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ORIGINAL ARTICLE

Updated epidemiology of hepatitis C virus infections and implications for hepatitis C virus elimination in Germany

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Abstract

In 2014, an analysis was conducted to evaluate the hepatitis C virus (HCV) epidemiology and disease burden in Germany. Since then, there have been considerable developments in HCV management such as the implementation of direct acting antivirals. The aim of this analysis was to assess the recent data available for Germany, establish an updated 2020 HCV prevalence and cascade of care and evaluate the impact of what-if scenarios on the future burden of disease using modelling analysis. A dynamic Markov model was used to forecast the HCV disease burden in Germany. Model inputs were retrieved through literature review, unpublished sources and expert input. Next, three "what-if" scenarios were developed to evaluate the status quo, COVID-19 pandemic, and steps needed to achieve the WHO targets for elimination. At the beginning of 2020, there were 189,000 (95% UI: 76,700–295,000) viremic infections in Germany, a decline of more than 85,000 viremic infections since 2012. Annual treatment starts went down since 2015. Compared with 2019, the COVID-19 pandemic resulted in a further 11% decline in 2020. If this continues for two years, it could result in 110 excess HCC cases and 200 excess liver related deaths by 2030. To achieve the

Abbreviations: COVID-19, coronavirus disease 2019; DEGS 1, German health interview and examination survey for adults; HCC, hepatitis C virus; RKI, hepatocellular carcinoma; HCV, Robert Koch Institute; SVR, sustained virologic response; UI, uncertainty interval; WHO, World Health Organization.

WHO targets, 81,200 people need to be diagnosed, with 118,600 initiated on treatment by 2030. This could also avert 1,020 deaths and 720 HCC cases between 2021 and 2030. Germany has made strides towards HCV elimination, but more efforts are needed to achieve the WHO targets by 2030.

KEYWORDS
COVID-19, elimination, Germany, hepatitis C virus

1 | INTRODUCTION

In 2014, an analysis was conducted to evaluate the hepatitis C virus (HCV) epidemiology and disease burden in Germany.[1] Since that time, the epidemiology of HCV has changed rapidly due to the vast implementation of direct acting antiviral (DAA) therapies since 2014 with high rates (>90%) of sustained virological response (SVR). Germany made advancements towards HCV elimination and was one of the first countries to provide universal access to the new therapies with no restrictions on the basis of fibrosis. Between 2014 and 2019, almost 90,000 patients were initiated on therapies,[2] accounting for approximately 34% of the 267,000 viremic infections estimated at the end of 2013.[3] However, the rates of screening and diagnosis have lagged, with fewer than 32,000 infections notified to the Robert Koch Institute (RKI) in the same time frame.[4] In Germany, clinicians and laboratories have to report viremic HCV infection to the patients' local health department. Population-based screening programmes did not exist until October 2021 and national guidelines only recommend to screen high-risk groups such as people who inject drugs (PWID) or patients on haemodialysis.[5]

In 2020, the coronavirus disease 2019 (COVID-19) pandemic posed a new challenge for HCV elimination efforts. Some countries report a drastic decrease of overall hepatological activity and HCV-screenings in ambulatory clinics and emergency departments.[6] As of 14 September 2021, over 4.1 million total COVID-19 infections in Germany were reported to RKI, and more than 55.4 million vaccine doses were administered (>66% of the population vaccinated).[4,7] The number of HCV infections reported to RKI dropped more than 20%, from 5953 in 2019 to 4559 in 2020, potentially as a result of health service disruptions.[4] Compared with the same time frame in 2019, the first 22 weeks of 2021 showed an even greater (25%) decline in HCV notifications.[4]

In the seven years that have passed since our original analysis, there have been considerable developments in HCV management such as high treatment availability and efficacy.[8–10] The objective of this analysis was to assess the recent data available for Germany and establish an updated 2020 baseline for the HCV prevalence and cascade of care, and then to evaluate the impact of what-if scenarios on the future burden of HCV disease in Germany using modelling analysis.

2 | MATERIAL AND METHODS

The data used for modelling were obtained through literature review, unpublished sources and expert input. Next, a dynamic Markov model was used. HCV prevalence,[11,12] prevalence by age and sex,[11,12] the number of persons newly diagnosed[4] and previously diagnosed[13] and the number initiated on the treatment[2] were used to seed and calibrate the model. Inputs parameters are included in Table 1. Many of these inputs have been described in detail previously, with newer inputs described briefly in the Supporting information Appendix.[14]

The number of true new (acute) infections is not systematically captured and estimates of acute infections are likely to be underreported. As a result, new infections were back-calculated in the model using known prevalence and considering trends in transmission risk factors over time (see Appendix in Supporting information). After the last year of data, the model calculated future incidence as a function of prevalence as has been described previously. In addition, the annual number of new viremic infections entering Germany via migration was calculated for 2019 considering net immigration data by country of origin,[15] country- and sex-specific anti-HCV prevalence among migrants[16] and viremic rate among refugees.[17]

TABLE 1 Model inputs and sources

Input	Year	Estimate	Source
Viremic prevalence	2012	274,700 (165,000–494,400)	Expert input14
Prevalence by age and sex	2012	20% DEGS; 80% RKI (see Appendix in Supporting information)	11,12
Previously diagnosed	2012	48%	13
Annual newly diagnosed (HCV-RNA+)	2019	5,940	4
Annual number treated	2019 2020	9,700 7,600	Prescription sales data
Annual new viremic infections associated with migration	2019	2,870	15,16

2.1 | Modelled scenarios for the elimination of HCV in Germany

Once the model was developed, a variety of "what-if" scenarios were run to evaluate the impact of future decisions. The scenarios included are as follows:

A baseline scenario (Base 2019) was developed using empirical diagnosis and treatment data through 2019, before considering the impact of the COVID-19 pandemic (Baseline scenario). After 2019, screening was assumed to remain constant, resulting in fewer newly diagnosed cases each year (Table 2). Assuming no major improvements in case finding or linkage to treatment, the number of patients starting treatment each year would decrease (Table 2).

A second scenario (COVID-19) was developed using empirical treatment data for the year 2020, and assuming the same number of patients treated in 2021, before returning to previous treatment forecasts (COVID-19 scenario).

A third scenario (WHO 2030) was developed to identify the steps needed to achieve the World Health Organization (WHO) elimination targets (90% diagnosed; 80% treated; 65% reduction in mortality; 90% reduction in incidence) by 2030 (Elimination scenario).

2.2 | Uncertainty analysis and model validation

Crystal Ball release 11.1.2.3.500 was used to calculate uncertainty intervals (UI) and conduct sensitivity analyses. β-PERT distributions were used for all uncertain inputs. A Monte Carlo simulation with 1000 trials was used to estimate 95% UIs. Uncertainty around the total number of HCV infections entering the country via migration was calculated similarly, considering reported ranges around country- and sex-specific anti-HCV prevalence among migrants.[16]

In addition, empirical hepatocellular carcinoma (HCC) data were collected to validate the model outcomes in Germany. The number of liver cancer cases,[18] proportion which are HCC,[19] and proportion attributable to HCV[20,21] were retrieved from government databases and published sources. The estimated number of HCV-related HCC cases was calculated and plotted against the model outcomes for HCV-related HCC cases.

3 | RESULTS

At the beginning of 2020, there were an estimated 189,000 (95% UI: 76,700–295,000) viremic infections in Germany among all ages (prevalence = 0.23% [95% UI: 0.09%–0.36%] HCV-RNA+), representing a decline of more than 85,000 viremic infections since 2012 (Figure 1). The change in infections was precipitated primarily through the treatment and cure of more than 89,000 HCV+ patients over the course of 2013–2019 but was offset by an estimated 26,000 new infections (including new infections entering the country through migration, as well as incident cases of HCV occurring within the country). Among prevalent viremic infections at the beginning of 2020, an estimated 37% (n = 70,500) were diagnosed and still HCV-RNA+, leaving 63% of all HCV-RNA+ patients undiagnosed (Figure 2).

3.1 | Baseline scenario

Before considering the impact of the COVID-19 pandemic, 5700 persons were projected to be newly diagnosed with viremic HCV in Germany with 8600 projected to start treatment in 2020. These estimates would represent a 5% decline in diagnosis and an 11% decline in treatment, with continued declines in treatment and diagnosis expected over the next ten years, in the absence of intervention. Under this base scenario, viremic cases in Germany would be expected to decrease by 55%, while decompensated cirrhosis, HCC and liver related deaths would be expected to decrease by 30%–40% from 2015 to 2030 (Figure 3 + Appendix 8 in Supporting information). Under this 2019 base scenario, Germany was projected to have exceeded all of the WHO 2020 targets (30% diagnosed, 30% reduction in incidence and 10% reduction in liver-related deaths), but was not on track to achieve any of the WHO 2030 targets (90% diagnosed, 80% treated, 90% reduction in incidence, 65% reduction in liver-related deaths).

TABLE 2 Annual number diagnosed and initiating treatment, as well as treatment eligibility and SVR under the 2019 Base and WHO targets scenarios, 2019–2030

Scenario input	Scenario	2019	2020–2021	2022–2023	2024–2025	2026–2027	2028–2030	Cumulative 2021–2030
Newly diagnosed (Viremic)	2019 base	5950	5700	5400	5100	4700	4300	49,000
	COVID-19	5950	4600	5400	5100	4700	4300	47,900
	WHO targets	5950	5700	8000	10,000	10,000	6500	81,200
Initiating treatment	2019 Base	9700	8600	8500	8400	8000	7700	81,700
	COVID-19	9700	7600	8500	8400	8000	7700	80,700
	WHO targets	9700	8600	9000	12,000	16,000	12,000	118,600
Treatment eligibility, fibrosis stage	All scenarios	≥F0	≥F0	≥F0	≥F0	≥F0	≥F0	–
Treatment eligibility, age (years)	All scenarios	All ages	All ages	All ages	All ages	All ages	All ages	–
SVR	All scenarios	97%	97%	97%	97%	97%	97%	–

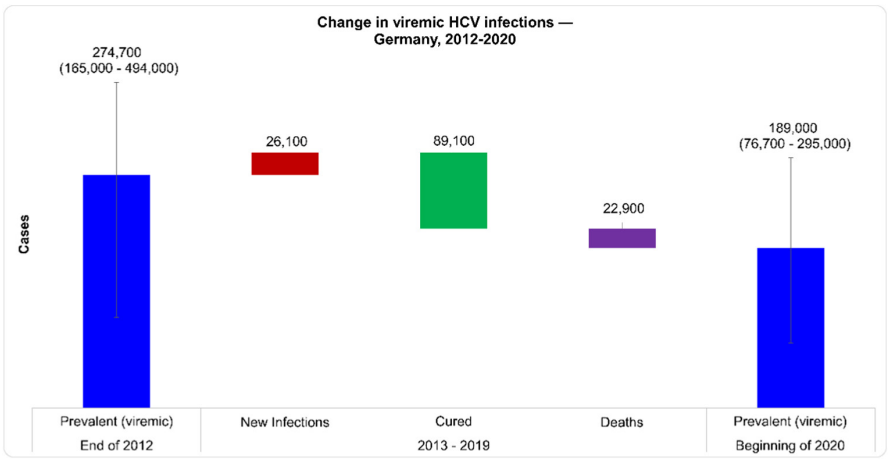

FIGURE 1 Waterfall chart indicating the number of viremic infections from 2012 to 2020, including the number of incident infections, treated/cured and deaths

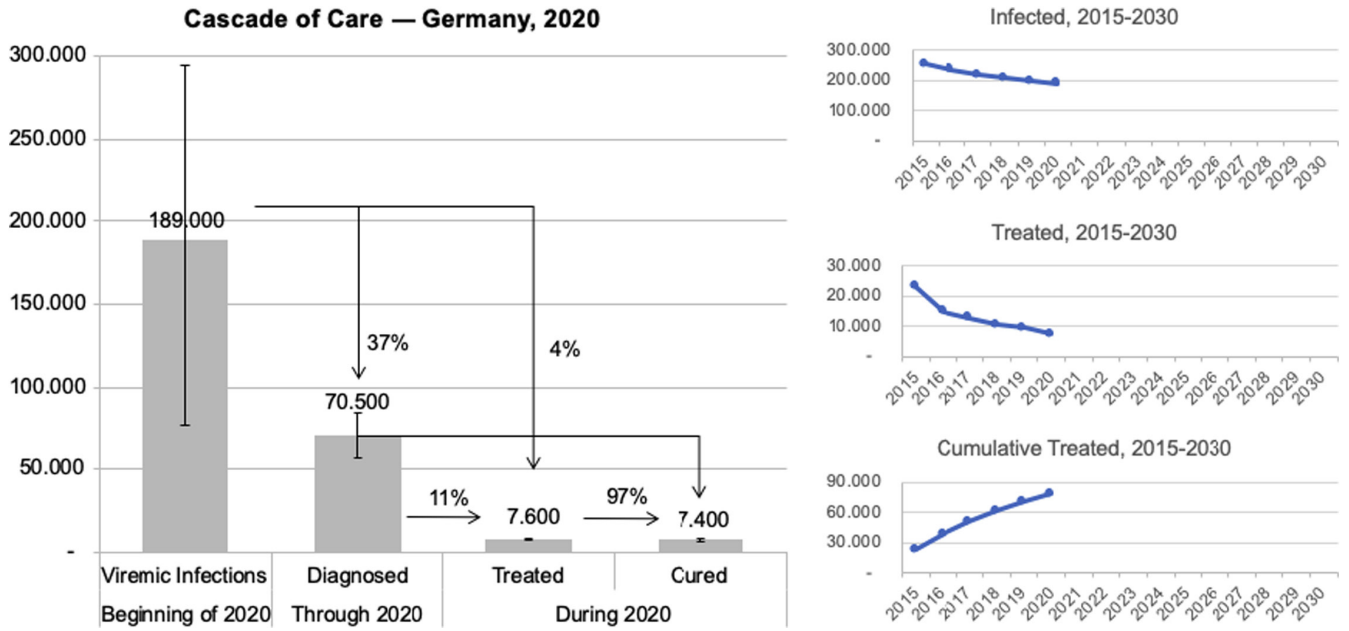

FIGURE 2 Cascade of care in 2020

3.2 | COVID-19 scenario

Empirical data collected at the beginning of 2021 found that in actuality, only 7,600 patients were initiated on treatment in 2020 due to the COVID-19 pandemic, an 11% decline relative to the previously forecast treatment estimate for 2020 (Appendix 8 in Supporting information). Two years of partial disruption to treatment (7600 treated per year) (Table 2) would result in nearly 110 excess HCC and 200 excess liver-related deaths through 2030.

3.3 | Elimination scenario

Achieving all of the WHO targets by 2030 would require an increased effort to screen and diagnose new infections, with 81,200 newly diagnosed and 118,600 patients initiated on treatment needed between 2021 and 2030 (Table 2 + Appendix 8 in Supporting information). Under this scenario, Germany would not only achieve the targets for elimination as defined by WHO but also would avert 1020 deaths and 720 HCC cases between 2021 and 2030, relative to the 2019 base case scenario (Figure 3). By 2030, there would be only 81,900 viremic infections remaining, a prevalence of 0.10%.

3.4 | Uncertainty analysis and model validation

The inputs which contributed to the greatest uncertainty in the 2020 viremic prevalence included basic model parameters (transition probabilities within the natural course of infection) as well as the input for anti-HCV prevalence in 2012 (Appendix 1–4 in Supporting information). Together, base 2012 prevalence and the rate of spontaneous clearance accounted for >96% of uncertainty around total infections in 2020.

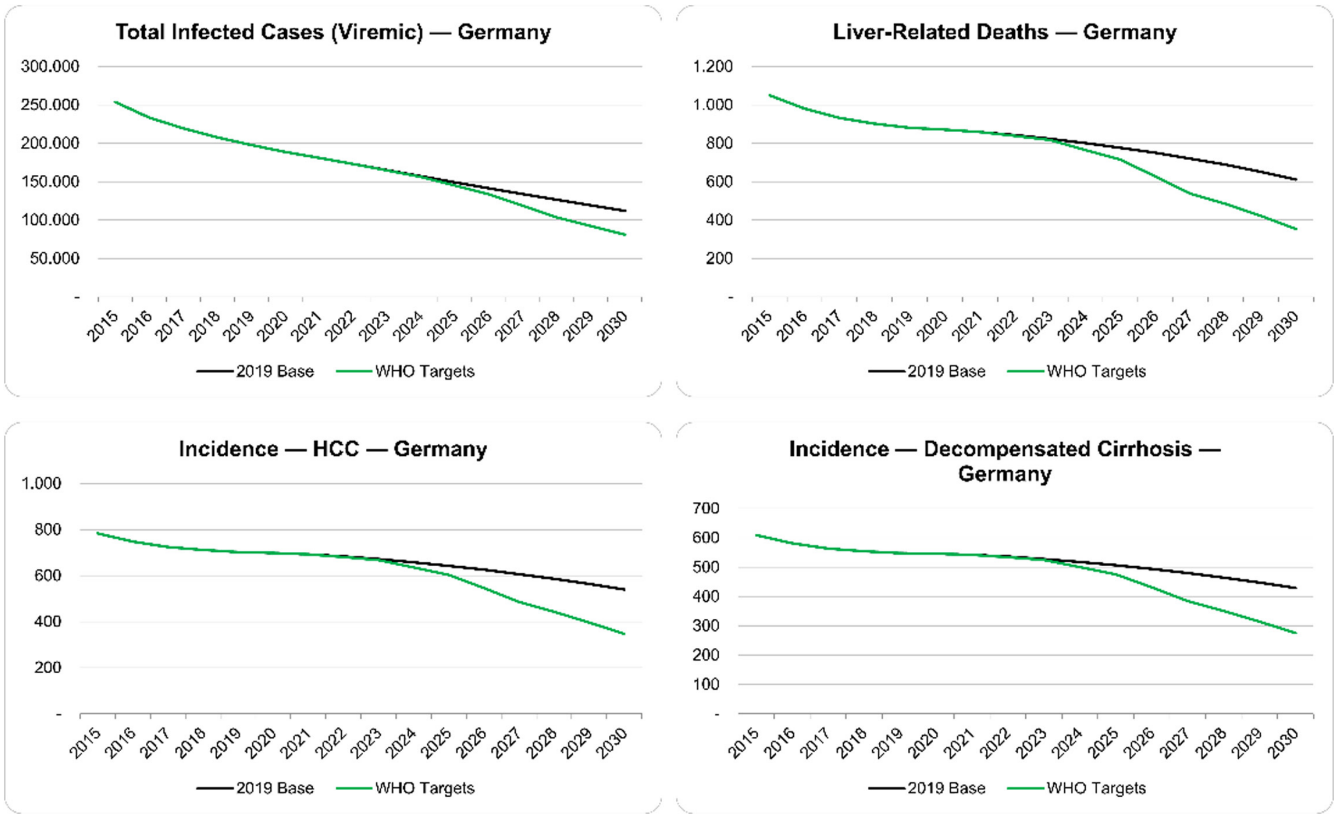

FIGURE 3 Progress toward the WHO 2030 targets for liver-related deaths and incidence of HCV under the Base 2019 and WHO targets scenarios, 2015-2030. Based on the assumptions provided in Table 1

In addition, uncertainty around the number of HCV infections estimated to enter Germany through migration was calculated. In 2019, around 5025 (95% UI: 4450–5610) anti-HCV+ infections were estimated to enter Germany through migration, although prevalence estimates, as well as the viremic rate, were based on studies of refugees. Using these sources, applied to the number of net immigrants in 2019, more than 50% of HCV infections among migrants would have been from countries listed as "other", with 16% from Russia (Appendix 5 in Supporting information).

Empirical data and expert input suggested between 390 and 1100 HCV-related HCC cases occur annually in Germany (Appendix 6 in Supporting information). In 2018, in the model forecast, there would be around 710 incident HCC cases among HCV-RNA+ persons.

4 | DISCUSSION

In its strategy to eliminate hepatitis B, C and D, the WHO has defined indicators to monitor the progress. However, these indicators are not systematically captured in Germany, making it challenging to assess whether the country is or is not "on track" for HCV elimination by 2030.[22] A 2019 analysis indicated that Germany would be on track to reach the WHO goals by 2030, assuming a minimum of 9900 patients would be initiated on treatment per year.[23] However, our data collection efforts demonstrated that in spite of a rapid initial response to the HCV epidemic in Germany, the number of patients treated annually dipped below the treatment threshold in 2019 (only 9700 patients initiated on treatment). Our baseline assumptions of continued treatment declines would mean Germany is no longer on track to achieve the WHO goals by 2030. Treatment declines seen in 2020 from the first year of the COVID-19 pandemic (7600 patients treated) additionally support that Germany is getting further from achieving the goals than it was in previous years. This may result in more late-presenting patients with advanced stages of liver disease. The present data indicate over 1000 additional liver-related deaths and over 700 additional cases of HCC until 2030, if the observed trend continuous. Under these assumptions, the WHO elimination goal will be delayed by approximately eight years. Importantly, diagnosis, therapy and monitoring of patients with HCV were impaired during the COVID-19 pandemic, even though the majority of centres do not see healthcare problems in the medium and long term.[24] To what extent the COVID-19 pandemic will impact the amount of liver-related deaths or HCC cases in the future will have to be determined in the next years. Yet, avoiding excess morbidity and mortality will need dedicated programmes.

Germany lacks an active wide-scale national screening strategy and is currently running out of patients to treat. Family physicians offer a check-up at age 35 to every adult that includes testing for anti-HCV since October 2021. Moreover, primary care physicians are allowed to prescribe DAA therapies. Thus, it is tempting to speculate that a large-scale-up in screening and treatment could occur

within the next years. Unfortunately, only about half of the population attends such a screening. Furthermore, one study indicates that people with lower socio-economic status and therefore potential high-risk groups are less likely to participate in this check-up.[25] However, to achieve the elimination targets, more patients need to be screened and diagnosed. In 2020, the United States expanded this effort by endorsing a one-time-screening of all adults over 18 years of age, alongside routine screening of pregnant women.[26] This was found to be a cost-effective strategy in any population with a prevalence of ≥0.1%.[26,27] In Egypt, a country with a historically high prevalence of HCV, a large-scale population-based active screening and treatment campaign resulted in a drastic decrease of HCV burden in the whole country.[28] This, however, was only possible due to political will and dedicated funding. As of now large-scale population based one-time screening that includes the younger population, seems to be the most effective way to eliminate HCV.

Targeting priority populations is a cornerstone to reach the WHO HCV elimination goal and intravenous drug use is the most frequent known mode of acquisition of HCV infection in Germany.[29] Risk for HCV infection is over 200 times higher compared with the general population. Between 2011 and 2015, a study of PWID revealed an HCV prevalence of 23%–54%.[30] The same study reported that only 13%–43% of all individuals with a treatment indication ever received antiviral therapy that led to SVR. Unfortunately, annual serosurveys are not available in this priority population and there are no data on the impact of DAA on HCV prevalence in this group. DAA therapy is well tolerated; so, treatment uptake may have increased.[31] A new pilot study is on the way suggest change to establish a surveillance system for blood borne viruses and sexually transmitted infections in PWID.[32] Furthermore, care could be facilitated through micro-elimination attempts. In Germany, opioid substitution therapy and NSP programmes are already available and could further be enhanced with the addition of point of care HCV testing.[33]

The true impact of migration on the HCV prevalence and disease burden in Germany is quite uncertain. First, most studies focus on refugees or asylum seekers, rather than the general immigrant population, which may result in a higher estimated prevalence. Second, as HCV treatment becomes more common even in developing countries, the number of persons migrating who are still HCV-RNA+ is expected to decline. Nonetheless, screening of migrants, especially from high-endemic regions such as sub-Saharan Africa or Eastern Europe, may be a useful strategy to identify infections and link patients to care.[34]

There are some limitations that should be considered when interpreting our study results, the first being the availability of nationally representative data. The prevalence of HCV in Germany is expected to be low, but a nationally representative random sample serosurvey for HCV has not been conducted since 2012. Although this type of survey is the gold standard, previous efforts have found that even well-conducted serosurveys may miss key populations for HCV (e.g., DEGS 1 study which identified no HCV infections in persons under the age of 40 years). This is particularly relevant for vulnerable groups at risk of (yet unidentified) HCV infections. To improve the data quality in Germany in the future, the RKI is working closely with the European Centre for Disease Prevention and Control, and technical study protocols to conduct HCV-serosurveys for European Union countries have already been established.[35]

Similarly, the estimate of percent of cases diagnosed was retrieved through a study of patients >35years of age who attended "check-up" visits (20%–25% of the population with a significant selection bias). The proportion of individuals aware of their infection is likely lower in younger age groups. To account for the limitations of an individual study, weighted estimates and/or ranges were employed as appropriate. In addition, the model outcomes were validated against empirical data around liver cancers in Germany. The model is calibrated to prevalence data (and prevalence by age and sex), with end-stage outcomes calculated according to the standard disease-specific progression rates. Without modifying these progression rates and considering the base model inputs described in this paper, the model was able to predict a reasonable number of HCC cases in Germany, providing further support for inputs selected.

To conclude, Germany has made strides towards HCV elimination, but more efforts are needed to achieve the WHO targets by 2030. Specifically, case finding to link previously diagnosed patients to care as well as screening coupled with timely treatment will be necessary to diagnose and treat an average of 8000 and 12000 infections per year respectively. These targets are feasible given previous numbers of patients diagnosed and treated; however, increased efforts and resources will be required to reach these remaining patients as the prevalence in the country declines.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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