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Estimated prevalence of undiagnosed HCV infected individuals in Italy: A mathematical model by route of transmission and fibrosis progression

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ABSTRACT

Background: The universal treatment of diagnosed patients with chronic HCV infection has been widely conducted in Italy since 2017. However, the pool of individuals diagnosed but yet to be treated in Italy has been estimated to end around 2025, leaving a significant proportion of infected individuals undiagnosed/without care. Estimates of this population are currently unknown.

Methods: A probabilistic modelling approach was applied to estimate annual historical HCV incident cases by their age-group (0–100 years) distribution from available literature and Italian National database (1952 to October 2019). Viraemic infection rates were modelled on the main infection routes in Italy: people who inject drugs (PWID), tattoos, sexual transmission, glass syringe use, blood transfusion and vertical transmission. Annual liver fibrosis stage transition probabilities were modelled using a Markov model. The number of HCV viraemic asymptomatic (fibrosis stage F0-F3:potentially undiagnosed/unlinked to care) and symptomatic (fibrosis stage F4: potentially linked to care) individuals was estimated.

Results: By October 2019, total viraemic HCV individuals in Italy (excluding treated patients since 1992) were estimated to be 410,775 (0.68 % of current population of Italy; 95 % CI: 0.64−0.71%, based on the current Italian population), of which 281,809 (0.47 %; 95 % CI:0.35−0.60%) were fibrosis stage F0-F3. Among different high risk groups in stage F0-F3, the following distribution was estimated: PWID; 52.0 % (95 % CI:37.9–66.6 %), tattoo; 28.8 % (95 % CI:23–32.3 %), sexual transmission; 12.0 % (95 % CI:9.6–13.7 %), glass syringe and transfusion; 6.4 % (95 % CI:2.4–17.8 %), and vertical transmission; 0.7 % (95 % CI:0.4–1.2 %).

Conclusion: Under the assumption that most untreated HCV-infected individuals with stage F0-F3 are undiagnosed, more than 280,000 individuals are undiagnosed and/or unlinked to care in Italy. Marked heterogeneity across the major routes of HCV transmission was estimated. This modelling approach may be a useful tool to characterise the HCV epidemic profile also in other countries, based on country specific epidemiology and HCV main transmission routes.

1. Introduction

Hepatitis C virus (HCV) is a blood-borne infection and the leading cause of liver-related morbidity and mortality worldwide. Recent estimates indicate that as many as 71 million individuals are infected with chronic HCV (CHC) worldwide (Polaris Observatory HCV Collaborators, 2017; World Health Organization, 2017).

HCV is characterised by a long incubation time, with many

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individuals remaining asymptomatic for decades, although disease progression has been shown to accelerate with age (Hajarizadeh et al., 2013; Sweeting et al., 2006).

With the availability of direct-acting antiviral drugs (DAAs) for the successful treatment of HCV infection, focus has not only shifted towards the identification of infected individuals, but also to scale up treatment. In 2017, this led the World Health Organization (WHO) to establish HCV elimination targets for 2030, through the Global Health Sector Strategy Goals for Hepatitis (WHO, 2019).

Forecasting the impact of treatment on disease burden has been evaluated using natural history models of HCV-related disease progression. Typically, these models are constructed via back calculation and use disease endpoints or other literature validation to calibrate/adjust mathematical estimates Deuffic et al., 1999; Hutchinson et al., 2005; Davis et al., 2010; Deuffic-Burban et al., 2012; Tan et al., 2018; Harris et al., 2019; Kondili et al., 2018.

Italy is recognised as having the highest HCV prevalence in Western Europe, with a peak prevalence observed in elderly individuals Guadagnino et al., 1997; Bellentani et al., 1999; Maio et al., 2000 and highest mortality rates from cirrhosis and hepatocellular carcinoma (Croce et al., 2016; Gardini et al., 2016a).

However, recent estimates on the number of infected individuals are currently unknown or at best unreliable. Many studies estimating HCV prevalence in the Italian general population were conducted over 20 years ago, with substantial heterogeneity across different regions (Marascio et al., 2014a) and marked differences between prevalence estimates (Andriulli et al., 2018; Lapi et al., 2017). Recent studies have also reported decreasing rates of HCV prevalence throughout the country (Andriulli et al., 2018; Guadagnino et al., 2013; Reau, 2014). Furthermore, previous estimates did not take into account differences in infection rates across high risk groups (Midgard et al., 2016; Tosone et al., 2014) and the impact of anti-viral treatment, that will account for a significant proportion of non-viraemic individuals, particularly in the past 20 years.

The Universal treatment of HCV infected individuals (independent of fibrosis stage) has been available in Italy since 2017 and thanks to DAA antiviral treatment more than 212,476 patients have been treated to date (Aggiornamento dati Registri AIFA DAAs, 2021). Consequently, the infection burden has been decreasing in Italy. However, forecasting infection and disease burden in Italy, based on previously reported prevalence data and real-life data on DAA treatment (Kondili et al., 2018, 2017a), it is estimated that the eligible pool of diagnosed patients requiring treatment will potentially end before the year 2025, leaving a significant proportion of infected individuals undiagnosed and without care.

An undefined number of people who have contracted HCV (and may not be aware that they are infected) do not develop obvious symptoms and therefore it is difficult to identify and treat these individuals. Consequently, current HCV estimates of this population in Italy remain unknown.

By using a mathematical-probabilistic approach and a Markov progression modelling for liver disease progression, we estimated the number of annual historical HCV incident cases to then calculate the number of infected asymptomatic individuals.

2. Methods

2.1. Study design

We estimated the number of HCV incident cases for each year, age group and fibrosis stage using a mathematical probabilistic approach. The transmission of infection was simulated decomposing the risk probability into transmission route, age, and year. Liver disease progression was modelled in the estimated infected individuals using a Markov chain. The input data for the model was based on the available literature and from the Italian National Statistical database (ISTAT) (Statistiche Istat, 2019) (1952-October 2019). Viraemic infection rates (excluding all treated patients from 1993 to October 2019; see Section 2.6 and Supplementary information S2 for further information) were modelled on the main infection routes in Italy. Annual fibrosis transition probability from a stage to a subsequent one of five (F0,F1,F2,F3,F4) progressive stages of liver fibrosis were derived from previous studies (Kondili et al., 2018; Linthicum et al., 2016; Razavi et al., 2014).

2.2. Study population and literature search

The age taken into consideration for people varied from 0 to 100 years and referred to the period from 1952 to October 2019. Data on HCV prevalence for routes of infection in high risk groups was obtained following a literature search, as previously described (Bruggmann et al., 2014). Additional information on the search strategy is provided as Supplementary Material S1. Briefly, the search included published (indexed on PubMed/Medline and Embase up to April 2019) and unpublished studies with epidemiological and/or clinical data on the prevalence of viral hepatitis in Italy. When data from indexed studies were unavailable, non-indexed sources of information, (websites and news articles) were considered, in addition to Expert opinion (Authors of the present study).

2.3. The probabilistic model

The present model is a probabilistic HCV transmission model, implemented using the open-source code Python 3.7 (a more detailed explanation is available in Supplementary Material S2). The model considered the 6 most relevant transmission routes in Italy (non-independent, i.e. including overlapping) and 5 liver fibrosis progression stages (non-infected, just-infected or F0, F1, F2, F3 and F4) evolving from 1952 (first year of ISTAT (Aggiornamento dati Registri AIFA DAAs, 2021)) up to October 2019. Annual ISTAT data were used to define the exact number of new-borns and the number of deaths in order to strengthen the model estimates, by considering their numbers dynamically in the risk distribution (Aggiornamento dati Registri AIFA DAAs, 2021). The model independently accounted for 101 age groups, from + 0 (new-born) to 100 years old. The model is described in further detail with a simplified boxed flow chart (Supplementary Material S2, Fig. 1).

Starting from 1952, we updated the viremic population adding the estimated newly infected people and evolving the disease according to annual Markov transition probabilities in infected individuals.

The procedure for any given year is as follows: for each age group, we calculated the number of new infected people due to the exposure to each transmission route (so that we obtain 6 × 101 groups of infected people), using the risk distribution defined in Methods, Section 2.4. The same person could be subjected to two or more transmission routes. Multiple counts (duplicity) were thus removed in what we term "overlapping removal" (see Methods, Section 2.5).

All estimated newly infected people had fibrosis stage F0. After that, the whole infected population (including new estimated individuals) follows the Markov chain liver disease transition probabilities each year until F4 liver cirrhosis. The basic principle is that each individual, depending on his/her current stage, has a certain probability to pass to the next stage. Therefore, considering the population in each age, route and fibrosis stage, a fraction of it passes to the next fibrosis stage. The final stage, (where no further evolution is possible) is F4. In our model, we accounted for HCV-related mortality by considered the average values of transition probabilities following the F4 fibrosis stage reported by Linthicum et al., 2016 and Kondili et al., 2017a; Dienstag et al., 2011; Wright et al., 2006; Townsend et al., 2011. All transition probabilities were adjusted for competing probabilities of death from other causes according to the official data [ISTAT]. From 1993, the model also included treated patients. From that year onwards, the number of treated patients were removed from the model.

The entire population aged by one year; both removal of deaths and

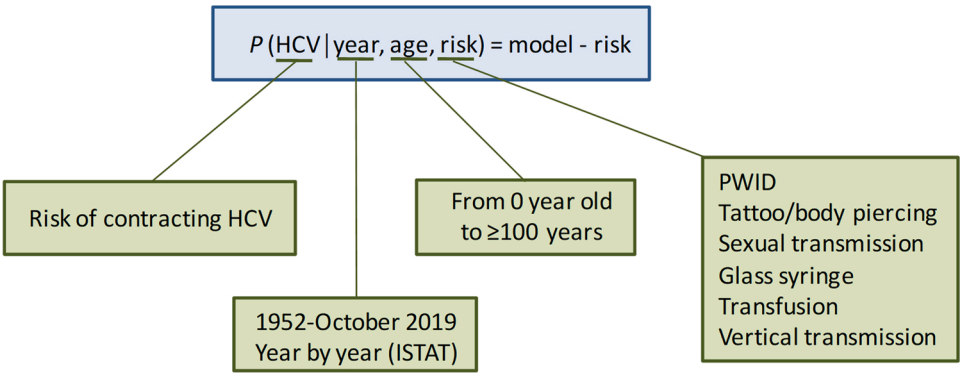

Fig. 1. Schematic presentation of the probabilistic model, where *P(HCV|risk)* is the probability of contracting *HCV* after exposure to an event *'risk'*. For our model, the single probability of acquiring HCV infection remains constant, whereas "risk factors" that conditioned it (year, individuals age and route of transmission), were taken into account by the model simultaneously. HCV = hepatitis C virus; ISTAT = Istituto nazionale di statistica; P = probability (of infection); PWID = people who inject drugs.

the inclusion of newborns are performed in accordance with ISTAT data (Statistiche Istat, 2019).

2.4. Transmission routes and associated risk

The model tracked each single route of transmission independently, distributing the weight of the effect of each route over time, when more routes were active at the same time the model accounted by weighting the overlapping effect. A more detailed description of transmission routes and associated risk is available in Supplementary Material S2. The conditional probability for each route of transmission was estimated by decomposing the risk into factors: one taking into account the year and another one the age. The probability of contracting *HCV* after exposure to a route (Fig. 1), can be broken down as follows:

$$P(HCVroute, age, year) = g(HCVroute, age) \times f(HCV|route, year)$$

Both *g* and *f* are probability density functions whose values are specific by route, year and age of infection and whose specifications are described in Table 1 and their shapes are plotted in Fig. 2.

The choice of routes was based on previous evidence (Andriulli et al., 2018; Lapi et al., 2017; Tosone et al., 2014; Gardini et al., 2016b; Marascio et al., 2014b; Sy and Jamal, 2006 and/or Author Expert opinion where evidence was insufficient. The following areas were excluded as routes of transmission, due to scarcity and or partiality of information available: surgical interventions, colonoscopy and other medical procedures, dental intervention/surgery, cosmetic/beauty and/or hair saloons/barbers. After literature search (see Supplementary Material S1 for further information), data for the following high risk routes of HCV transmission in Italy were obtained for the six different transmission routes: PWID, tattoos or body piercing, sexual transmission, glass syringe, blood transfusion, and vertical transmission and are summarised in Table 1 and Supplementary Material S3. Relevant input to construct the model with regard to age and year of infection were defined for each risk group (Supplementary Material S3). Based on HCV prevalence retrieved from literature and by considering the Italian population over time from ISTAT, we reconstructed the probability of infection for ages 0–100 years and for years from 1952 to October 2019 for the 6 different infection routes (Fig. 2). The probability of contracting HCV per route per year for all ages can be summarised in the following formula:

$$Newly - Infected(route, year) = \sum_{age}[g(HCVroute, age) \times f(HCVroute, year) \times F(route) \times I(route)]$$

Where *F* and *I* are the fraction of the total Italian population exposed to the route and the viraemic population respectively. The fraction of exposed people, the viremic population as well as the functions f and g, are obtained from assumptions. Therefore, the risk of infection does not depend dynamically on the computed prevalence for that year. In order to construct probability curves, the following assumptions were fixed (see also Supplementary Material S2, Section 2).

Table 1
Data input from literature used to provide information for model*.

Risk group	Age		Year		Fraction of total and % infected	
PWID	Start age	10	Start year	1970	Fraction of total	1.3
	Peak age	27	Peak year	1980	Infected	65.5
	End age	50	Decline year	2009		
			End year	2019		
Tattoo/ body piercing	Start age	15	Start year	1987	Fraction of total	19
	Peak age	35	Peak year	1995	Infected	2.1
	End age	70	End year	2019		
Sexual transmission	Start age	15	Start year	1952	Fraction of total	5.7
	Peak age	35	Peak year	2008	Infected	2.7
	End age	65	End year	2019		
Glass syringe	Start age	0	Start year	1952	Fraction of total	10
	Peak age	8	Peak year	Constant	Infected	6
	End age	100	End year	1975		
Transfusion	Start age	0	Start year	1952	Fraction of total	6
	Peak age	60	Peak year	1957	Infected	8.5
	End age	100	End age	1992		
Vertical transmission	Start age	N/A	Start year	1952	Fraction of total	N/A
	Peak age	N/A	Peak year	1980	Infected	5
	End age	N/A	End year	2019		

N/A = not applicable. PWID = people who inject drugs.
* See Supplementary Material S2 for notes on assumptions/calculations from literature.

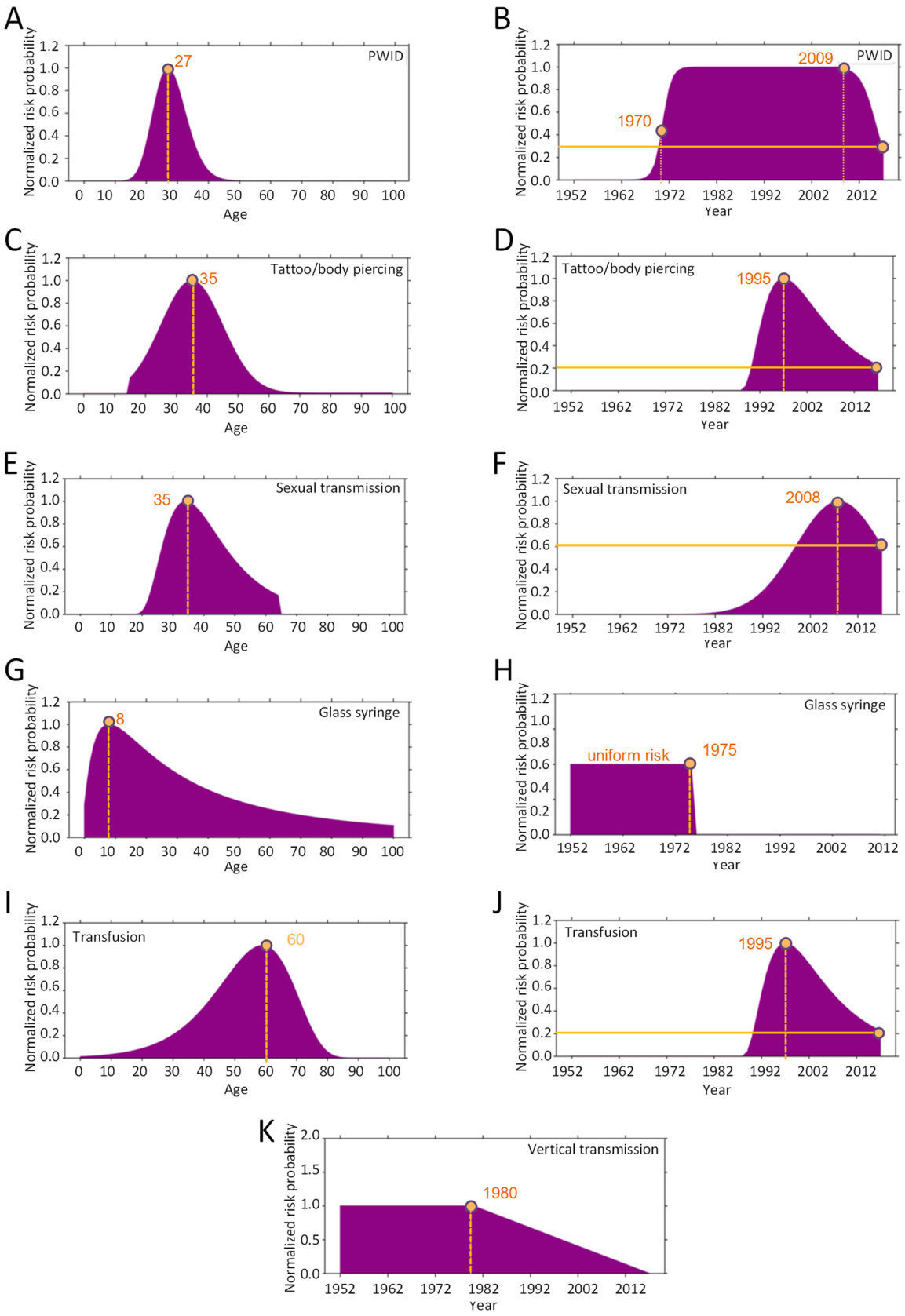

Fig. 2. Shape of the risk distribution (normalized in order to have peak value equal to one) by age (A, C, E, G, I) (*g*, in the main text) and year (B, D, F, H, J, K) (*f*, in the main text) for the six different routes. Relevant input data of interest are indicated.

2.4.1. People who inject drugs

A recent report by European Monitoring suggests an average age of 22, however, it has been adjusted to 27 years of age to allow smooth fading probability at later as well as earlier ages. The spread of HCV infection through PWIDs was assumed to begin in 1970. HCV positive individuals within the PWID group remain elevated and constant throughout the years (Fig. 2B).

2.4.2. Tattoo or body piercing

The affected ages of individuals were assumed to be between 15 and 70 years. The overall tattoo prevalence was estimated at around 19 %. The overall HCV prevalence was estimated at 2.1 % (Table 1 and Supplementary Material S3). This risk was observed to be variable, with larger values around 22–23 % and lower values around 10 %. A weighted mean suggests a value just below 20 % and a value of 19 % was therefore used.

2.4.3. Sexual transmission

Sexual promiscuous behaviour spanned from 15 to 65 years of age. The peak age for this behaviour is around 35 years. The peak year is 2008 and it quickly decreases with an exponential shape around 1982 (Fig. 2E and Supplementary Material S3).

2.4.4. Glass syringes

Historically, infection due to glass syringe use was reported as one of the main routes of infection in Italy (non-single-use of non-sterilized glass syringes for parenteral treatment, administration of drugs, vaccinations as well as unnecessary adjuvants, such as vitamins, mineral and tonics) responsible for the earliest transmission rates of infection. This route of infection was prevalent in the first wave of infection occurring around the years 1950 in Italy (Guadagnino et al., 1997, 2013), which is also reported as being the main cause of higher burden of infection in Italy compared to other European countries. In the present study, it was assumed that the risk of HCV infection via this route drastically decreased after the year 1975, when the single use of plastic disposable syringes became law in Italy, substituting glass syringes nationwide.

A higher prevalence was assumed to have occurred at an early age (0–8 years) due to glass-syringe based vaccination since the year 1950. Ten percent of individuals were assumed to be exposed to glass syringe and 6% to be infected. The risk distribution in the model begins in 1952 and ends in 1975, however, the risk remains very low and unchanged over this period (see Fig. 2G and H, Supplementary Material S3).

2.4.5. Transfusion

Since blood transfusion was more likely to occur at older ages due to surgical intervention, the peak risk was centred around 60 years of age (Fig. 2I and Supplementary Material S2 and S3). The year distribution profile starts when the model begins and stops in 1992 when the virus was finally isolated (when blood transfusion was considered safe; see Supplementary Material S3).

2.4.6. Vertical transmission

The risk of vertical transmission was calculated from the number of estimated infected mothers; the estimated infected female population transfer the virus with a given percentage to new-born babies (these last values retrieved from ISTAT (Statistiche Istat, 2019)). The risk is present for all periods, from the beginning of the model to the end. The risk was estimated to be around 5.8 %. This reduction in the risk has been modelled with a linear decrease with up to 0.015 % risk (Supplementary Material S3).

2.5. Overlapping

The model accounted for route overlapping. Initially each route was treated independently, where the non-infected population are subjects independently belonging to the six transmission routes without accounting for any individual that might be exposed to two (or more) routes at the same time. Based on recent evidence (42 Congreso AEEH, 2019), our model considered that if 61 % of the infected population were infected by a single route of transmission, the remaining 39 % need to be balanced across other transmission routes (42 Congreso AEEH, 2019). The model can therefore be described as a linear proportion model and can be considered as dynamic with respect to overlapping. It counts how transmission routes are active at the same time for a given year and assigns the correct value of overlapping to each transmission route. Further information on how overlapping was calculated is described in Supplementary Material S2, Section 3, Table 1.

2.6. Patients treated with anti-virals

The estimated number of treated patients, interferon based and DAA treatment was subtracted from the estimated infected population, since the overall population is distinguished by infected and not infected over time. For some of the years considered, the source gives an indication of how this number is distributed among the different fibrosis stage groups; otherwise we used a uniform distribution. From the estimated total number of viraemic patients at risk, we subtracted the number of probable non-viraemic individuals from the model due to interferon-based treatment and DAA-based treatment from 1993 to 2019. This number of treated patients was based on expert data provided by the Italian association for patients with hepatitis (The Italian Liver Patients' Association (EpaC), 2019) report until 2014 and Italian Drug Agency of Medicines (AIFA) (Aggiornamento dati Registri AIFA DAAs, 2021) DAA monitoring registry data since 2015. Estimates from Italian Platform for the Studies of Viral hepatitis Therapies (PITER) cohort, for unclassified fibrosis stage by AIFA Registry (Kondili et al., 2017a) were also used (Supplementary Material S2, Table 2).

2.7. Markov-Chain progression

Annual fibrosis stage transition probabilities were modelled using a Markov-Chain (Kondili et al., 2017a; Linthicum et al., 2016; Razavi et al., 2014; Alagoz et al., 2010) (see Supplementary Material S2, Fig. 3). Every year an infected person can either progress (evolve into the subsequent HCV stage, with a certain probability) or remain unchanged (the majority of infected individuals). Potential spontaneous liver fibrosis regression was not considered. Progression of HCV liver disease was considered as an increase in the severity of liver fibrosis (from F0 to F4 fibrosis according to the Metavir classification) (Bedossa and Poynard, 1996). Five stages were considered: F0 −HCV contraction, F1-F2-F3-F4 with F4 the final fibrosis stage. Based on the aim of this study, we did not consider further evolution of the disease, in that F4 fibrosis stage was assumed to be symptomatic, thus potentially diagnosed. It was assumed that no more than one transition per year can occur per patient. For liver-related mortality rate, we considered the average probabilities of Linthicum et al., 2016 and those used by Kondili et al. 2017 from the stage of F4 to death (Kondili et al., 2017a; Dienstag et al., 2011; Wright et al., 2006, (Townsend et al., 2011). Once the number of infected, and the date of contraction of the virus were estimated, the evolution of the disease in terms of fibrosis stage was calculated. This estimate was calculated by comparing the transition probabilities between the different stages of liver disease based on different studies (Kondili et al., 2017a; Linthicum et al., 2016; Razavi et al., 2014). Based on the choice of parameters listed for age and year among the six different high risk groups, we ran the model to estimate the absolute number of HCV infected individuals.

2.8. Sensitivity analysis

Sensitivity analysis was performed using a Monte Carlo approach. In brief, we repeatedly ran the model, each time randomly picking the value of some input parameters (still around the values) and we assessed

Table 2
Estimates of the absolute number and % of viraemic HCV individuals in Italy (excluding treated patients) according to fibrosis stage and high risk groups, obtained as final results of the computation (October 2019).

	Absolute number			% based on current Italian population*			Proportion based on risk groups (%)		
	Reference	Lower 95 % CI	Upper 95 % CI	Reference	Lower 95 % CI	Upper 95 % CI	Reference	Lower 95 % CI	Upper 95 % CI
Total	410,775	388,627	425,800	0.68	0.64	0.71			
Total F0-F3	281,809	209,531	364,910	0.47	0.35	0.60	100	–	–
Total F4	128,966	44,471	198,119	0.21	0.07	0.33	100		
High risk groups									
PWID									
F0-F3	146,652	106,911	187,821	0.24	0.18	0.31	52.0	37.9	66.6
F4	58,001	17,356	95,199	0.10	0.03	0.16	45.0	13.5	73.8
Tattoo/body piercing									
F0-F3	81,153	64,865	91,101	0.13	0.11	0.15	28.8	23.0	32.3
F4	11,928	2791	27,734	0.02	0.005	0.05	9.2	2.2	21.5
Sexual transmission									
F0-F3	33,871	26,922	38,691	0.06	0.04	0.06	12.0	9.6	13.7
F4	2615	404	7750	0.004	0.001	0.01	2.0	0.3	6.0
GS + transfusion									
F0-F3	18,038	6867	50,081	0.03	0.01	0.08	6.4	2.4	17.8
F4	54,567	22,598	65,670	0.09	0.04	0.11	42.3	17.5	50.9
Vertical transmission F0-F3	2095	1058	3331	0.003	0.002	0.006	0.7	0.4	1.2
F4	1854	589	2634	0.003	0.001	0.004	1.4	0.5	2

Fibrosis stages: F0-F3 = asymptomatic; undiagnosed/unlinked to care and F4 = symptomatic; potentially linked to care and cure.
* Current population of 60,391,000 according to Istat (42). GS = glass syringe, PWID = people who inject drugs.

the effect of this randomization on the results of the model. Our Monte Carlo scheme intercepts two different types of randomization: the risk distribution and the transition probabilities. Regarding the transition probabilities, two scenarios were initially investigated whereby we took into consideration two different fibrosis transition probability functions as reported by Linthicum et al. Linthicum et al. (2016) and those described within the report by Kondili et al. Kondili et al. (2017a); (Dienstag et al., 2011; Wright et al., 2006, (Townsend et al., 2011) (see Supplementary Material S2, Fig. 3 and Fig. 5). The first approach assumes a linear fibrosis progression, while the second assumes a non-linear (stagnating) evolution around F1/2. Sensitivity analysis was later performed by leveraging (due to the number of variables involved) on Monte Carlo simulations. To strengthen the approach, and by following the consideration that all different transition probabilities are all valid at the same time, we chose a multiple randomization using different transition probabilities (in report by Kondili et al. (2017a); Dienstag et al., 2011; Wright et al., 2006, (Townsend et al., 2011), Linthicum et al. (2016) and (Razavi et al., 2014)). The choice of transition probability was based on the following: if we randomize the parameter around a reference case the Monte Carlo will return a solution around the reference value, by further randomizing the transition probability to include as large error bars as possible. Confidence intervals for these distributions are provided in Supplementary Material S2, Table 5.

For the risk distribution, the following were modified in combination: peak age (generally, but not necessarily the mean risk age), age variance, chronological year at which the phenomenon peaks and eventually other parameters on which the shapes of the distribution depend (in Supplementary Material S2, Table 4 they are indicated by age/year shape parameters).

Five thousand simulations were run to verify sensitivity and identify confidence intervals for our model. Curves derived from Monte Carlo output for each route are represented by a different colour and the shaded regions represent 95 % confidence interval (CI), from 2.5th to 97.5th percentiles were summarised via their medians (Supplementary Material S2, Fig. 4). Due to age and different transmission routes considered (model granularity) a different confidence interval was retrieved per age-year and route. Changes to these variables were undertaken according to the following distributions: discretized-normal and uniform. The Monte Carlo approach has been described in further detail in Supplementary Material S2.

3. Results

3.1. Overall HCV prevalence estimates

Estimates for the absolute number and % prevalence HCV individuals in Italy (excluding treated patients) according to fibrosis stage and high risk groups are summarised in Table 2. In October 2019, total viraemic HCV individuals in Italy were estimated at 410,775 (0.68 %, 95 % CI:0.64−0.71% based on the current Italian population of 60,391,000 (National demographic balance, 2019), of whom 281,809 (0.47 %, 95 % CI: 0.35−0.60%) were in liver fibrosis stage F0-F3, thus assumed as asymptomatic and potentially undiagnosed. HCV estimates for asymptomatic individuals were calculated by subtracting the number of assumed symptomatic individuals (stage F4) from the total population (i.e. 410,775-128,966=281,809).

3.2. Stratification of HCV prevalence rates according to risk groups

In October 2019 for the different high risk groups, the following distribution among asymptomatic individuals (stage F0-F3; N = 281,809) was estimated: PWID, 146,652 (52.0 %; 95 % CI: 37.9–66.6 %); tattoo, 81,153 (28.8 %; 95 % CI: 23–32.3 %), sexual transmission, 33,871 (12.0 %; 95 % CI: 9.6–13.7 %), glass syringe and transfusion, 18,038 (6.4 %; 95 % CI: 2.4–17.8 %), vertical transmission, 2095 (0.7 %; 95 % CI: 0.4–1.2 %).

Stratification of the 5 high risk groups by age and disease stage revealed some marked differences (Fig. 3). For asymptomatic individuals (stage F0-F3), it was shown that for PWID and tattoo groups (together accounting for approximately 80 % of all individuals) and sexual transmission, to a lesser extent (12.0 %), infection occurred at a peak age between 40–60 years (Fig. 3A). Glass syringe and transfusion groups were shown to have a lower F0-F3 prevalence, mainly affecting individuals aged >60 years.

People infected by glass syringe and transfusion (54,567; 42.3 %, 95 % CI: 17.5–50.9 %) represented the elderly population and represented the highest proportion of symptomatic individuals (stage F4) in 2019; followed by the PWID (58,001; 45.0 %, 95 % CI: 13.5–73.8 %), (Fig. 3B). Complete estimates of the number of HCV individuals by different ages (0–100 years) and disease stage (F0−3 and F4) are presented in Supplementary Material S4 and S5.

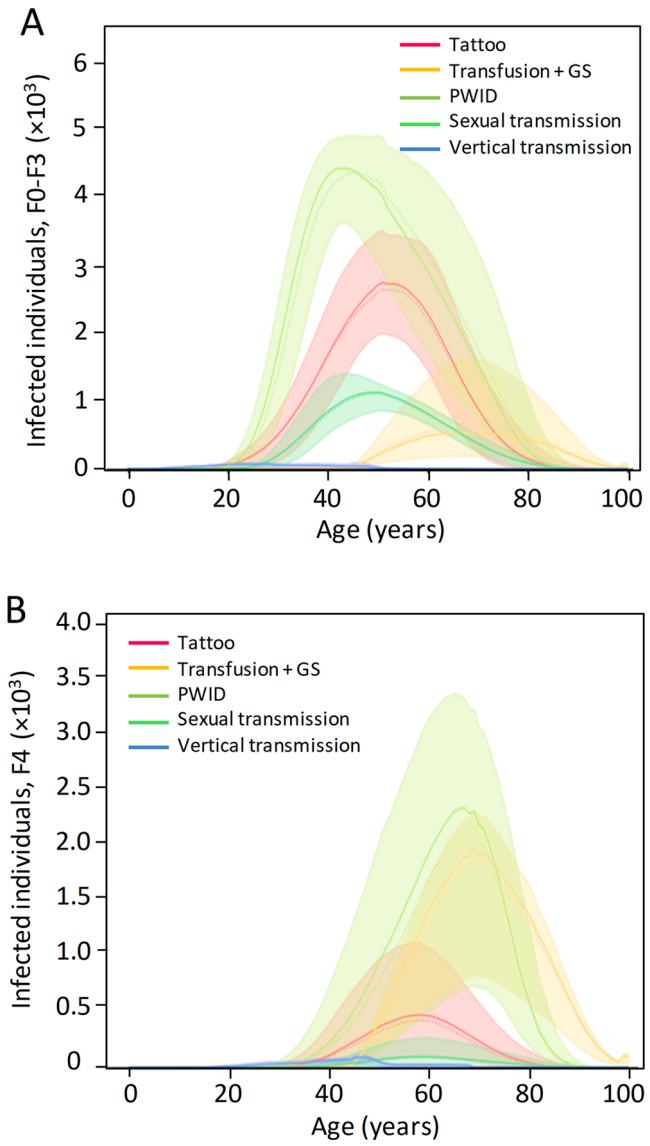

Fig. 3. Probability distribution for the 5 high risk groups by age and fibrosis stage obtained as final results of the computation (October 2019). A) Infected individuals with F0-F3 liver fibrosis stage. B) Infected Individual with F4 liver fibrosis stage. Solid lines represent the reference model and dotted lines represent median values. The shadow filled curves represent lower and upper 95 % confidence intervals. GS = glass syringe, PWID = people who inject drugs.

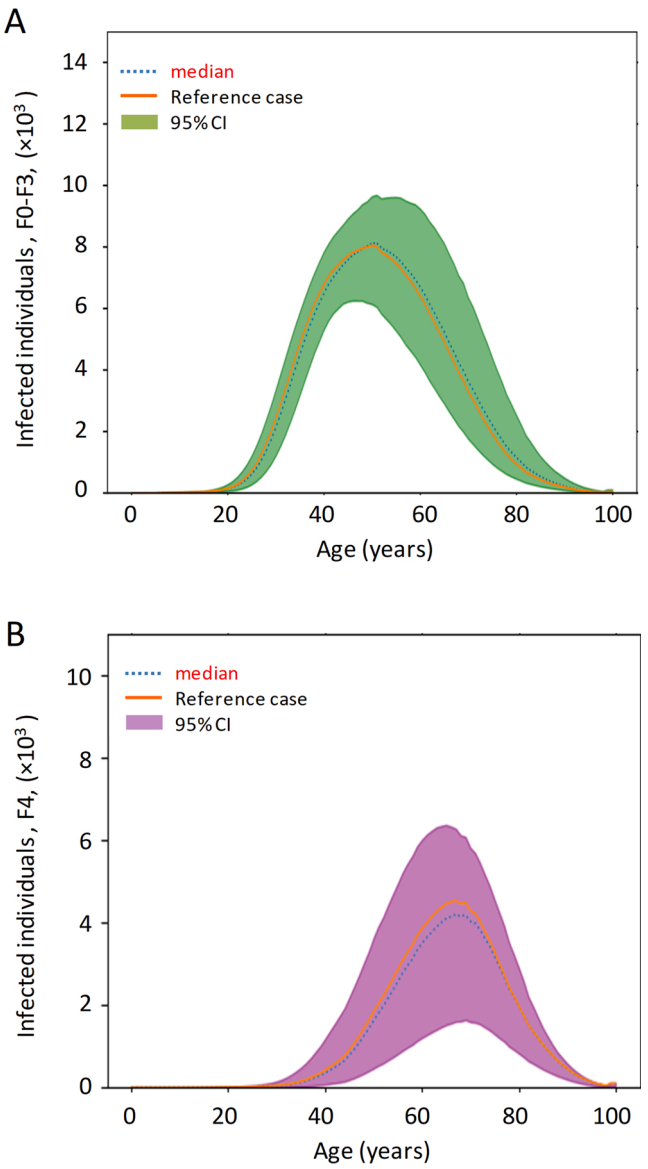

Fig. 4. Probability estimates of variations according to fibrosis stage by sensitivity analysis, obtained as final results of the computation (October 2019). A) Infected individuals with F0-F3 liver fibrosis stage. B) Infected Individual with F4 liver fibrosis stage. Solid lines represent the reference model and dotted lines represent median values. The shadow filled curves represent lower and upper 95 % confidence intervals.

3.3. Sensitivity analysis

Linear transition probabilities reported by Linthicum et al. (Statistiche Istat, 2019), represented the reference case (solid line). Distribution of different liver fibrosis stage according to age by different transition probabilities is presented in Supplementary Material S2, Fig. 5 A. Peak ages for F0-F3 lie between 46 and 55 years. In contrast, the peak ages for F4 are 66–75 years (Supplementary Material S2, Fig. 5B). The sensitivity of our model by route of transmission and fibrosis stage are shown in Figs. 3 and 4 respectively. As observed by fibrosis stage and by route of transmission (Fig. 3), median curves (dotted line) lie close to the reference curve (solid line) according to high-risk groups. For the different transmission routes, median curves (dotted lines) were also observed to lie close to the reference case (Fig. 4).

Stratifying by route of infection for asymptomatic individuals, we can observe that the highest infection rates occurred in the PWID and tattoo groups, mainly centred around the 40–60 age range (Fig. 3A). For the transfusion and glass syringe groups, the age of infection increased approximately 10 years. People infected by these routes smoothly evolve towards F4 and natural death reduces the number of living infected.

Sensitivity analyses show different behaviours for F0-F3 and F4 (Figs. 4 and 5). In the first case (F0-F3), CI are fairly narrow for the lower age categories (20–45 years), with a slight asymmetric profile (Figs. 4A and 5 A). This is due to choosing different distributions for each single scenario yielding slightly non-symmetric intervals. In contrast, CI of the older age categories for F0-F3 and for F4 are wider (by approximately 50 %) and also display a slight asymmetry (Figs. 4B and 5 B). The asymmetric profile is derived from the different progressions considered in the model while CI narrow at the end of the distributions. This "narrowing effect" is due to higher mortality on the right hand side of the graph (decrease in population reduces error) and lower mortality at early ages on the left hand side of the graph (number of births are known and infection can only be attributed to vertical transmission). The Monte Carlo model confirms that the F0-F3 population peaks around 46–55

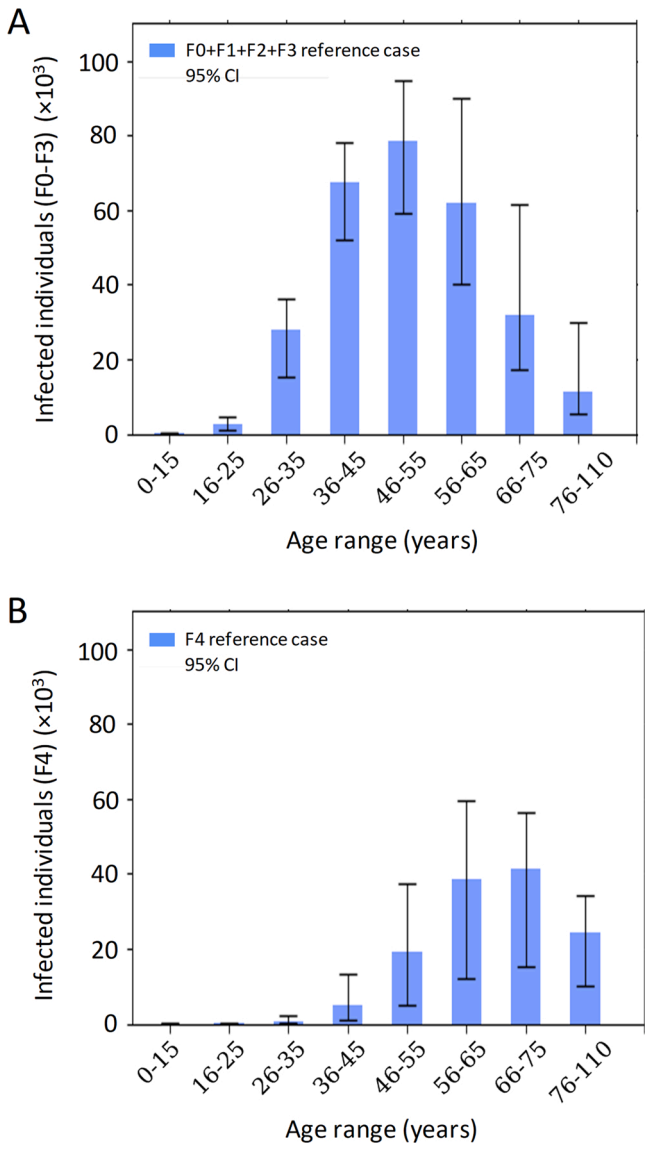

Fig. 5. Range in variability of estimates by fibrosis stage and age of cohort by sensitivity analysis, obtained as final results of the computation (October 2019). Error bars represent lower and upper 95 % confidence intervals.

years of age, while F4 has a higher age (>65 years). CI are presented in Fig. 4 by age and also presented in an aggregated form in Fig. 5. CI derived from sensitivity analyses correspond to a variation of 15 % compared to the reference case scenario.

4. Discussion

Through a mathematical probabilistic approach, this study estimated the prevalence of HCV viraemic individuals in Italy, with the final goal to better characterise the burden of undiagnosed viraemic individuals according to transmission route. This novel modelling approach allowed us to estimate potentially undiagnosed individuals in Italy with the aim to implement targeted screening strategies in order to achieve WHO elimination goals (WHO, 2019).

In Italy, an intense epidemic wave is estimated to have occurred during the 1950s to 1960s via iatrogenic transmission resulting in a peak in infection in 1969 (Deuffic-Burban et al., 2012). Past incidence of HCV infection, mainly attributed to nosocomial transmission, defined as "glass syringe risk" in this modelling, was assumed to decrease over time as that estimated by Mariano et al. 2009, that is, from a 21 % decline in 1970 to a 98 % decline in 2000 (Mariano et al., 2009). Considering that the glass syringe and transfusion population were infected much earlier than individuals infected by other transmission routes, it may be assumed that they would have the highest probability of reaching the stage of advanced liver disease (F4 fibrosis stage), being symptomatic and diagnosed before the year 2019. On the other hand, considering the younger age of exposure in individuals with other risk factors different from glass syringe and transfusion, there is a higher proportion of these individuals estimated to be in the F0-F3 fibrosis stage, thus potentially undiagnosed. In particular, up to October 2019, the proportion of undiagnosed individuals was estimated mainly in PWID, tattoo and sexual transmission (accounting for 92.8 % of infected individuals) vs. 6.4 % in both the glass syringe and transfusion groups.

Regarding the role of treatment in the estimated prevalence values in Italy, oral DAA therapy became available in 2015 and the reimbursement criteria by the NHS provided prioritized access to treatment to cover urgent care based on severe liver disease. Beginning in 2017, treatment was expanded to all patients independent of fibrosis score (Archivio aggiornamenti, 2019). In the present study, treatment data was modelled according to their real-life use according to fibrosis stage. People with F4 fibrosis stage have been extensively treated and this is reflected in the lower number of F4 fibrosis stage compared to the F0-F3. In addition, in older individuals, natural mortality has also contributed to reducing the expected prevalence values compared to the PWID and to the population in which other risk factors such as sexual transmission and tattoo/body piercing were considered.

Among the well documented risk factors, (glass syringes and blood transfusion, which were not relevant after 1993 and not considered to be an important risk factor in Italy currently), intravenous drug use (PWID) stands out clearly. In the'80 s and '90 s injecting drug users have been the largest transmission group for new HCV infections in many European countries (Andreoni et al., 2012). Major risk factors reported to be associated with acute symptomatic HCV infection in Italy include intravenous drug use, promiscuous sexual activity, percutaneous exposure in the course of medical procedures or surgery and beauty treatments (Bollettino Seieva, 2019).

The distribution curves for the majority of transmission routes were shifted forward in age in years for F4 liver fibrosis stage (advanced in age by about 15 years) compared to F0−3, suggesting that the development of progressive liver disease is a long process though independent of the age of acquisition of the infection or route of infection, as recently demonstrated elsewhere (Modin et al., 2019).

Regarding the estimated number of individuals with F4 liver fibrosis stage, there is still a high burden of infected individuals estimated as yet not treated, similar in prevalence between PWID and glass syringe (54,567 vs. 58,001 respectively). These individuals could be considered as potentially diagnosed and not yet linked to care. In fact, around 20 % patients diagnosed with cirrhosis were treated in 2019 (AIFA Registry (Aggiornamento dati Registri AIFA DAAs, 2021)) which highlights an urgent need to increase the awareness of patients and clinicians regarding the importance of not only diagnosis but also immediate linkage to care and cure of infected individuals. Moreover, specific attention needs to be placed on those with advanced liver fibrosis (estimated in the model to be around 130,000).

The results of this modelling approach have been validated to some extent by taking into account specific data from the literature. Specifically: a) Despite using a totally different modelling approach, these estimates are not markedly different from the prevalence of the overall infected individuals estimated by (Andriulli et al., 2018) considering the Italian population of HCV infected in 2015. Compared with (Andriulli et al., 2018), viraemic population reported in the present study is lower because our modelling considers viraemic infected individuals up to October 2019, and therefore this modelling has excluded those individuals not alive by competitive mortality as well as the number of patients treated from 2015 to October 2019. b) Furthermore, the population estimated to have a higher proportion of F0-F3 in Italy are those

born between 1948 and 1988, which mainly contributed to the population of HCV undiagnosed individuals, also previously observed using a completely different modelling approach (Kondili et al., 2018). c) Regarding the mean age of F4 patients, our modelling data are corroborate with data reported by the PITER cohort (Kondili et al., 2017a). PITER is a representative cohort of diagnosed linked-to-care patients in Italy and fits perfectly in terms of mean age of estimated diagnosed individuals in our study. Specifically, the mean age of patients enrolled in PITER was 61 (range 18-94) years of age (Kondili et al., 2018), of whom the mean age of patients in F4 cirrhosis stage was 59 years (range: 34–84) (Kondili et al., 2017b) and of advanced cirrhosis; 64 years (23–86) (Quaranta et al., 2020). d) Furthermore, regarding the estimated age of F0-F3 according to our modelling data, very recent data from studies conducted in the PWID population in Italy validate our findings. In the study by (Messina et al., 2020), the mean age of the population followed, (with the aim of HCV elimination) in the substance use disorder facility (42 % of were PWID) was 39 years (18–73) in pre-intervention period and 41 years (20–74) in the post-intervention period, of whom more than 70 % were in fibrosis stage F0-F3 (Messina et al., 2020). Similar results, in terms of mean age of infected undiagnosed individuals (42 ± 9 years), are also reported in a recent paper by Persico and colleagues conducted in the key populations screened for HCV infection (Persico et al., 2019).

There are no active screening strategies currently available for asymptomatic patients in Italy. There is active promotion of HCV testing through harm reduction, but this is not systematically undertaken nationwide. Very recently, a law decree has been approved that has invested 71.5 million Euro for an experimental active screening through high risk groups and the 1969-1989 birth cohort of the general population (Redazione. Epatite C, 2020), yet this has still to be implemented. To date, the estimated number does not take into consideration an active screening strategy to detect F0-F3 individuals. Thanks to a recent study that demonstrates the optimization of a screening strategy in Italy (Kondili et al., 2020), the availability of a specific fund will hopefully accelerate the diagnosis of those who are estimated but not yet diagnosed F0-F3.

4.1. Study limitations

This study has several potential limitations that could affect the robustness of the model and impact upon the results.

We acknowledge that variation in prevalence rates was estimated considering baseline rates derived from studies that were not always designed as prevalence studies. To partially overcome these limitations, the prevalence retrieved from these articles was not used as a uniform probability throughout all years and ages, but a shape (probability density function modelling) has been derived from different sources to more realistically model the prevalence over different periods (age and years). Furthermore, the reported prevalence estimated by the modelling considered the uncertainties in the prevalence values and transition probabilities according to age in the sensitivity analysis which showed the robustness of the results presented in the base case. This model does not dynamically estimate reinfections, and this could underestimate prevalence rates. However, considering the high rate of treatment rates in Italy in the past 5 years and considering DAA treatment as a preventative measure, the rate of reinfection and new infections will be low and this could decrease this underestimation.

In the base case analysis, we used single linear transition probabilities for all ages and genders over time, assuming a constant annual progression rate of fibrosis. This uncertainty affects all modelling studies and it may impact the proportion of the diagnosed vs. undiagnosed individuals, but not the overall prevalence values. The fibrosis progression is not linear, and its rates are extremely variable and can be influenced by host, viral and environmental factors (Westbrook and Dusheiko, 2014). To limit this bias we randomized the probability of transition using both linear and non-linear probabilities assuming different rates for later liver fibrosis stage (F4) compared to fibrosis stages F0–F3. In addition, in the sensitivity analysis, transition probabilities were assumed to follow a nonlinear progression by using the linear progression as reference case and also other nonlinear progression rates in order to estimate the range of uncertainties around the reference case estimations. Using this approach, we tried to minimize the error in the classification of the proportion of undiagnosed vs. the diagnosed individuals.

In this modelling approach, we assumed all infected individuals in stages F0-F3 that have not been treated remain undiagnosed. It is possible that a portion of these individuals could be diagnosed and not yet linked to care since in the real-life scenario not all F0-F3 are undiagnosed. However, these data do not influence the infection burden, because although these individuals could be diagnosed, they are estimated as not treated.

The “Glass syringe” was the main risk factor of HCV infection in Italy in the years from 1950 to 1975. After 1975, the glass syringe was not considered to be a risk factor. However, a very low risk of nosocomial infection was maintained empirically in the model to account for nosocomial infections (Bollettino Seieva, 2019). In this regard, the impact of other potential routes of transmission as surgical interventions, colonoscopy and other medical procedures, dental intervention/surgery, cosmetic/beauty and/or hair saloons/barbers was not considered separately, and this could underestimate the overall prevalence rate and the number of both diagnosed and undiagnosed individuals.

Immigrants and people that are in prison were not considered in this study. However, based on expert opinion and review of the literature, the migrant population does not have a higher HCV prevalence (considering their countries of birth) compared to the Italian population (considering those resident in Italy for several years that are included in general population estimates) (Falla et al., 2018).

Regarding the prison population, most prisoners have a history of high-risk sexual behavior, injection drug use and tattooing and it seems that the risk of acquisition of HCV infection is linked to these behaviours which are considered in this modelling. For the aim of this study, in the evaluation of the number of untreated individuals in Italy the main routes of infections were considered separately by risk factor and not specific settings, mainly due to the lack of reliable National data. In this study, the prison in itself has not been considered as an important route of infection and this could result in potential underestimation bias. However, intravenous drug use is also reported as main route of infection in inmates and this route of transmission and the affected population have been considered in this modelling and this could have partly balanced this potential underestimation (Vescio et al., 2008). Further analysis should explore this setting separately.

4.2. Conclusion

In Italy, a high burden of HCV infected individuals, estimated in October 2019 to be about 281,809 individuals, still remains undiagnosed. The target for new diagnosis needs to be shifted from nosocomial infection through glass syringes and blood transfusions, mostly detected and cured in elderly individuals (aged 66–75 years), to other risk factors responsible for a more recent wave of infections (PWID, tattoo) in younger individuals (age 46–55 years). These findings underline the need to promote specific country-based screening strategies to reach HCV elimination goals. This modelling approach may play an important role as a tool to characterise the HCV epidemic profile also in other countries besides Italy considering the country specific epidemiology and risk factors for HCV infection.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.epidem.2021.100442.

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