Hepatitis C virus (HCV) prevalence estimation in the adult general population in Belgium : a meta-analysis

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Abstract

Background and study aims : **Although multiple HCV prevalence studies were recently performed in the general population from Belgium, they suffer from a lack of geographical representativeness, an insufficient number of participants or a lack of inclusion of high prevalence groups. The aim of this study is to provide robust information on the HCV burden.**

Methods : **Recently performed HCV prevalence studies in the general, adult population were included in this study, based on well-defined selection criteria. A meta-analysis was performed to estimate the seroprevalence, the prevalence of participants with viremia and the prevalence estimation for people with viremia which were unaware of their status.**

Results : **Eight studies fulfilled the criteria for inclusion of the quantitative prevalence estimation. Based on the meta-analysis on these 8 studies, we estimated an HCV seroprevalence of 1.01% [95% CI : 0.66-1.42%], representing a total of 90,722 adult, HCV seropositives of which 64,412 individuals (0.71%) were confirmed seropositive. Based on the RNA presence, an estimated viremic prevalence of 0.33% [95% CI : 0.21-0.47 %] was determined, corresponding with 29,642 individuals. This is 46,0% of the true HCV seropositive residents. Further, based on the availability of patient information in 5 out of the 8 studies, a prevalence of 0.18% [95% CI : 0.07-0.33] representing 16,168 individuals from the adult Belgian population are unaware of their HCV status.**

Conclusions : **We believe that the quantitative measurement by the meta-analysis will be more reliable for their use in the design of a screening strategy or in the development of prevention campaigns as compared to the prevalence estimations performed at local level.**
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Keywords : meta-analysis, prevalence, hepatitis C virus.

Introduction

Rationale

Hepatitis C virus (HCV) infection is a major public health burden in many countries (1). Currently, several new treatment options became available with a high efficacy (cure rates >90%), a shorter duration of treatment (8-12-24 weeks) and fewer side effects and contra-indications as compared to previous treatment options (2,3). In the light of this evolution, clinicians and governmental agencies will require reliable data to make the necessary decisions for patient care and in general for public health.

The estimation of HCV prevalence is needed to determine the burden of the infectious diseases. This will provide robust strategic information for policy makers to install a national screening strategy to search for newly diagnosed patients and to install updated prevention campaigns or develop clinical practice guidelines. Also, it will allow estimating the global cost of providing direct acting antivirals (DAA's) to cure infected patients and further eliminating the infectious disease.

The estimation of the prevalence of HCV within a population is considered as a core indictor (C1b) in the evaluation plan of the WHO to eliminate hepatitis by 2030 (4). The prevalence of HCV was defined as the number and proportion of people living with chronic HCV infection (HCV RNA positive or HCV antigen [Ag] positive). It is also used as denominator for the determination of the core indicator 6, people living with HCV ; and the additional indicator 8, viral hepatitis C care coverage.

An anti-HCV prevalence of 0.87% (range 0.12%-1.1%) in serum samples from the general population at regional level (Flanders region) was estimated in 1993-1994 (5) and was for years considered as the reference estimation. Subsequently, in 2003, a mail-based study in the Flanders region was conducted to measure the HCV antibodies in oral fluid, resulting in a prevalence estimate of 0.12% [95% CI :0.09-0.39%] (6). The lower prevalence was generally attributed to the lower sensitivity of the oral fluid testing and the likely under-sampling of high prevalence populations. Since HCV is not a notifiable disease in Belgium (7,8), a rough estimation of the burden of the HCV incidence could only be provided using the sentinel network of clinical laboratories (9) or based on the reimbursement data of clinical acts (10).

Meanwhile the prevalence was estimated based on a literature review followed by country expert interviews to

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Table 1. — **Overview of the included prevalence studies listed in alphabetical order**

Reference	Study characteristics	Selection criteria participants	Study period	Region of sample collection
Bielen R. et al. (14)	Monocentric cross sectional study	Patients presenting at the emergency department	Jan-Nov 2017	Genk, Flanders
Bottermans R. et al. [§]	Monocentric cross sectional study	Patients admitted to emergency unit	Sep 2016-Nov 2016	Gent, Flanders
Bourgeois St. et al. [§]	Cross sectional study	People invited by press release at the central hall of the hospital	4-6 Oct 2017	Antwerp, Flanders
Colle I. et al. [§]	Cross sectional study	Patients with appointment at the outpatient gastro-enterology clinic and patients presenting at ICU, excluding the patients known with hepatitis C	May-Jun 2017	Aalst, Flanders
Deressa B. et al. [§]	Interventional study (Clinical trial)	Patients coming to the laboratory for a blood sample or admitted to the one day clinic for surgery and gastroenterology	Sep 2015-Dec 2017	4 Brussels hospitals
Lanthier N. et al. (15)	Monocentric cross sectional study	People present in the main hall of an academic hospital	25 April 2018	Brussels
Litzroth A. et al. (16)	Cross sectional study	Samples preferably collected from emergency, surgery/orthopaedic and otorhinolaryngology wards. Samples from oncology or intensive care wards as well as samples for which information about an immunosuppressed condition or multiple transfusions is available were excluded.	Jun 2013-Jan 2015	National (28 labs)
Verhelst X. et al. (17)	Monocentric cross-sectional study	Patients visiting primary care physicians for whom a blood examination for whatever indication was performed	Nov 2016-Oct 2017	Non-urban, Flanders

[§] Unpublished data.

identify missing inputs (11), allowing its use in modelling studies to determine the level of intervention required to achieve the WHO targets for elimination of HCV (12). The number of viremic HCV infections (n = 70,000 ; range 10,000-91,000) as of 2011 in Belgium, number of cases diagnosed (n = 22,900) with approximately 2800 new viremic HCV diagnoses annually, and the number of patients treated (n = 710/yearly) were estimated (11). Currently no screening strategy is installed in Belgium. However, almost 750.000 individuals, nearly 7% of the Belgian population is yearly screened for the presence of HCV antibodies, a test reimbursed by the social security system in Belgium (13). Also the confirmation test, based on molecular diagnosis either by qualitative or quantitative analysis and the genotyping are reimbursed by the social security system (10). The last one is mainly performed when intention to treat.

In recent years several HCV prevalence studies were conducted in Belgium to answer a long period of missing data (14-17), table 1. However, these studies suffer from a lack of geographical representativeness, an insufficient number of participants or a lack of inclusion of high prevalence groups.

Nevertheless, there is a need for robust HCV prevalence measurement. We therefore summarized in this study the available data from recent studies and performed a meta-analysis.

Objectives

The objective of the study was firstly to assess an HCV prevalence (seroprevalence and viremic prevalence) estimation for Belgium allowing the development of national strategies (screening program and prevention campaigns). Secondly, to demonstrate whether there is a need for a national study including sufficient participants to improve on the representativeness by region, age, gender, and risk profile.

The analysis within this study will be as much as possible in line with international recognized and standardized prevalence protocol allowing the comparison between countries (18).

Methods

Protocol and registration

The analysis method and the inclusion criteria (see below) were specified in advance and documented in a protocol. This protocol was distributed, for endorsement and readiness to participate to all principal investigators of the selected prevalence studies.

Eligibility criteria

HCV prevalence studies, performed from 2013 onwards in the general population were considered eligible for the meta-analysis study. The selection criteria from the participants were adult general population (18 years or older) with residence in Belgium. The test criteria were anti-HCV antibodies by ELISA and/or Immunoblot and/or RNA-HCV determination (RT-PCR). Finally, the availability of the results of the study in a scientific report was not required.

Participants were classified seropositive for HCV if they had either a positive or an undetermined anti-HCV antibodies result. Among these, participants confirmed with a reactive second ELISA test or immunoblot test, were considered as true or confirmed seropositives while the non-reactive participants were considered as false positives. Based on the serological confirmation analysis, the positive predictive value was estimated by the percentage of confirmed seropositives on the number of seropositives as determined by the first serology test, and will be further called the seropositive predictive value. Seropositive participants with a reactive viral RNA test were defined as participants with viremia while the remaining were considered as resolved HCV infection, either spontaneously or by treatment.

Information sources

HCV prevalence studies were identified, based on the above-mentioned eligibility criteria, by searching through peer reviewed publications, poster presentations and trial registries as well as by consultation of experts in the field of HCV, hepatitis and gastroenterology. No limits were applied for language in which the results were scientifically reported.

Data collection

A data extraction sheet was distributed to the principal investigators of the selected prevalence studies. Further, a pilot meta-analysis was shared with these participants to allow for further refinements in case information that has not been, or was unclearly, reported. It allowed the investigator as well to update the data in case the study was extended by the inclusion of additional participants after the time point of publication.

Data items

The following information was extracted from each included prevalence study : (1) characteristics of the trial participants (i.e. age group, the trial's inclusion and exclusion criteria) ; (2) time period and duration of the study ; (3) number of participant and number of participants reactive for the different diagnostic test ; (4) algorithm of testing and type of test used ; (5) information on the use and outcome of a questionnaire in relation with the reactivity in the diagnostic tests.

Risk of bias in individual studies

To explore variability in study results (heterogeneity) we specified the following hypotheses before conducting the analysis. We hypotized that the test methods used in the different studies are equivalent in sensitivity and specificity towards the detection of the HCV positive cases.

We ignored that inclusion criteria (visit of different hospital unit) of the participants differ according to the methodological quality of the studies. Also, the impact on the prevalence due to selection of participants from rural or urban region was ignored.

We considered that the trend in time of the prevalence from the first to the last trial was negligible.

Summary measures

The primary outcome measure was the mean and range (95% confidence interval) of the prevalence of seropositive cases and viremic cases.

Meta-analysis method

Heterogeneity between studies was assessed by I^2 statistics. If the I^2 value was less than 50%, the meta-analysis was performed using the fixed-effects model. Otherwise, the random-effects model was adopted. Potential publication bias was examined by funnel plots, although the low number of studies (n=8) did not allow a solid analysis. Incidence was calculated using R software [R version 3.3.2 (2016-10-31)] with package Meta and Metaprop function (19).

Results

Study selection and study characteristics

The selected studies and their study characteristics are summarized in table 1, giving an overview of the included trials information i.e. the geographical distribution of the selected participants, inclusion criteria and the study period.

Between 2015 and 2018, a total of 8 HCV seroprevalence studies were registered in Belgium as described in table 1 (14-17).

Five out of the 8 studies were performed in the Northern part of the country (Flemish community), 2 in the Brussels capital region and for 1 study the included samples had a national coverage (16).

In order to allow the comparison between studies, participants older than 18 years were selected from all included studies.

For 4 studies, participants were included based on medical visits at a local hospital respectively in the region of Genk (Bielen R. *et al.* (14)), Ghent (Botterman R. *et al*. [unpublished data]), Aalst (Colle I. *et al.* [unpublished data]), and Brussels (Deressa B. *et al.* [unpublished data]). Three other studies were either based on visits at primary care givers (Verhelst X. *et al*. (17)) or based on an open screening campaign in the main hall of the hospital (Bourgois St. *et al*. [unpublished data] and Lanthier N. *et al*. (15)). No questionnaire was available for the only study which was based on anonymized residual serum samples (16).

Table 2 shows an overview of the results obtained by the 8 selected studies described in table 1 : number of participants, outcome of diagnostic assays used in the studies and outcome of the questionnaire.

Table 2. — **Overview of the results of the included prevalence studies described in table 1**

Reference	Bielen R. *et al.* (14)	Bottermans R. *et al.* §	Bourgeois St. *et al.* §	Colle I. *et al.* §	Deressa B. *et al.*. §	Lanthier N. *et al.* (15)	Litzroth A. *et al.* (16)	Verhelst X. *et al.* (17)
Number of participants	2366	1233	723	239	1897	200	1670	560
M/F ratio	1291/1075	682/551	ND	ND	ND	ND	839/831	219/341
Questionnaire available	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Reactive in first serology test (%)	31 (1.31%)	24 (1.9%)	7 (0.97)	0	22 (1.16%)	3 (1.5%)	10 (0.60%)	5 (0.89%)
Positive/UND serology confirmation test (%) =Confirmed seropos	NA	NA	NA	NA	NA	NA	4/3 (0.24%/0.18%)	NA
Positive/UND HCV RNA (%) =viraemia	12 (0.51%)	6 (0.49%)	3 (0.4%)	0	5 (0.26)	ND	3 (0.18%)	4 (0.71)
Newly diagnosed participants with viraemia	5	ND	2	NA	3	0	ND	4

ND : Not described. NA : Not applicable. UND : undetermined result. § Unpublished data.

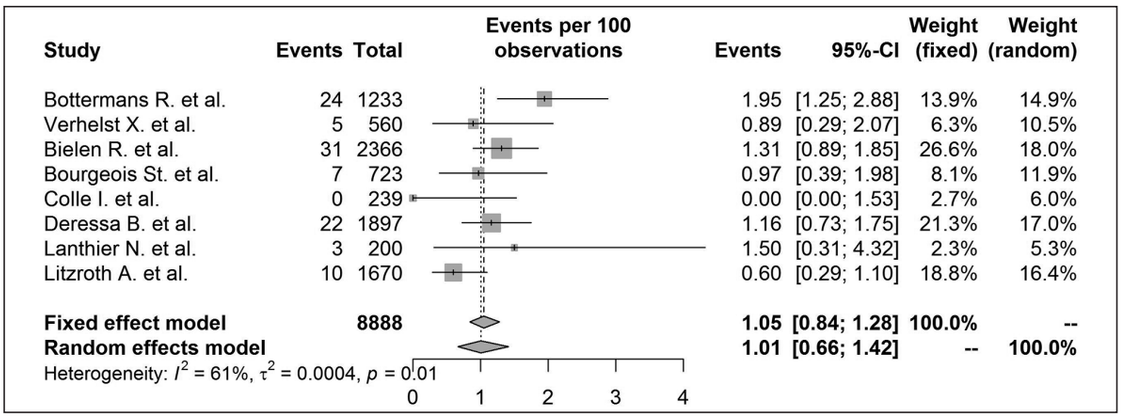

Fig. 1. — Meta-analysis, proportion seropositive cases (not confirmed) from 8 studies. Data used for this meta-analysis is described in table 2.

HCV seroprevalence

After meta-analysis, the seroprevalence in the adult general population as measured by either an ELISA or fingerstick screening test was 1.01 % [95% Confidence interval (95%CI) : 0.66-1.42%] (fig. 1). Considering a population of 8,982,329 inhabitants in Belgium >18y on 1/1/2016 (20), this represents a population of 90,722 [95% CI : 59,283-127,549].

Seropositive predictive value

The presence of HCV specific antibodies was only confirmed in the study of Litzroth *et al*. (16) allowing the estimation of the seropositive predictive value (Fig. 2). Three out of 10 cases were not confirmed by the immunoblot confirmation test. Even if the sensitivity and specificity of the test method is nearly 100%, this low seropositive predictive value (7/10) finds its origin by the low prevalence in the Belgian population.

Combining the seropositive predictive value with the obtained seroprevalence (1.01%), results in a true seroprevalence of 0.71% or 64,412 individuals.

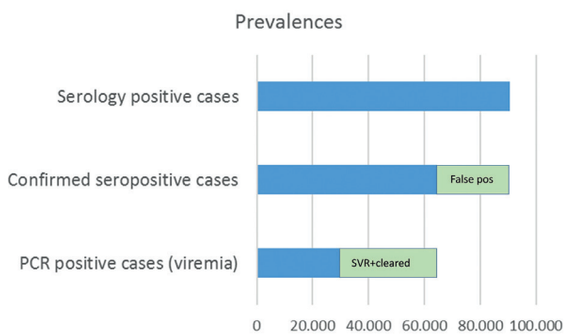

Fig. 2. — Schematic presentation of the estimated anti-HCV cases and PCR positive cases in the Belgian adult population as measured by the meta-analysis. The estimation of the seropositive predictive value was based on the single measurement after confirmation analysis (16). SVR : sustained viral response

Viremia (active viral replication)

Demonstration of the presence of RNA by RT-PCR, allowed to estimate the prevalence of viremic participants. Meta-analysis of the data from the different

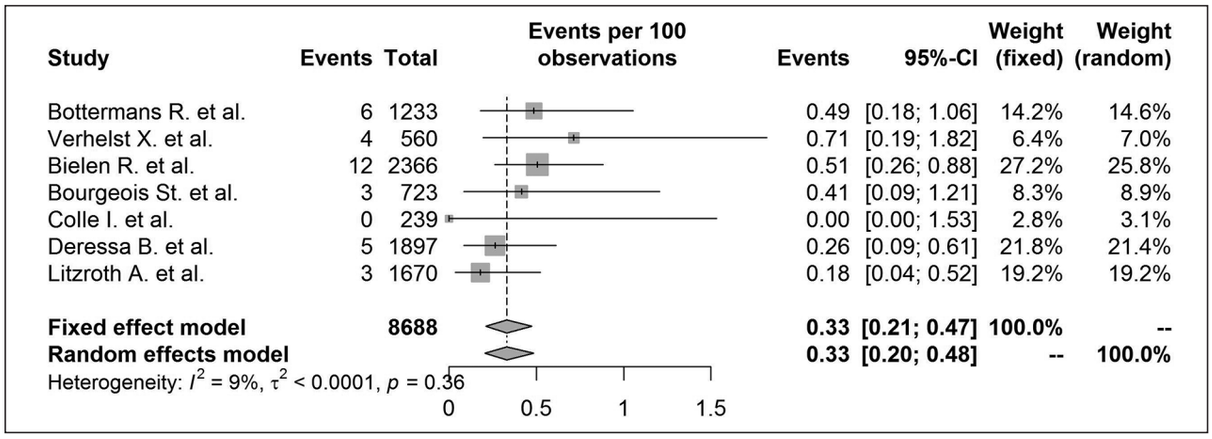

Fig. 3. — Meta-analysis, proportion on viremic cases (RNA+) from 7 studies. Data used for this meta-analysis is described in table 2 questionnaire and follow-up.

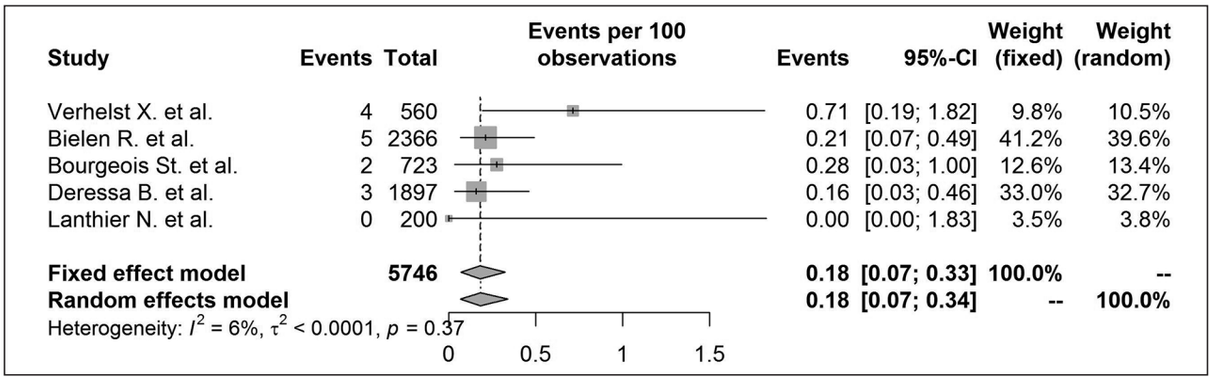

Fig. 4. — Meta-analysis, proportion on newly diagnosed patient with viremia from 5 studies. Data used for this meta-analysis is described in table 2.

studies showed a prevalence of 0.33 % [95% CI : 0.21-0.47%] (fig. 3). This represents 29,642 individuals [95% CI : 18,863-42,217] from the adult Belgian population. By the absence of the confirmation of the reactive HCV antibodies by a second antibody test for 7 out of the 8 studies, a meta-analysis of the fraction of patients with spontaneously cleared virus and sustained viral response after treatment could not be estimated.

For 5 out of the 8 studies (table 2), patient information (i.e. risk profile, awareness of HCV infection status) was collected through a questionnaire. This allowed to estimate the number of viremic participants who were unaware of their HCV status.

Meta-analysis of these data showed a prevalence of 0.18 % [95% CI : 0.07-0.33%] of the participants with viremia who were unaware of their HCV status (fig. 4). This represents 16,168 individuals [6,288-29,642] from the adult Belgian population.

Additional analyses

Seen the limited number of positive cases in each study, it was hardly possible to stratify the prevalence by region, age group or risk profile.

Discussion

Summary of prevalence's

Here we estimated the prevalence of HCV through a meta-analysis, based on a selection of previously performed prevalence studies in Belgium. We believe that this quantitative measurement will be more reliable in the design of a screening strategy or in the development of prevention campaigns. Based on the meta-analysis of studies performed from 2013 onwards, a total of 90,722 Belgian adult residents were estimated to be seropositive of which 64,412 individuals are confirmed seropositive. From these, 29,642 (46.0%) individuals have viremia as defined by HCV-RNA reactive of which 16,168 (54.5%) are unaware of their HCV status.

The estimated HCV seroprevalence of 1.01% [95% CI : 0.64-1.42%] is slightly higher, although not significant, than the 0.87% [95% CI : 0.12-1.1%] found in the Flemish community in 1993-1994 (5). Whether this was due to historical changes or to the differences in inclusion criteria could not be investigated.

Due to the reimbursement of the diagnostic tests in Belgium (10), patients are screened for presence of

antibodies by ELISA test and in case of a reactive test, the patients are invited for a confirmatory HCV-RNA test. The study performed by Litzroth *et al.* (16) demonstrated that a considerable fraction of the reactive antibody test is false positive even if the sensitivity and specificity of the screening test are nearly 100%. Therefore, given the low HCV seroprevalence, the confirmation of the serology screening test by a second ELISA or immunoblot test should be considered in seroprevalence studies to estimate the true positives and thereby the positive predictive value.

Also, the estimated viremic prevalence of 0.33 % [95% CI : 0.21-0.47%] or 29,642 individuals is lower, although not significantly, the 70,000 (range 10,000-91,000) estimated by the model fit method (11).

Based on a study for measuring the distribution of HCV genotypes in Belgium during an overlapping period (2008-2015) analogue with this study, genotyping tests were performed for 11,003 unique patients or yearly for 1,374 patients (range 1,123-1,616) (21). We therefore believe that the estimated viremic prevalence of 0.33% is more in line with the Belgian situation unless transmission of newly infected patients is still ongoing.

Need for national study

Pilot studies at local level are very helpful to estimate the seroprevalence but are seldom representative at national level. The seroprevalence estimates obtained by multiple prevalence studies are an essential step towards the determination of the sample size in case national studies should be performed. Therefor we believe that the accuracy of the sample size calculation will profit from the estimated prevalence from this meta-analysis. An effort should now be made to conduct studies at national level and with a geographical representativeness, rather than performing studies at regional level. Based on an adult population size of 9.000.000 inhabitants in Belgium and a prevalence of 0.33% +/- 0.1%, a sample size of 12,618 should be taken (95% confidence interval) (22). The obtained result from such a national study will be of particular help in the design of an eventual population-based screening program.

Comparison with data from other countries

Within Europe, nationwide prevalence estimates range from 0.4% to 3.5%, with countries in Southern and Eastern Europe generally being the most affected (23). However, differences in prevalence studies are known to be due to differences in test method, inclusion criteria of the patients, regional observations and therefore necessitate a standardized prevalence study protocol.

The patient groups with high prevalence's such as prisoners, people linked to endemic regions, men who have sex with men (MSM) and persons who inject drugs (PWID) should not be excluded as recommended by the harmonized seroprevalence protocol developed by ECDC (18).

Prevalence and baby boom generation

Different statements concerning the baby boom generation were concluded throughout the selected prevalence studies. Botterman R. *et al*. [unpublished data] demonstrated that the seroprevalence of HCV in the booming cohort, defined as born between 1945-1965, was 1.9% as compared to the 2.0% and 2.1% for respectively the younger and older test population. On the contrary Litzroth A. *et al*. (16) showed that 66% of HCV seropositive individuals in Belgium belong to the so called "baby boom generation" (born between 1945 and 1965). Bielen R. *et al.* (14) found a higher seroprevalence of HCV in males born between 1955 and 1974 and the 3 positive cases reported by Lanthier N. *et al*. (15) were middle-age people (50-60 years). Finally, Deressa B. *et al.* [unpublished data] compared different bird cohorts and their data evoked another birth cohort of 1940-1965. Based on these findings, it seems that larger studies or pooled data from other screening studies are certainly warranted before designing screening strategies based on the baby boom generation. Also, a harmonized definition of the baby boom generation or the determination of the cohort which maximally could profit from the screening strategy should be determined.

Limitations

The meta-analysis reported here combines data across studies to estimate the prevalence with more precision than possible by a single study. The main limitation of this meta-analysis, as with any overview, is that the inclusion criteria of the participants are not the same across studies. Therefore, no standardization towards sex, age group or risk profile could be made.

No case from the southern part or the French speaking region (Wallonia) was found positive. Mainly because 5 out of the 8 studies were conducted in the Flemish community (North of Belgium), and 2 in the Brussels capital region. Nevertheless, we extrapolated that the obtained estimation from the different studies are representative for the entire Belgian population.

Conclusions

In conclusion, the determination of the prevalence of HCV seropositivity and viraemia in the Belgian general population could provide Belgian policy makers with the necessary information to develop a screening strategy for detecting newly diagnosed patients, design prevention campaigns and to estimate the global cost of HCV treatments.

The obtained prevalence data together with the recently published genotyping distribution at national level (21) and the availability of the exact number of patients under therapy and their success of viral response by the aim of a newly installed register (24), are valuable missing data. These data can be used to replace the

outdated or incorrect data used in the models to estimate the economic impact of hepatitis C in Belgium (25).

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Conflict of interest

R. Bielen has received travel grants from Abbvie, MSD and Gilead to attend scientific congresses. St. Bourgeois has acted as a consultant for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, and MSD and has given sponsored lectures for Gilead Sciences, Janssen, MSD and Abbvie. I. Colle and S. Platteau received travel grants from GIlead, Abbvie and Bayer for their participation to congress. G. Robaeys has received research grants from MSD, AbbVie, Janssen Pharmaceuticals, and has acted as a consultant/advisor for Gilead Sciences, Abbvie, MSD and BMS. N. Lanthier received travel grants from Abbvie and MSD for his participation to congresses and has given sponsored lectures for Gilead Sciences. H. Van Vlierberghe has received grant support from AbbVie, Astellas, Ferring, Gilead Sciences, Johnson & Johnson, and Novartis, has acted as a consultant for AbbVie, Bristol-Myers Squibb, Gilead Sciences, and Johnson & Johnson, and has given sponsored lectures for Gilead Sciences.

G. Muyldermans, R. Bottermans, B. Deressa, G. Devolder, Y. Horsmans, V. Hutse, L. Lasser, S. Platteau, V. Suin, X. Verhelst, L. Van Baelen report no conflict of interest.

No one other than the authors had control over the study design, data, data analysis or interpretation, or wording of conclusions.

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