Double Jeopardy: Persistently High Hepatitis C Rates in Haemodialysis Patients in Brazil: A Systematic Review and Meta-Analysis

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Research Article

Keywords: haemodialysis, patients, Brazil, hepatitis, infection, average time, people

DOI: https://doi.org/10.21203/rs.3.rs-539209/v1

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Double Jeopardy: persistently high hepatitis C rates in haemodialysis patients in Brazil: a systematic review and meta-analysis

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Acknowledgments: The authors thank the National Research Council (CNPq) and the Rio de Janeiro Research Council (FAPERJ) for their support. The senior co-authors are career scientists of those institutions. The junior members of IFRJ (DCMB and JSF) received scholarships from them.

FIB and LSB are members of the “Brazil's Fight Against Hepatitis C: Surveillance, Control, and Care” collaborative network, comprised by FGV [Getúlio Vargas Foundation, Brazil], FIOCRUZ [Oswaldo Cruz Foundation] & LSE [London School of Economics and Political Science. The consortium is core funded by the Newton Fund (“Institutional Links” initiative), in partnership with the Brazilian institutions.

Disclosure: The opinions expressed in this paper are the sole responsibility of the authors and do not necessarily reflect those of their institutions and funding agencies.
Abstract (340 words):

**Background:** We conducted a systematic review and meta-analysis of studies assessing HCV infection rates in haemodialysis patients in Brazil.

**Methods:** A systematic review was carried out, followed by two independent meta-analyses. The 1st included studies with data on HCV prevalence. The 2nd included previous studies with a confirmatory PCR (i.e. active infection of hepatitis C). We used both Bayesian and classical statistical concepts and methods. A comprehensive set of different methods and procedures were used, including forest plots and respective statistics, polynomial regression, meta-regression, subgroup, influence, and trim and fill analysis.

**Results:** 11,290 individuals were assessed in the pooled analyses. The average time patients were in haemodialysis varied from 23.5 to 56.3 months. Prevalence of HCV infection was highly heterogeneous, with a pronounced decrease from 1992 to 2001, followed by a plateau and a slight decrease in recent years. The summary measure for HCV prevalence was 34% (95%CI:26%-43%) for studies implemented before 2001. For studies launched after 2001, the corresponding summary measure was 11% (95%CI:8%-15%). Estimates for prevalence of active HCV infection were also highly heterogeneous. There was a marked decline from 1996 to 2001, followed by a plateau and a slight increase after 2010. The summary measure for active HCV infection was 19% (95% CI:15%-25%) in studies launched before 2001, with a high degree of heterogeneity. For studies implemented after 2001, the corresponding summary measure was 9% (95% CI: 6%-13%), again with high heterogeneity. The different analyses helped to identify the underlying sources of heterogeneity. Besides the year each study was conducted, the findings differed markedly between geographic regions and were heavily influenced by the size of the various studies and by publication biases.

**Conclusions:** CKD should be targeted with specific interventions to prevent HCV infection, and if prevention fails, prompt diagnosis and treatment. Although the goal of HCV elimination by 2030 in Brazil appears elusive, it is possible and necessary to adopt measures to achieve micro-elimination and to launch initiatives towards targeted interventions to curb the spread of HCV among people with CKD, among other high-risk groups.
Introduction

Severe renal failure (SRF) is a serious, potentially life-threatening medical condition. SRF is a likely outcome of chronic kidney disease (CKD) when several underlying conditions (e.g., diabetes, hypertension, chronic renal infection, renal cancer) lead to a progressive decrease in the glomerular filtration rate (GFR) and the decrease cannot be reversed or at least substantially ameliorated (Webster et al., 2017). SRF can evolve to end stage kidney disease (when GFR is no longer compatible with homeostasis).

From a complementary perspective, hepatitis C infection is widespread in the world, despite concerted efforts by international agencies such as the World Health Organization (WHO) and different national health systems to curb the disease and ideally to eliminate it by 2030 (Waheed et al., 2018). Currently, the prospects for timely elimination of hepatitis C remain elusive, and several authors have focused on the concept of micro-elimination, i.e., elimination of hepatitis C in some populations and contexts (Idilman et al., 2020). Unfortunately, this is not the case of people with CKD in haemodialysis. They continue to be disproportionately affected by hepatitis C and several other infections (Eleftheriadis et al., 2011).

The management of end stage kidney disease usually includes haemodialysis and kidney transplantation. Dialysis is key, since it is both an essential strategy for keeping patients with severe renal failure alive and healthy as well as an interim procedure to keep patients fit for kidney transplantation (Chen et al., 2018). In Brazil, the process mediating the demand for kidney transplantation has been both complex and slow (Peres-Penteado et al., 2015).

Patients with SRF have to deal with a severe medical condition, subjected to a chronic, invasive intervention (haemodialysis) and suffering from the stress and anxiety associated with long waiting lines for transplantation (Vermeulen et al., 2005, on waiting lines for lung transplantation and associated psychological distress).

Most legislations worldwide exempt “an accused person from being tried on similar charges following a valid acquittal or conviction” (known as double jeopardy or “non bis in idem”). However, people with CKD in haemodialysis have faced multiple additional burdens. Many such burdens might be substantially reduced if proper biosafety measures were adopted rigorously. This is the case of most blood-borne infections, including hepatitis B and C. To impose any additional harms and risks on such patients is unethical and unfair.
Despite the efficient control of HCV infection in this group of patients in some high-income countries, this is unfortunately not the case of Brazil, a middle-income country with a population of more than 212 million. Considering both the persistently high HCV infection rates over the years as well as the magnitude of even relatively rare conditions when considering the high numbers of patients, it is crucial to address this challenge in Brazil.

The current article focuses on one such infection or disease: HCV infections or hepatitis C among haemodialysis patients. We conducted a systematic review and meta-analysis of studies assessing HCV infection rates in haemodialysis patients in Brazil.

**Methods**

The systematic search deployed a search procedure conducted in four different reference databases (PubMed/Medline, SCOPUS, Web of Science/ISI, and LILACS). LILACS (the acronym for “Literatura Latino-Americana e do Caribe em Ciências da Saúde” [Latin American and Caribbean Literature on Health Sciences]) is a reference database seldom browsed by English-speaking researchers. Still, it is particularly useful in Latin America and the Caribbean, since it summarizes publications not available in other databases and basically those written in Spanish and Portuguese (with a few publications in French). The search covered articles published up to December 31, 2019. The procedures and scripts used in the search process were fully available at Web Appendix 1.

Papers from 2020 were not included in our search. The COVID-19 epidemic has deeply affected the Brazilian health care system as a whole and specifically hit the haemodialysis centres. The latter are on the verge of collapse. This impact of the COVID-19 epidemic on haemodialysis has not been properly evaluated yet. Information remains far from comprehensive (Pio-Abreu et al., 2020).

The search strategy can be briefly described as follows:

The fields included in the search were “title”, “abstract”, and “keywords”. There was no restriction according to language of publication, with the aim of minimizing the biases associated with the common procedure of limiting search strategies to English, usually viewed as the “lingua franca” of science worldwide (Morrison et al., 2012).

The basic search syntax was the following: (prevalence OR seroprevalence OR incidence OR rate) AND ("hepatitis C" OR HCV OR "liver disease") AND (haemodialysis OR dialysis) AND (Brazilian OR Brazil). Concerning the latter, Brazil was replaced with each of the Brazilian states in successive search rounds. This strategy aimed to minimize
biases associated with the frequent use of the name of the different Brazilian states, but not of the country as a whole in several studies. Brazil’s continental size and pronounced heterogeneity usually prevent the generalization of findings from most studies conducted in specific contexts of the country. This was performed repeatedly with the Boolean operator “OR”.

Additional searches were performed in LILACS using the equivalent terms in Spanish and Portuguese.

**Inclusion criteria**

Articles included in this study followed three basic criteria:

1. Assessment of the target population (haemodialysis patients in Brazilian healthcare units) whether or not as the article’s exclusive focus;
2. Probabilistic samples of the population covered by a given healthcare unit or network of facilities, or adoption of a census approach (i.e., aimed to include all patients from a given setting/service or network of facilities);
3. Performance of HCV serological tests with or without further confirmation using HCV RNA PCR (polymerase chain reaction).

**Exclusion criteria**

The following criteria were used to exclude articles from the current review:

1. Studies exclusively based on secondary data, with no first-hand empirical data (i.e., the researchers asked local managers to send the data, but did not double-check the data through any on-site assessment);
2. Failure to provide basic information on where the studies had been conducted (at least the municipality or state of Brazil);
3. Lack of information on the year the study was performed;
4. Lack of information on the sample size, or samples with fewer than 30 patients (in order to avoid the small numbers fallacy; Rabin, 2002);
5. Lack of information on HCV infection rates in the target population or insufficient reliable data that might help calculate the rate;
6. Lack of information on the test(s) used to diagnose HCV infection;
7. Studies that used no additional tests besides first and second-generation ELISA/EIA (since their lower sensitivity and specificity can introduce further
heterogeneity and less accuracy in the efforts to find reliable pooled estimates of point prevalence and respective confidence intervals) (Gretch, 1997; Tang et al, 2017);

(8) Studies that only provided data on “dialysis”, without further specifying subsets of patients in peritoneal dialysis versus haemodialysis and the respective prevalence rates;

(9) Studies in a series assessing the same sample. In this case, our review only included the most comprehensive study in the series (in order to avoid duplicate/multiple counts of the same group of patients).

The criteria are in sync with the CoCoPop guidelines, which are fully described in the Web Appendix 2.

Steps and procedures

The first step was a detailed reading by three independent reviewers of the titles of all articles selected with the search algorithm. Articles with no clear link to the study’s purpose and inclusion criteria were excluded immediately (i.e., before any further steps).

The second step consisted of the analysis (again, by three independent reviewers) of the contents of abstracts from all the articles approved in step 1. Abstracts were screened for their relevance to the study’s objectives and criteria. When the abstracts/articles were consistent with these criteria, the full texts were read by the reviewers.

The reviewers extracted core information from the articles selected for full-text reading, using a standard form completed independently by each of the three reviewers. The standard form included the following variables: name of the first author; the year(s) the study was implemented and concluded; the major geographic region of Brazil (among five) where the study was conducted; the target population/patient group; sample size; laboratory tests used for diagnosis of HCV infection; prevalence of HCV infection; proportion (%) of individuals who had ever received blood/blood products; average age (in years) of the haemodialysis patients; and average time on haemodialysis. Averages were defined as arithmetic means. In the absence of means, the medians or interpolated values were used.

The fourth and final step consisted of the application of the exclusion criteria to all the articles. When the three independent reviewers failed to reach the same decision; the article was discussed until a consensus was reached.
The findings of the successive steps can be visualised in Figure 1.

**FIGURE 1 ENTERS HERE**

**Data analysis**

Initially, a descriptive analysis of all information extracted from the selected articles was performed.

Two independent meta-analyses of the data were carried out. The first one included all studies with data on HCV prevalence, defined by third-generation ELISA (enzyme-linked immunosorbent assay) (hereinafter “III”), MEIA (microparticle enzyme immunoassay), or EIA (enzyme immunoassay).

Articles in which HCV prevalence was defined according to positive ELISA III results with or without additional tests such as LIA (line immunoassay) were included. For articles in which HCV prevalence was defined according to CLIA (chemiluminescence immune assay) and ECLIA (electro-chemiluminescence immunoassay) (taken together), this option was also defined for our purposes as a valid diagnosis of HCV infection.

The second analysis included all studies selected for the first analysis with a confirmatory test using PCR (polymerase chain reaction). The combination indicates active infection, i.e., that HCV persists in the individual and viral load exceeds the detection threshold.

The findings from the two analyses were summarized and displayed as graphs showing HCV prevalence according to the year the study was implemented (in order to distinguish between when the fieldwork began and the respective study’s actual publication). The five major geographic regions of Brazil were displayed with different colours. The major geographic regions represent the gross geographic division of the country, as defined by the Brazilian Institute of Geography and Statistics (IBGE).

The analyses and corresponding graphs made the following assumptions: i) the number of HCV-positive patients in each study $Y$ followed a binomial distribution, with a parameter $n$ corresponding to the number of patients tested in the context of each study and ii) the *a priori* distribution was also assumed as uniform $(0, 1)$ for the different studies.

The subsequent distribution of studies was defined as a beta ($\beta$) distribution $(y+1,n-y+1)$. The 95% credibility intervals were calculated based on this distribution.
The graphs were produced by fitting a local polynomial regression (loess), taking the year each study was launched and *a posteriori* mean prevalence as the predictor.

Based on such data and graphs, study heterogeneity (I$^2$ statistics) was calculated (Chen & Peace, 2013). Study heterogeneity was classified according to the criteria proposed by Higgins et al. (2003): absence of any relevant heterogeneity for P values close to 0%; and heterogeneities defined as low, moderate, and high for levels of 25%, 50% and 75%, respectively.

Meta-analyses were implemented to calculate the summary statistics, comprising point estimates and their respective 95% confidence intervals (95% CIs). The studies were divided into two subsets, before versus after 2001. This year was defined as the cut-off, because after 2001 standards for the operation of health units performing haemodialysis were issued by the Brazilian Ministry of Health (BMoH) (BMoH - RDC no. 8, January 2 2001; BMoH - RDC no. 154, June 15 2004). We also estimated prevalence rates and respective 95% CIs for each major geographic region of Brazil, before and after 2001, using random effects models.

All the analyses were performed with the open-source software R 3.6.3 ([https://www.r-project.org/](https://www.r-project.org/)). The R scripts are available on request.

Besides the abovementioned analyses which results are fully presented in the main body of the article, a comprehensive set of complementary analyses based on classic/frequentist statistics were carried out and are fully available at the [Web Appendix 3](#).

They comprise the analysis as follows (in full compliance with the PRISMA statement and respective check-list): Forest plots and their respective statistics; subgroup analysis; meta-regression; influence analysis, as well as the assessment of publication biases using the trim-and-fill statistics based on funnel plot graphs.

Their findings are briefly mentioned in the body of the article and are presented and discussed in detail in the abovementioned [Web Appendix 3](#).

**Results**

The search strategy yielded 292 articles (54 from PubMed/Medline, 76 from SCOPUS, 58 from Web of Science, and 87 from LILACS, with an additional 17 articles listed in the previous articles’ references). Due to overlapping, 115 articles retrieved from more than one database were excluded.

Among the remaining 177 articles, 48 were excluded after three independent assessments of their titles. Fifty more were excluded after assessing their abstracts. Seventy-
nine articles were then read as full texts. After this last step, 29 articles were selected for the systematic review and meta-analysis (Figure 1).

Two studies (Carneiro et al., 2005 and Callegaro et al., 2006) presented data for three periods (1993, 1996, and 1999) and two periods (2000-2002 and 2006), respectively. Data were stratified according to the above-mentioned periods of data collection. Thus, although 29 articles were analysed, the N for point prevalence and respective 95% CIs was 32 (Table 1).

Overall, 28.1% (n=9) studies were based on data from the South of Brazil, 25.0% (n=8) from the Northeast, 21.9% (n=7) from the Central-West, and 12.5% (n=4) from both the North and the Southeast. A total of 11,290 individuals were assessed in the pooled analyses, 32.9% (n= 3,717) of which from the Northeast, 26.6% (n=3,005) from the Central-West, 17.5% (n= 1,974) from the South, 15.0% (n=1,687) from the North, and 8.0% (n=907) from Southeast (Table 1). More than half (62.5% [n=20]) of the studies were conducted after 2001 (Table 1).

The point prevalence estimates varied substantially, from as high as 68.0% in a study in 1992 in Southeast Brazil (Oliveira et al., 2001) to as low as 2.8% in a study in 2014 in the North (Cordeiro et al., 2018). Studies addressing active HCV infection, i.e., consisting of patients that tested for HCV antibodies and HCV-RNA, also varied considerably, but not as much as in the previous studies. The highest point prevalence for active HCV infection was 27.3%, in a study in 1998 in the South (Carvalho et al., 1999), whilst the lowest was 2.9%, in a study in 2006, also in the South (Callegaro et al., 2006b) (Table 1).

Besides the comprehensive list presented in Table 1, findings were depicted as forest plots (Web Appendix 3). Summary measures and respective statistics using both Fixed Effects Models (FEM) and Random Effects Models (REM) are fully presented in the Web Appendix 3.

Findings from all analyses are presented despite the fact some minor discrepancies may be observed here and there. We opted for a full disclosure of all findings aiming to improve transparency and reproducibility (Marcus, 2014).

**TABLE 1 ENTERS HERE**

Considering the above-mentioned stratification of two articles (n=32 for 29 articles), 34.4% (n=11) were conducted in a single healthcare unit where haemodialysis was performed, whilst 15.6% (n=5) analysed data from a pool of 10 or more facilities. The vast majority of
articles (96.9%), considering the same stratification, followed a census design, i.e., researchers ordered testing for each single patient. However, 62.5% (n=20) did not provide any information on refusals (Table 2 and Web Appendix 2). Since refusals and non-response are likely to be differential, the absence of this information represents a limitation.

Considering the 23 studies with data on the central tendency measures of patients’ age, the lowest age was 42.2 years (Carneiro et al., 2005a) and the highest was 56.9 years (da Silva et al, 2013). The weighted average for the 23 studies with available data on age was 48.3 years, with lower ages in studies before 2001 (n=8; 45.7 years) and higher ages (49.9 years) in studies after 2001 (n=15) (Table 2).

Information on age range was available in 16 studies. Half of the studies only included patients over Brazil’s age of majority (18), whilst the other half also included children and adolescents. Data on the latter (numbers and/or proportions) were not available in the original studies and could not be obtained from the authors (Table 2 and Web Appendix 2).

The average time patients were in haemodialysis varied from 23.5 months (Souza et al., 2003) to 56.3 months (Galperim et al., 2010). The weighted average (considering studies with available data [n=20] and their respective samples) was 39.3 months; lower (35.1 months) for studies launched before 2001 (n=6) and higher (40.9 months) for those after 2001 (n=14) (Table 2).

The proportion (%) of patients that reported having received blood and/or blood products varied from 32.9% (Fontenele et al., 2015) to 96.0% (Souza et al., 2003). The weighted average for studies that provided this information (n=15) was 74.3%; higher (75.4%) among studies launched before 2001 (n=3) and lower (73.8%) for those after 2001 (n=12) (Table 2).

| TABLE 2 ENTERS HERE |

Prevalence of HCV infection (defined as a positive HCV antibody test) among the pool of studies on haemodialysis patients was highly heterogeneous ($I^2=98$), with a pronounced decrease from 1992 to 2001, followed by a plateau and a slight decrease in recent years (Figure 2).

Additional analyses presented in detail in the Web Appendix 3 show that such heterogeneities are a complex combination of several factors, among them the year each study was carried out and the geographic region. These two factors are expected, given the deep
regional heterogeneity of the country and the abovementioned decline of HCV prevalence over time.

But other factors are also key: studies summarise data from health services with heterogeneous clienteles, including small clinics as well as large referral centres and there are relevant publication biases (as shown by the trim-and-fill statistics and the underlying funnel plots; Web Appendix 3).

As discussed below, nothing can be inferred about services which are not officially registered or for which the official registration has not been updated. There is no comprehensive and updated registry, precluding the matching of studies and the database partially updated by the surveys carried by the Brazilian Society of Nephrology (as discussed below).

Last but not least, Baujat plots (Web Appendix 3) made evident the influence of studies which findings should be viewed as outliers. They were not excluded from the analysis, but rather analysed in detail in the abovementioned Appendix.

FIGURE 2 ENTERS HERE

The summary measure for HCV prevalence was 34% (95% CI: 26%-43%) for studies implemented before 2001, with a high degree of heterogeneity ($I^2=96\%$). For studies launched after 2001, the corresponding summary measure was 11% (95% CI: 8%-15%), with persistently high heterogeneity ($I^2=95\%$).

Estimates for prevalence of active HCV infection (i.e., patients with both positive HCV antibody and HCV-RNA results) were also highly heterogeneous ($I^2=94\%$). There was a marked decline from 1996 to 2001, followed by a plateau and a slight increase after 2010 (Figure 3). The summary measure for active HCV infection was 19% (95% CI: 15%-25%) in studies launched before 2001, with a high degree of heterogeneity ($I^2=86\%$). For studies implemented after 2001, the corresponding summary measure was 9% (95% CI: 6%-13%), again with high heterogeneity ($I^2=93\%$) (Figure 3).

FIGURE 3 ENTERS HERE

The results from the random effects models fitted to data from studies implemented before 2001 (the cut-off we adopted for the entire period) for HCV prevalence (anti-HCV
prevalence) were as follows: 52% (95%CI:35%-70%) for Northeast Brazil, 36% (95%CI:19%-52%) for the Central-West, and 31% (95%CI:15%-47%) for the South and Southeast. No studies were conducted in the North of Brazil in that period (Table 3).

Prevalence of active HCV infection (i.e., positive HCV antibody + HCV-RNA) was as follows: 25% (95%CI: 6%-44%) in the Central-West, 21% (95%CI:3%-38%) in the South, and 14% (95%CI:7%-30%) in the Southeast. No estimates were available for the North and Northeast since no studies reported on the two tests in those regions during the period (Table 3).

TABLE 3 ENTERS HERE

The results from the random effects models fitted to data from studies implemented after 2001 for HCV prevalence were as follows: 23% (95%CI:9%-33%) in the South, 15% (95%CI:3%-27%) in the Central-West, 15% (95%CI:2%-27%) in the Southeast, 8% (95%CI:4%-18%) in the North, and 7% (95%CI:5%-16%) in the Northeast. For active HCV infection, the results are as follows: 18% (95%CI:1-35%) in the South, 10% (95%CI:9%-23%) in the Central-West, 11% (95%CI:7%-24%) in the Southeast, 7% (95%CI:4%-17%) in the North, and 6% (95%CI:5%-17%) in the Northeast (Table 3).

Discussion

Our systematic review and meta-analysis documented a substantial decline in HCV prevalence among Brazilian haemodialysis patients from 1992 to 2015. These findings are corroborated by data from the regular surveys conducted by the Brazilian Society of Nephrology (SBN in the Portuguese acronym). The SBN reported a pronounced decline from 1999 to 2018 with prevalence rates of 19.9% and 3.2%, respectively, in the network of clinics under the SBN umbrella (Romão Jr et al., 2003; Neves et al., 2020).

These are optimistic findings, roughly comparable to those of a recent study in the United States (Deshpande et al., 2019). However, Brazil is a highly heterogeneous country, and results from pooled surveys of officially accredited clinics should be viewed with caution, as discussed below.

The surveys conducted by the SBN were not included in the current meta-analysis, with the caveats briefly summarized as follows: (i) they are not first-hand empirical studies, but rather web surveys, and the haemodialysis clinics complete the e-forms on a voluntary basis, with no subsequent double-checking; (ii) haemodialysis and peritoneal dialysis are frequently
pooled indistinguishably; and (iii) a progressive decrease in the proportion of services with valid responses has been observed over time, with a 37% response rate in 2018 (Neves et al., 2020).

Both the SBN web surveys and our own review were subject to biases, although to a much lesser extent in our review and meta-analysis. Empirical studies tend to be implemented in more accessible services with better infrastructure. Thus, neither our study nor the SBN surveys can properly overcome a key limitation that is more challenging than the customary publication bias. The latter do exist and was made evident in the trim and fill analysis. The procedures allow to include hypothetical studies inferred from the analysis and depicted as blank circles (Web Appendix 3).

Only services with some link to research groups have the opportunity to publish their results, but beyond this fundamental bias, some services are simply excluded from any assessment. Such services lack the necessary accountability. We believe that such “invisible” services are likely to perform worse with the management of equipment and supplies. Therefore, they may have higher rates of various infections, including HCV. However, this limitation cannot be addressed fully without a comprehensive nationwide survey including all haemodialysis clinics, regardless of affiliation with the SBN.

In our meta-analysis of studies implemented from 2001 to 2015, the summary measures were 11% for HCV prevalence (95%CI:8%-15%) and 9% for active HCV infection (95%CI:6%-13%), with pronounced heterogeneity. For the same period, estimates of HCV prevalence made available by the Brazilian Society of Nephrology varied from 4% to 17%, with a progressive decline over time, unfortunately in tandem with a progressive decrease in the proportion of services that provided valid responses to the SBN web survey itself (Romão Jr et al, 2003; Thomé et al., 2019).

It is essential to compare our findings with those of the single nationwide population-based survey on hepatitis C in Brazil. This probability survey, implemented in 2005-2009, found an overall estimate of 1.4%(95%CI:1.1%-1.6%) in Brazil’s general population (Pereira et al., 2013). Such figures are substantially lower than our summary measure for the pool of studies implemented after 2001 (11%). It appears clear that patients with CKD should be targeted with specific interventions to prevent HCV infection, and if prevention fails, prompt diagnosis and treatment.

Although the goal of HCV elimination by 2030 in Brazil appears elusive, especially in the context of the COVID-19 pandemic and budget restrictions (Greer et al., 2021), it is
possible and necessary to adopt measures to achieve micro-elimination in some settings and to launch initiatives towards targeted interventions to curb the spread of HCV among people with CKD, among other high-risk groups.

There are relevant limitations that recommend caution when interpreting the summary measures of our meta-analysis, as a valid synthesis for haemodialysis patients all over Brazil: i) there is pronounced heterogeneity between (and within) Brazil’s five major geographic regions. Our study basically addressed interregional heterogeneities in order to avoid dealing with the small numbers in intraregional heterogeneities; and ii) the under-representation of the Southeast, which is the most densely populated and most industrialized region of Brazil.

According to the National Censuses of 2000 and 2010 and estimates for 2020 by the IBGE (Brazilian Institute of Geography and Statistics, or National Census Bureau), more than 40% of all Brazilians live in the Southeast (IBGE, 2020). This region concentrates roughly 50% of the country’s haemodialysis services (Neves et al, 2020). According to our data, only 12.5% of the studies were conducted in services located in the Southeast, corresponding to 8.0% of the overall sample. Such pronounced underestimation appears to be associated with a high degree of redundancy: whereas some referral services have been repeatedly assessed by several studies over time, a fraction of services remain “invisible”. Due to the complexity and high costs associated with such procedures, it is unlikely that fully illegal services (i.e., not registered in the CNES, the Brazilian registry which is mandatory for the implementation of any legal health service) exist, as happens with low-complexity, informal facilities (Santos & Gerschman, 2004).

Our estimates of HCV prevalence (after 2001) for the five major geographic regions of Brazil included those published by the Brazilian Society of Nephrology for 2002: Northeast (12%); Central-West (12%); South (20%); Southeast (15%); and North (12%) (Romão Jr et al, 2003).

Both our study and the SBN survey highlight the South as the region of Brazil with the highest HCV infection rates in haemodialysis patients.

Considering the South of Brazil as a sentinel setting to target with preventive and/or curative interventions, it is important to note that HCV prevalence there (23%, 95%CI:9%-38%) is comparable (with overlapping 95%CIs) to the prevalence rates in Iraq (20%; 95%CI:12%-28%) and Turkey (23%;95%CI:18%-28%) and lower than the prevalence rates reported in Egypt (50%; 95%CI:46%-55%) and Syria (54%; CI95:50%-59%), according to a meta-analysis of studies conducted from 2006 to 2016 (Ashkani-Esfahani et al., 2017). For
historical reasons, Egypt has the world’s highest HCV rates (Kamal & Abdelhakham, 2018), and Syria has been affected by a prolonged civil war, impacting the country’s overall infrastructure, including health services (Abbara et al., 2015).

A review of articles published before 1999 highlighted marked heterogeneity in a wide range of countries. Although it is difficult to infer consistent information for such a large, heterogeneous pool of countries, one can easily conclude that before the 21st century, HCV control in haemodialysis patients was far from optimal everywhere in the world, as shown by the following HCV prevalence rates: 4-14% in the UK, 5-10% in Denmark, 12% in Sweden, 12% in India, 4-23% in Germany, 14%, 5-44% in the USA (Wreghitt et al., 1999). Rates as high as 71% in Kuwait or exceeding 40% in a long list of countries should obviously be defined as a totally uncontrolled situation and as a major source of new HCV infections. And this public health disaster struck when treatment was far from adequate.

With strict adherence to biosafety standards concerning equipment, supplies, and health workers and ancillary staff, most high-income and some middle-income countries have curbed various infections in haemodialysis patients. In Brazil, the impact of such procedures appears to be mixed, with some referral centres presenting infection rates comparable to high-income countries, whereas other centres present persistently high rates of various infections, including HCV. Overall, the situation is worrisome in several low-income countries (even when haemodialysis is available, not always the case) and middle-income countries (Bernieh, 2015). The lack of comprehensive multi-centre studies precluded a careful assessment of services located in the most deprived areas or the adoption of sound policies (Bernieh, 2015).

Several factors suggest that the available data underestimate the actual infection rates. High non-response rates and absence of documentation from some services have been mentioned before. In addition, even third-generation immunoassays can yield false-negative results. The latter tend to be especially relevant among immunosuppressed patients, as frequently happens with CKD patients in haemodialysis, including low and/or intermittent viremia, besides poor antibody responses (Constancio et al., 2018).

However, the abovementioned limitations should inform initiatives to improve surveillance and documentation, beyond any reasonable doubt, that HCV infection remains a serious concern among Brazilian haemodialysis patients. A substantial decrease has been observed, still far from optimal. Improvements have been uneven, with major advances in some services and no discernible improvement in others, where even the most basic information is simply lacking.
A comprehensive combination of preventive and curative initiatives should be adopted: prevention can be achieved through safer, state-of-the-art procedures (Nguyen et al., 2019), timely diagnosis and referral, and drug regimens with direct-acting antivirals (DAAs) presenting low levels of nephrotoxicity (Borgia et al., 2019). The literature has documented this as a feasible goal. Patients with CKD in haemodialysis units can and must be properly managed in order to prevent HCV infection, and in case they become infected, for them to be cured of hepatitis C, as recently reviewed by Brazilian researchers (Constancio et al., 2019).

As of 2018, there were 123,187 patients in Brazil with CKD and undergoing haemodialysis (Neves et al., 2020). The lack of proper surveillance and policies to curb the spread of HCV and prompt management and treatment tends to be a key source of sustained transmission and unnecessary suffering and avoidable deaths.
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Figure 1

Flow of information and stages of the systematic review
Figure 2

Prevalence rates of HCV infection and 95% credibility intervals in haemodialysis patients in Brazil from 1992 to 2015 according to major geographic region.

Figure 3
Prevalence rates for active HCV infection and 95% credibility intervals in haemodialysis patients in Brazil from 1996 to 2013 according to major geographic region of Brazil in which the studies were performed

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