (236–1082)	1·4% (0·8–3·7)	432 (248–1135)
Nigeria	0·7% (0·3–1·2)	1352 (496–2234)	0·7% (0·2–1·1)	1362 (500–2251)

95% uncertainty intervals are shown in parentheses. Viraemic infection was defined by HCV RNA-positive status. HCV=hepatitis C virus. *2015 and 2020 beginning-of-year estimates are model output projections based on historic data. †Numerators (viraemic infections) and denominators (population) include all ages (≥0 years from birth).

Table 1: **Modelled HCV viraemic prevalence and number of viraemic infections for 110 countries and territories with approved or estimated models**

The 2020 country and territory prevalence estimates and 95% UIs were consolidated and defined as assumption variables. Sensitivity analysis was run to identify countries and territories that accounted for the greatest variation in global prevalence through their estimated prevalence range and inclusion in regional averages. Due to the scarcity of low or high ranges around the collected (largely empirical) diagnosis and treatment data, uncertainty in these inputs could not be modelled. Given the limitations of these input data, we applied the uncertainty in prevalence to regional and global cascades of care.

The **IMS Health MIDAS data** are available from http://www.imshealth.com/

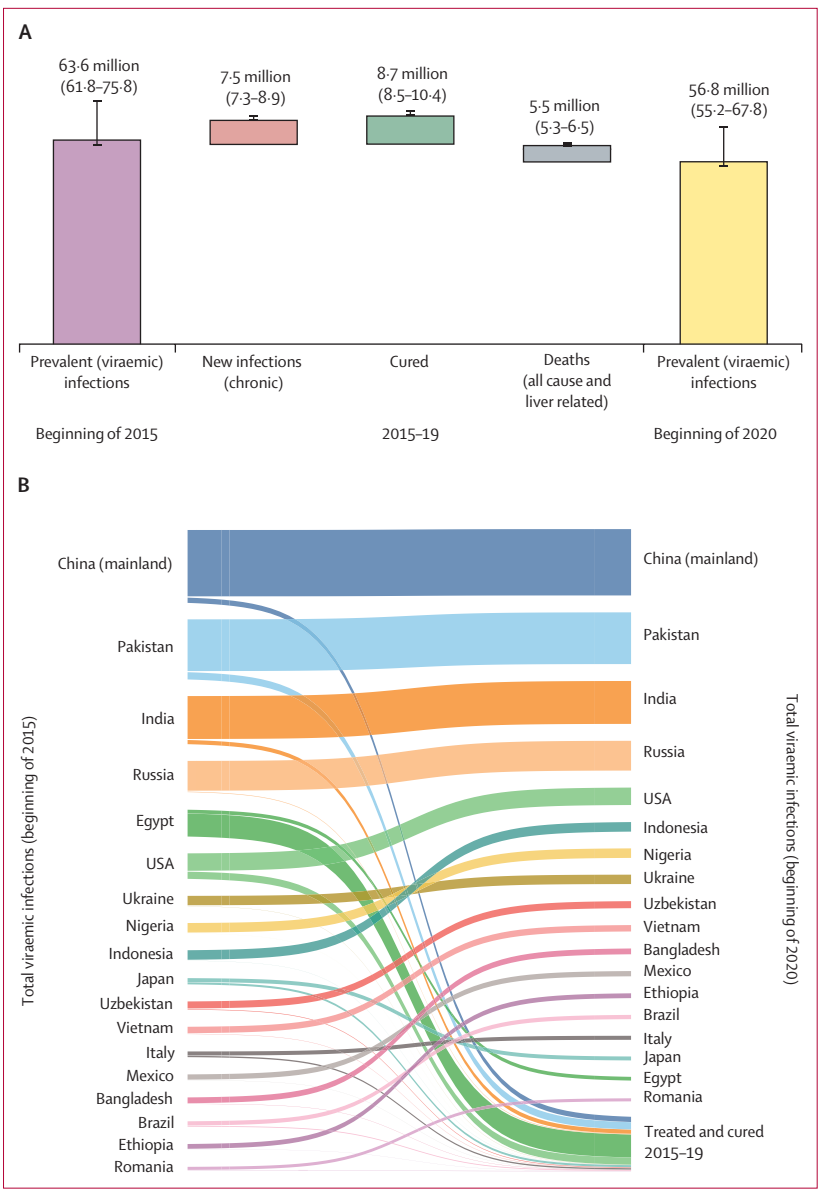

Figure 2: **Global change in viraemic HCV infections, 2015–20**
(A) Waterfall chart indicating the number of global viraemic infections from 2015 to the beginning of 2020, including the number of incident infections, infections treated (cured), and deaths. Error bars show 95% uncertainty intervals. (B) Sankey diagram of viraemic HCV infections in 2020, compared with viraemic infections at the beginning of 2015, including the fraction attributable to treatment and cure, among countries accounting for more than 70% of viraemic infections in 2015. Bar width is proportional to the size of the viraemic population. HCV=hepatitis C virus.

The outcomes of our current analysis were compared with outcomes from our previous analyses of global HCV prevalence. For the Polaris Observatory studies, quality scores (on a scale of 1–3, 1 being lowest quality, 3 being highest quality) were compared by country to identify countries with improving data and were summarised as the number of country prevalence estimates by quality score, by each global prevalence study,[7,11] to estimate the change in data quality across studies (appendix p 37). Building on a waterfall chart published in our last analysis,[11] the change in published prevalence estimates was updated to include outcomes from the present analysis. Prevalence by country was compared for this analysis and our last analysis in 2015[11] to identify where novel data obtained by the literature search and modelling was responsible for changes in global prevalence estimates.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to publish.

Results

We identified 7881 studies, after removal of duplicates, in PubMed with a publication date between April 1, 2016, and March 31, 2021. When combined with prevalence studies published before 2016[7,11] and expert input, prevalence estimates were available for 115 countries and territories, accounting for 93% of the world's population (as reported by the UN). Treatment data were available for 110 countries or territories. Diagnosis data were available for 93 countries or territories (for annual diagnoses) and 87 countries or territories (for total previous diagnoses). Among countries reporting treatment data, data were obtained from drug sales data (including generics; 39%), expert consensus (27%), national databases (26%), and published studies (8%; categories are not mutually exclusive). Among countries with diagnosis data, previous diagnosis estimates were obtained from expert consensus (45%), published studies (33%), and national surveillance or blood donor databases (22%). Estimates of annual diagnoses were from national surveillance or blood donor databases (42%), expert consensus (41%), and published studies (16%).

Models were built for 110 countries and territories that had (at minimum) data for HCV prevalence by age and sex. The inputs and outputs for 83 models were approved by country or territory experts and 27 were estimated with use of published data alone. This total set represents the addition of 12 new countries that were previously not included as approved or estimated, and the validation of 16 country models that were previously estimated and updated to approved (appendix p 18).[7,11] The remaining countries and territories (n=125) had insufficient data to create a model. Treatment data were available for 15 countries that had insufficient data to create a model, representing 5% of the world's population, but less than 1% of HCV treatments from 2015 to 2019.

The quality scoring of input prevalence data for approved or estimated countries and territories (1 being lowest quality, 3 being highest quality) is shown in the appendix (p 34). The viraemic HCV prevalence (percent and number; Jan 1, 2020) among the same countries and territories is shown in figure 1A, and the prevalence for all countries and territories, including those with an extrapolated prevalence, is shown in figure 1B. The

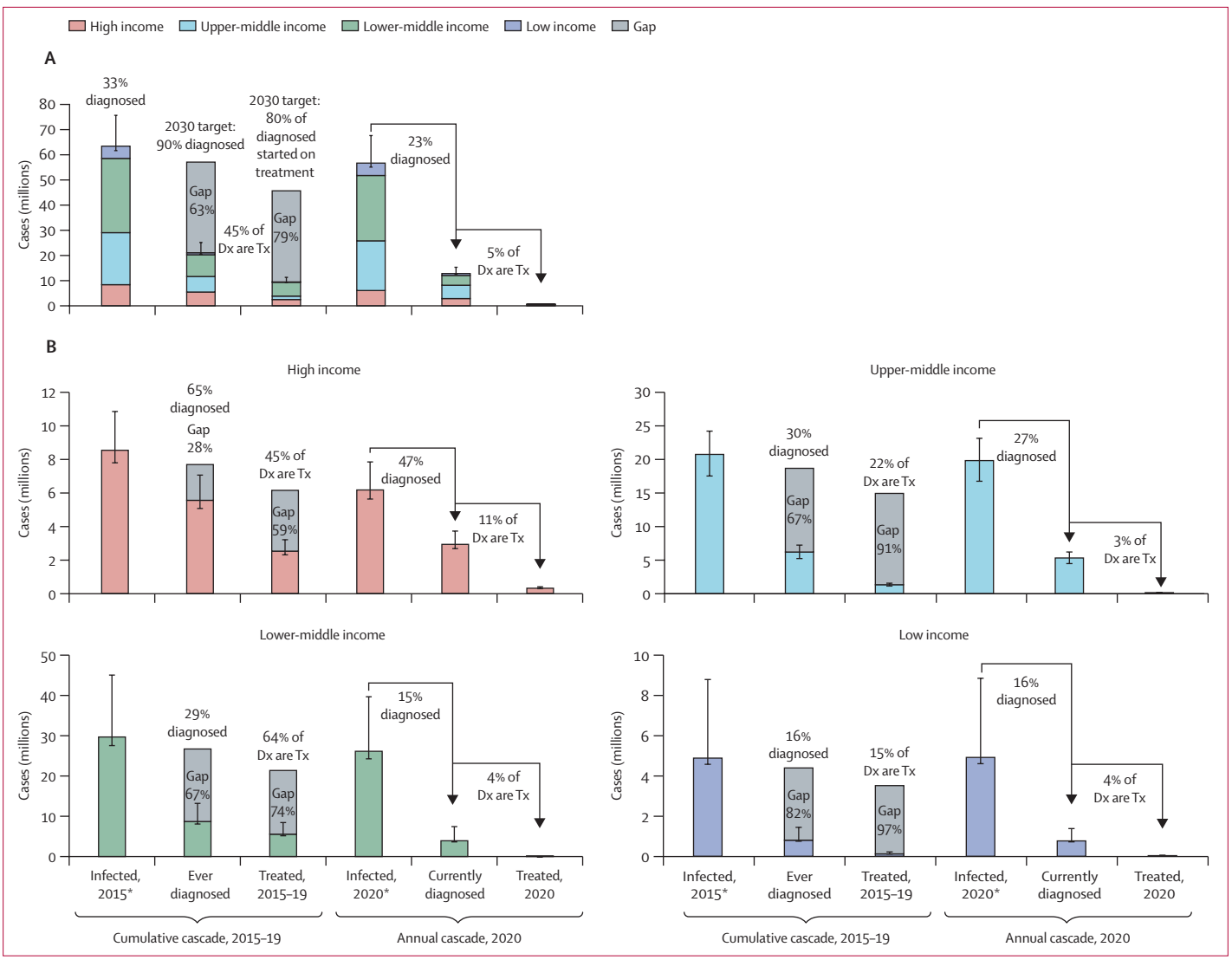

Figure 3: **Cumulative and annual cascade of care from 2015 to 2020**

(A) Globally by income group, compared against the WHO 2030 targets.[4] (B) By individual income group, compared against the WHO 2030 targets.[4] Error bars show 95% uncertainty intervals. Gap represents the percent of the WHO 2030 target remaining, and is calculated as follows: gap for diagnosed=1–[number ever diagnosed/(number infected in 2015 × 90% diagnosed by 2030)]; gap for treated=1–[treated in 2015–19/(number infected in 2015 × 90% diagnosed by 2030 × 80% treated by 2030)]. Dx=diagnosed. Tx=treated. *Data are for the start of the year (Jan 1).

number of viraemic infections at the beginning of 2020 for all countries and territories is shown in figure 1C.

The numerical prevalence and total infections in 2015 and 2020, for approved and estimated countries and territories, are shown in table 1. The model input data for prevalence, quality score, year of prevalence estimate, uncertainty range, viraemic rate, source of prevalence age distribution, and all corresponding references, by country and territory, are included in the appendix (pp 22–27). Input data, by country and territory for total diagnosed and newly diagnosed patients, annual number treated, and all corresponding references are included in the appendix (pp 28–33).

The global prevalence of viraemic (HCV RNA-positive) HCV infection was estimated to be 0·7% (95% UI 0·7–0·9) at the beginning of 2020, corresponding to 56·8 million (95% UI 55·2–67·8) viraemic infections. This represents a reduction of 6·8 million viraemic infections from a revised 2015 (beginning of year) estimate of 63·6 million (61·8–75·8) viraemic infections (0·9% [0·8–1·0] prevalence). The change in viraemic infections resulted from the addition of 7·5 million (7·3–8·9) new chronic infections, the subtraction of 8·7 million (8·5–10·4) cured infections, and the subtraction of 5·5 million (5·3–6·5) deaths (both all cause and liver related) from 2015 to the end of 2019 (figure 2A). The progression of viraemic infections from 2015 to 2020 among the 20 countries with

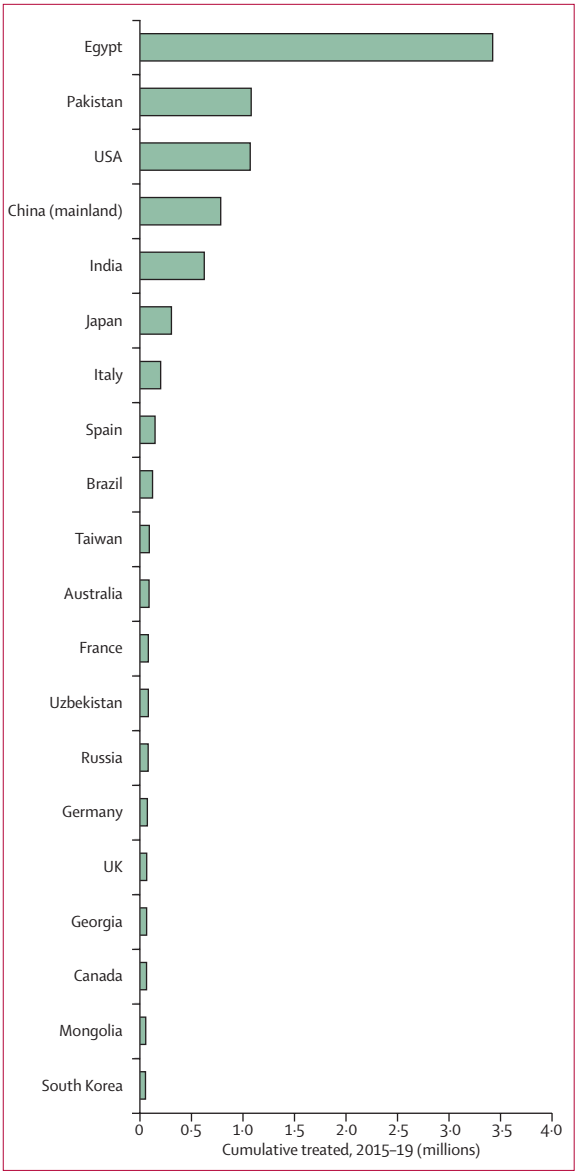

Figure 4: **Cumulative number of patients initiated on treatment from 2015 to the end of 2019**
For countries and territories accounting for more than 90% of treatment initiations.

the largest number of viraemic infections is shown in figure 2B. Most notably, Egypt's national treatment programme treated almost 3·5 million people from 2015 to 2019; the country moved from having the fifth most infections globally in 2015 to the 17th most infections globally by 2020.

The cascade of care was estimated in two ways (figure 3). First, a cumulative cascade was calculated relative to the 2015 baseline, which showed that 33% (21·1 million [95% UI 20·5–25·2]) of the viraemic population in 2015 had ever received a diagnosis (figure 3), with 9·5 million (95% UI 9·2–11·3) people cumulatively initiated on treatment (45% of 21·1 million diagnosed) between 2015 and 2019 (figure 3, figure 4, appendix p 35). Second, in the annual cascade in 2020, an estimated 23% (12·9 million [12·5–15·4]) of the viraemic HCV population was diagnosed and living with a viraemic infection (figure 3); and only 1% of prevalent cases (5% of diagnosed cases) were initiated on treatment (641 000 [623 000–765 000] treated out of 56·8 million viraemic; table 2). The total number of treated patients was 10·1 million from 2015 to the end of 2020 (figure 3).

We calculated regional estimates for 2020 HCV prevalence and the cascade of HCV care (table 2). In 2020, prevalence among GBD regions was highest in eastern Europe (2·9% [95% UI 2·3–3·2]) and central Asia (2·6% [2·4–2·8]), while the largest numbers of viraemic infections were estimated in south Asia (14·5 million [95% UI 13·2–24·2]) and east Asia (10·0 million [8·6–11·9]). The number of viraemic infections remained constant or decreased between 2015 and 2020 in all regions, with the exception of eastern Sub-Saharan Africa (marginal increase from 2·9 million infections to 3·0 million infections). In 2020, as in 2015, most viraemic infections were concentrated in lower-middle income countries (26·0 million [24·1–39·5]) and upper-middle income countries (19·8 million [16·7–23·1]).

Based on annual treatment trends, more than 1 million people were expected to have been initiated on treatment in 2020 (figure 5A). Empirical treatment data for the year 2020 were available for 31 countries and territories. In countries and territories reporting 2020 data, the number of treated patients was estimated to have decreased by 44% relative to 2019 (376 000 treated in 2020, compared with 675 000 treated in 2019). Of note, in 2020, Rwanda's screening and treatment campaign resulted in a more than 20-times increase in the number of treatments, relative to actual 2019 data (unpublished). Removing Rwanda from the calculation would suggest a 47% decrease in the number treated globally in 2020 (360 000 treated in 2020 compared with 674 000 treated in 2019). Global treatment decreases in 2020 were not only experienced as a result of the COVID-19 pandemic. In 2019, Egypt treated 1·9 million patients in the height of their elimination programme (Imam Waked, 2020 Polaris Epidemiology Update, unpublished), and future treatment numbers were expected to be markedly lower in the subsequent years following this success (figure 5A).

On the basis of empirical data and future treatment forecasts, the global annual number of new (incident) chronic infections in the total population was expected to remain relatively constant (2% decrease from 1·43 million in 2020 to 1·40 million in 2030) with a mean of 1·42 million new infections expected each year up to the end of 2030 (figure 5B). By 2030, end-stage outcomes in the adult population (age ≥18 years; liver-related deaths, hepatocellular carcinoma, and decompensated cirrhosis) were expected to increase by 14–17%

	2015		2020			
	Viraemic prevalence, %	Viraemic-HCV infected, millions	Viraemic prevalence, %	Viraemic-HCV infected, millions	Total diagnosed, millions*	Annual treated, 1000s†
Global Burden of Disease Study regions						
Asia Pacific, high income	0·7% (0·6–0·7)	1·2 (1·1–1·4)	0·4% (0·3–0·4)	0·7 (0·6–0·8)	0·5 (76·3%)	40·8 (6·1%)
Asia, central	2·8% (2·6–3·1)	2·5 (2·3–2·7)	2·6% (2·4–2·8)	2·4 (2·3–2·7)	0·3 (12·5%)	25·8 (1·1%)
Asia, east	0·7% (0·6–0·9)	10·7 (9·1–12·7)	0·7% (0·6–0·8)	10·0 (8·6–11·9)	2·6 (25·5%)	114·3 (1·1%)
Asia, south	0·9% (0·8–1·4)	14·6 (13·3–24·3)	0·8% (0·7–1·3)	14·5 (13·2–24·2)	2·4 (16·5%)	89·6 (0·6%)
Asia, southeast	0·6% (0·5–0·9)	3·9 (3·6–6·0)	0·6% (0·5–0·9)	3·9 (3·6–5·9)	0·5 (13·9%)	26·6 (0·7%)
Australasia	0·8% (0·6–1·0)	0·2 (0·2–0·3)	0·5% (0·4–0·6)	0·2 (0·1–0·2)	0·1 (87·0%)	9·1 (5·6%)
Caribbean	0·7% (0·4–1·3)	0·3 (0·2–0·6)	0·6% (0·4–1·2)	0·3 (0·2–0·6)	0·1 (32·8%)	0·7 (0·2%)
Europe, central	0·9% (0·8–1·2)	1·1 (1·0–1·3)	0·8% (0·8–1·0)	0·9 (0·9–1·2)	0·2 (19·7%)	18·1 (1·9%)
Europe, eastern	2·9% (2·3–3·2)	6·1 (4·9–6·6)	2·9% (2·3–3·2)	6·1 (4·9–6·6)	2·1 (34·5%)	20·5 (0·3%)
Europe, western	0·5% (0·4–0·6)	2·2 (1·9–2·6)	0·3% (0·3–0·4)	1·4 (1·3–1·7)	0·7 (50·0%)	57·8 (4·0%)
Latin America, Andean	0·5% (0·2–0·5)	0·3 (0·1–0·3)	0·5% (0·2–0·5)	0·3 (0·1–0·3)	<0·1 (11·0%)	1·8 (0·6%)
Latin America, central	0·6% (0·6–0·7)	1·6 (1·4–1·7)	0·6% (0·5–0·7)	1·5 (1·4–1·7)	0·2 (12·2%)	3·7 (0·2%)
Latin America, southern	0·6% (0·3–1·1)	0·4 (0·2–0·7)	0·5% (0·3–1·0)	0·4 (0·2–0·6)	<0·1 (6·3%)	1·4 (0·4%)
Latin America, tropical	0·4% (0·3–0·4)	0·7 (0·6–0·8)	0·3% (0·2–0·3)	0·6 (0·5–0·7)	0·1 (21·6%)	19·9 (3·2%)
North Africa and Middle East	1·2% (1·1–1·4)	6·6 (6·2–7·9)	0·5% (0·5–0·6)	3·2 (3·0–3·8)	1·1 (35·2%)	26·7 (0·8%)
North America, high income	1·0% (0·8–1·2)	3·5 (2·8–4·2)	0·7% (0·6–0·9)	2·7 (2·1–3·2)	1·1 (41·3%)	153·1 (5·8%)
Oceania	1·1% (0·8–3·8)	0·1 (0·1–0·4)	1·1% (0·8–3·6)	0·1 (0·1–0·4)	<0·1 (10·6%)	NA
Sub-Saharan Africa, central	0·6% (0·4–2·1)	0·8 (0·4–2·5)	0·6% (0·3–1·8)	0·8 (0·4–2·5)	0·1 (12·7%)	NA
Sub-Saharan Africa, eastern	0·8% (0·7–1·3)	2·9 (2·6–4·7)	0·7% (0·6–1·1)	3·0 (2·7–4·8)	0·3 (10·5%)	26·3 (0·9%)
Sub-Saharan Africa, southern	0·5% (0·3–0·8)	0·4 (0·2–0·6)	0·4% (0·3–0·7)	0·4 (0·2–0·5)	0·1 (21·9%)	0·1 (<0·1%)
Sub-Saharan Africa, western	0·9% (0·7–1·2)	3·5 (2·6–4·7)	0·8% (0·6–1·1)	3·5 (2·6–4·7)	0·2 (6·7%)	4·3 (0·1%)
WHO regions						
African region	0·8% (0·7–1·2)	7·8 (6·5–12·2)	0·7% (0·6–1·1)	7·8 (6·6–12·2)	0·8 (10·0%)	30·7 (0·4%)
Region of the Americas	0·7% (0·6–0·8)	6·8 (5·7–8·3)	0·6% (0·5–0·7)	5·7 (4·8–7·0)	1·6 (27·3%)	180·6 (3·1%)
Eastern Mediterranean region	2·0% (1·7–2·5)	13·3 (11·4–16·5)	1·4% (1·2–1·7)	10·2 (8·7–12·6)	3·0 (29·6%)	75·1 (0·7%)
European region	1·3% (1·1–1·5)	11·9 (9·8–13·5)	1·2% (1·0–1·3)	11·0 (9·0–12·5)	3·3 (29·7%)	122·4 (1·1%)
South-east Asia region	0·5% (0·4–1·2)	9·7 (7·9–22·2)	0·5% (0·4–1·1)	9·5 (7·7–21·7)	0·8 (8·0%)	47·0 (0·5%)
Western Pacific region	0·7% (0·6–0·9)	14·1 (12·0–17·7)	0·6% (0·6–0·8)	12·7 (10·8–16·0)	3·5 (27·6%)	184·8 (1·5%)
World Bank income groups						
Low income	0·8% (0·8–1·5)	4·9 (4·6–8·8)	0·7% (0·7–1·3)	4·9 (4·6–8·9)	0·8 (15·6%)	28·2 (0·6%)
Lower-middle income	1·0% (0·9–1·4)	29·5 (27·4–44·8)	0·8% (0·7–1·2)	26·0 (24·1–39·5)	3·9 (15·0%)	144·5 (0·6%)
Upper-middle income	0·8% (0·7–1·0)	20·7 (17·5–24·2)	0·8% (0·6–0·9)	19·8 (16·7–23·1)	5·3 (26·8%)	159·5 (0·8%)
High income	0·7% (0·6–0·9)	8·4 (7·7–10·7)	0·5% (0·5–0·6)	6·1 (5·6–7·7)	2·9 (47·5%)	308·2 (5·1%)
Total	0·9% (0·8–1·0)	63·6 (61·8–75·8)	0·7% (0·7–0·9)	56·8 (55·2–67·8)	12·9 (22·7%)	640·6 (1·1%)

Values in parentheses are 95% uncertainty intervals or %. HCV=hepatitis C virus. NA=not available. *Proportion diagnosed was calculated as the number of total cumulative diagnoses (2015–20; excluding deaths and cures) divided by the viraemic-HCV infected in 2020. †Proportion treated was calculated as the number treated (2020) divided by the viraemic-HCV infected in 2020.

Table 2: **Regional and global viraemic prevalence (beginning of years 2015 and 2020) and annual cascade of care in 2020**

relative to 2020 (257 000 liver-related deaths in 2020 to 290 000 in 2030; 190 000 incident hepatocellular carcinoma cases in 2020 to 220 000 in 2030; and 148 000 incident decompensated cirrhosis cases in 2020 to 174 000 in 2030; figure 5B).

The top ten drivers of uncertainty contributing the most to the global prevalence range (as per the sensitivity analysis) are shown in the appendix (p 36). These top ten drivers of uncertainty accounted for more than 95% of the total variance in global prevalence.

We compared the present analysis with previous analyses (appendix p 37). Improvements in the quality (scale of 1 [lowest] to 3 [highest]) and availability of prevalence data were observed since our last analysis, with the addition of high-quality estimates in countries where data were previously unavailable, including Armenia (score=2), Bhutan (score=3), the Democratic Republic of the Congo (score=2), Kyrgyzstan (score=2), Rwanda (score=3), and Tanzania (score=3). Additionally, countries and territories have engaged in high-quality screening programmes and serosurveys, to monitor progress (eg, Egypt [score=3]) or update older, lower quality estimates (eg, Vietnam [score=3, previous score=1]). In total, 39 countries and territories had a new

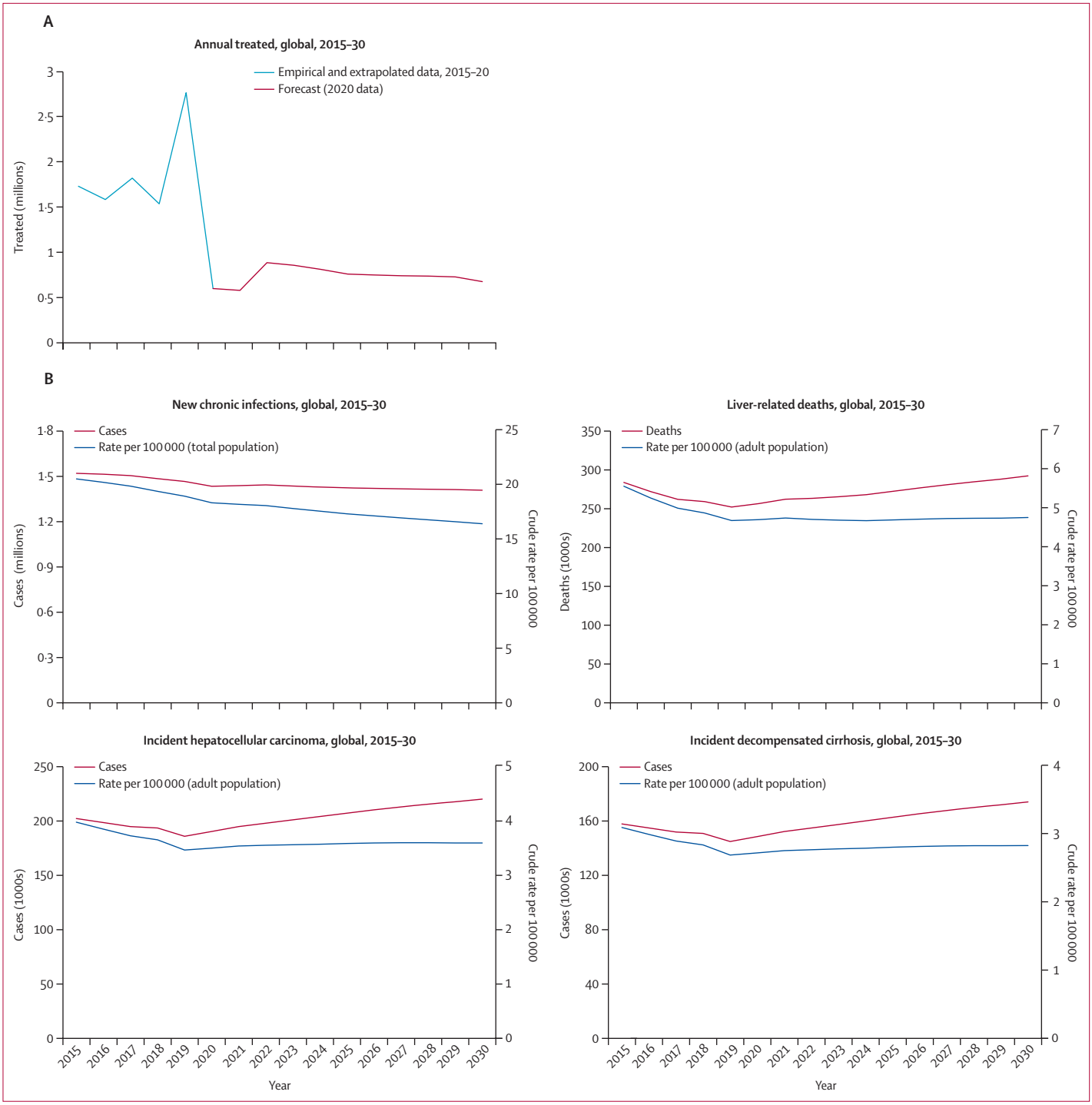

Figure 5: **Global forecasts for HCV disease burden, 2015–30**

A) Annual patients treated, with empirical and extrapolated data up to the end of 2020, as well as global forecasts based on country-level data up to the end of 2020 and with projections up to the end of 2030. The increase in 2019 is largely due to the treatment of 1·9 million patients in Egypt. Treatment forecasts are based on treatment data from 2015–20 assuming no expansion of national elimination programmes (status quo assumption). (B) Forecasted number and crude annual rate of new chronic infections (total population) and liver-related deaths, hepatocellular carcinoma, and decompensated cirrhosis (adult population aged ≥18 years).

model or study that resulted in the country or territory-level 2015 prevalence estimate deviating by up to 20% from our previous analysis.

Discussion

The 2020 global HCV prevalence estimate of 0·7% (95% UI 0·7–0·9) or 56·8 million (95% UI 55·2–67·8)

viraemic infections is lower than estimates from previous years.[9–11] This difference is primarily due to two factors, the first being newer published serosurveys identified through our literature search or expert panel meetings, which resulted in a reassessment of the baseline 2015 prevalence estimate. The uncertainty intervals captured uncertainties in country-level and territory-level prevalence estimates on the overall forecasts. Notably, we were able to develop a new model for the Democratic Republic of the Congo using data from a large-scale dried blood spot survey.[19] This survey tested for HCV RNA and found a viraemic prevalence of 0·9%,[19] which resulted in a lower number of infections than our previous estimate derived from the regional average (2·1%).[11] Additionally, relative to our previous study, more than 1 million fewer viraemic infections in 2015 were estimated in both Egypt and Brazil, where new prevalence studies were available. Overall, our new 2015 prevalence estimate (0·9% [95% UI 0·8–1·0]) is still within the range of our original estimate (1·0% [0·8–1·1]).[11] However, the current estimate represents the start of 2015, while the initial analysis reflected the end of 2015.[11]

The second factor contributing to a lower 2020 prevalence than previous estimates is the cumulative effect of time (aging, all-cause and liver-related deaths, and incident infections) as well as treatment. The Markov model forecasts 2020 prevalence with annual adjustment for incidence, mortality, and cure. Between 2015 (63·6 million [95% UI 61·8–75·8] viraemic infections) and 2020 (56·8 million [55·2–67·8] viraemic infections), there were an estimated 7·5 million (7·3–8·9) new chronic infections, 5·5 million (5·3–6·5) deaths (both all cause and liver related), and 8·7 million (8·5–10·4) cured infections. The ability to calculate and present modelled prevalence estimates over time by country and globally, alongside cascade of care, reflects the utility of modelling in elimination monitoring activities.

Our results are in line with the recent WHO global 2021 progress report on HIV, viral hepatitis, and sexually transmitted infections,[20] although there are some notable differences in the analyses and outcomes. Data for the WHO global progress report was collected through a series of activities that included sharing 2019 data from the CDAF and other partners with countries and territories, to be used as a reference point for their global reporting activities. Countries and territories then chose to either keep the data or replace them with their own estimates. In the event that the data available to and reported by national programmes reflected only part of the story (eg, old data were reported because new data were not available; or data were reported from the public sector but excluded efforts from the private sector), WHO could only report what had been provided or endorsed by countries. Although many of the underlying data sources overlap with our analysis, the main difference in outcomes was that the CDAF team worked with country and territory experts to determine the appropriate way to adjust subnational data to the national level, and then model forward the results to the latest year (in this case, 2020). The Delphi process and engagement of panels of country or territory experts including a range of stakeholders represents a strength of our analysis. CDAF facilitators are trained to identify and challenge cognitive and motivational biases, including in situations in which the ministry of health is either not familiar with the data or would anchor to specific studies. The Delphi process allows us to engage a range of national stakeholders and experts (from inside and outside ministries of health) to provide balanced feedback and challenge one another's assumptions. As a result, the outcomes of the two analyses are complementary, but not identical.

Of the 9·5 million people estimated to have been initiated on DAA therapy between 2015 and the end of 2019, more than a third (3·5 million [36%]) were in Egypt. In the future, this effort is expected to reduce the number of hepatocellular carcinoma cases and liver-related deaths in the country, and the cost associated with managing HCV.[21] Globally, the number of patients initiated on treatment was estimated to have decreased in 2020 relative to 2019; the cause of this decrease is likely to be multifactorial. First, the Egyptian programme has nearly concluded,[21] thus reducing Egypt's relative contribution to global treatment efforts after 2019. Additionally, in many settings, previously diagnosed patients under care have already received treatment. Treatment efforts in special populations (including incarcerated populations or people who use drugs) vary substantially by country, with many countries still enforcing sobriety restrictions.[22] Efforts to extend treatment to patients other than those already diagnosed and under care might be hindered as many countries do not have general population screening programmes that could allow the numbers of patients treated to be maintained in the future. Although disease notification systems and patient registries exist in a number of countries, they are not universally reliable for estimating the number of people currently diagnosed and in need of treatment. According to the Polaris Observatory Dashboard, many countries with high-quality patient registries are finding that only 20–30% of diagnosed cases have been treated, indicating that linkage to care remains a bottleneck. As a result, current outreach efforts to test and link to care the undiagnosed patients, and patients lost to follow-up, especially among vulnerable populations, have not been sufficient to maintain the annual number treated. Additionally, the COVID-19 pandemic affected logistics and distribution systems, as well as access to health care and hepatitis screening and treatment services. Countries also reported decreases in new diagnoses and access to testing services.[23,24] These decreases might signal a problem for future elimination efforts. The overall impact of the pandemic is uncertain and will depend on the strength of current and future hepatitis elimination programmes, and the future impact of COVID-19,

For the **Polaris Observatory Dashboard** see https://cdafound.org/polaris-countries-dashboard/

especially in view of COVID-19 vaccination efforts with substantial variations in vaccine availability.

To monitor progress toward the 2020 and 2030 elimination goals, and to guide future efforts in elimination planning, the cascade of care is presented in two formats in the present study (cumulative and annual). The cumulative 2015–19 cascade of care compares ever diagnosed and ever treated cases against a baseline of viraemic prevalence in 2015, providing an easy visual for progress toward the 2020 and 2030 targets. However, since the true number of viraemic infections changes each year with the addition of new infections and the subtraction of mortality and cured cases (unlike other diseases such as HIV or hepatitis B virus without curative therapies), this cascade format might hide a growing viraemic population, and is less useful for understanding the current needs in a country or territory, or region. The annual cascade of care provides a snapshot of current progress and future needs but does not fully appreciate previous efforts. A great example of the different insights obtained from the two cascades was observed in our analysis for lower-middle income countries and territories (figure 3C). Furthermore, up to the end of 2019, 21·1 million (33%) of the 63·6 million infected population were ever diagnosed, and 9·5 million (45%) of 21·1 million ever diagnosed patients were initiated on treatment (figure 3B). However, because 95% of patients initiated on treatment are cured of their HCV (and HCV must first be diagnosed before it can be cured), the annual cascade reflects that only 12·9 million (23%) of 56·8 million infections remaining in 2020 were living with a diagnosis. Focusing only on cumulative efforts misses the fact that most of the currently infected population remained undiagnosed. Similarly, focusing on cumulative treated might obscure annual decreases in treatment. As countries evaluate their progress toward elimination, they should not only monitor cumulative past efforts but also maintain an annual snapshot of the cascade to highlight current gaps.

Our study has some limitations, many of which have been discussed previously.[11] The availability and quality of data continue to limit the accuracy of forecasts. The inclusion of ranges addresses the uncertainty in the available data; however, these uncertainty intervals might not capture all sources of bias, including measurement bias, selection bias due to missing data, and model misspecification bias. Small improvements in the quality and availability of data have been observed since our last analysis, with the addition of high-quality estimates in countries or territories where data were previously unavailable (including Armenia, Bhutan, the Democratic Republic of the Congo, Kyrgyzstan, Rwanda, and Tanzania). Additionally, countries and territories are engaging in high-quality screening programmes and serosurveys, to monitor progress (eg, Egypt), or update older, lower-quality estimates, (eg, Vietnam and Nigeria). Nevertheless, paucity of data remains a problem for many parts of the world. Of 250 countries and territories in the world, only 110 countries and territories had sufficient data to generate a model. Uncertainty in treatment data is also a concern, especially in countries and territories producing generic medications, where some of the produced treatments will remain in-country and some will be shipped overseas (eg, India) and countries and territories where national programmatic data are collected but only reflect the public sector. Where possible, these uncertainties have been addressed by comparing multiple sources of data (eg, national programme data, generic sales data, humanitarian programme data, and expert consensus). As described previously,[11] use of models to forecast 2015 and 2020 HCV prevalence runs the risk of being inaccurate. Although we report the cascade of care for the calendar year 2020, the prevalence estimate is emphasised for the beginning of 2020 to acknowledge uncertainty around country responses due to the COVID-19 pandemic. For the model forecasting, we assume 2 years of disrupted treatment, followed by a return to previous trends. However, many countries have reported disruptions to new screening and diagnosis in 2020,[23,24] which might mean our treatment projections for future years are overly optimistic.

We estimated a decrease in the global prevalence of HCV from 2015 to 2020; however, 56·8 million viraemic infections were still estimated in 2020, with only 12·9 million diagnosed. More than 10 million people were estimated to have initiated DAA therapies in 2015–20, with more than a third of treatments occurring in Egypt. With the Egyptian programme reaching near completion in 2019, global treatment forecasts declined substantially. Treatment further declined in 2020, partially due to the depletion of patients awaiting DAA treatment, the COVID-19 pandemic, and other factors. If treatment remains below 1 million patients per year, as is currently estimated, then liver-related deaths and other end-stage outcomes could be expected to increase globally by 2030. Thus, countries should continue to pursue HCV elimination efforts through screening, diagnosis, and timely treatment. The data presented herein provide a call to action for the global hepatitis community and can serve as a reset point for countries revisiting HCV elimination efforts in the wake of the COVID-19 pandemic.

Contributors

HR and SB conceived the study. All authors curated data. SB, CE, DMR-S, ElM, HR, IG, and KR-S did the formal analysis. HR acquired funding. SB designed the methodology. SB was responsible for project administration. HR and SB supervised the study. All authors validated data. CE and SB were responsible for data visualisation. SB, CE, DMR-S, ElM, HR, IG, and KR-S wrote the original draft. All authors reviewed and edited the manuscript. CE, DMR-S, ElM, HR, IG, KR-S, and SB had access to the underlying data and models. SB, CE, DMR-S, ElM, IG, and KR-S accessed and verified the data. All authors had full access to the data for their country and accept responsibility to submit for publication.

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Data sharing

For a period of 1 year after publication, the authors will share the data used in the maps and figures in a Microsoft Excel format after a written request is made to the corresponding author. Data sharing will be limited to government agencies, academic institutions, and non-profit organisations, and will not apply to for-profit or consulting organisations. Additionally, select country level, regional, and global data from the manuscript will be available publicly on the Polaris Observatory Dashboard.

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