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Vertical transmission of hepatitis C: Systematic review and meta-analysis

Lenka Benova[1,2], Yousra A. Mohamoud[1], Clara Calvert[2], Laith J. Abu-Raddad[1,3,4]
[1]Infectious Disease Epidemiology Group, Weill Cornell Medical College - Qatar, Cornell University, Qatar Foundation - Education City, Doha, Qatar
[2]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK
[3]Department of Healthcare Policy and Research, Weill Cornell Medical College, Cornell University, New York, New York, USA
[4]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA
Corresponding author: Lenka Benova, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom, Tel: +44 (0) 20 7636 8636, Email: lenka.benova@lshtm.ac.uk.

Alternate corresponding author: Laith J. Abu-Raddad, PhD, Infectious Disease Epidemiology Group, Weill Cornell Medical College – Qatar, Qatar Foundation - Education City, P.O. Box 24144, Doha, Qatar. Telephone: +(974) 4492-8321. Fax: +(974) 4492-8333. Email: lja2002@qatar-med.cornell.edu.

Key point summary

Updated pooled estimates of vertical Hepatitis C (HCV) infection risk to children of HCV RNA-positive mothers ranges between 5.8% and 10.8% depending on maternal HIV-co-infection. Additional risk factors need to be captured and reported by future studies.

Abstract

Background: We conducted a systematic review of estimates of hepatitis C virus (HCV) vertical transmission risk to update current estimates published over a decade ago.

Methods: PubMed and Embase were searched and 109 articles included. Pooled estimates of risk were generated for children born to HCV antibody positive and viraemic women, at age 18 months or older, separately by maternal HIV co-infection.

Results: Meta-analysis of the risk of vertical HCV infection to children of HCV-antibody positive and RNA-positive women was 5.8% (95% confidence interval [CI]: 4.2-7.8) for children of HIV-negative and 10.8% (95%CI: 7.6-15.2) for children of HIV-positive women. Adjusted meta-regression model explained 51% of the between-study variation in the 25 included risk estimates. Maternal HIV co-infection was the most important determinant of vertical transmission risk (adjusted odds ratio 2.56, 95%CI: 1.50-4.43). Additional methodological (follow-up rate and definition of infection in children) and risk factors independently predicted HCV infection and need to be captured and reported by future studies of vertical transmission. Studies assessing the contribution of non-vertical exposures in early childhood to HCV prevalence among children at risk of vertical transmission are needed.

Conclusions: More than one in every 20 children delivered by HCV chronically infected women is infected, highlighting that vertical transmission constitutes probably the primary transmission route among children. These updated estimates are a basis for decision-making in prioritization of research into risk-reducing measures, and inform case-management in clinical settings, especially for HIV-positive women in reproductive age.

Introduction

Hepatitis C virus (HCV) infection is an important global health issue, with as much as 2-3% of the world's population affected.[1, 2] Following the implementation of blood and blood product screening, vertical transmission has gained importance as the primary HCV transmission route among children.[3] Assessment of the burden of vertical transmission is essential in countries with high HCV prevalence, such as Egypt.[4] It is also important in countries where HCV is primarily contained in high-risk groups such as people who inject drugs, many of whom are of reproductive age and co-infected with HIV.[5]

Vertical transmission encompasses several potential transmission routes from an infected woman to her newborn - intrauterine, intrapartum and postnatal.[6-9]_ENREF_10 The risk of HCV vertical transmission has been assessed by several reviews.[10-13] Yeung et al (2001), the most recent systematic review and meta-analysis to provide the pooled risk of vertical HCV infection, showed that the risk was 1.7% among children born to all HCV-antibody positive women and 4.3%_ENREF_13_ENREF_13 among children of HCV RNA-positive women.[14] Presence of maternal HCV viraemia is a critical factor in mother-to-child transmission of HCV[11]_ENREF_14 and maternal human immunodeficiency virus (HIV) co-infection is an important risk factor. In children born to HCV-viraemic women, the odds of infection was found to be between 1.97 and 2.82 higher among those born to HIV-positive compared to HIV-negative mothers.[15, 16] While strongly associated with HIV co-infection, mother's injecting drug use appears to be an independent risk factor for HCV vertical transmission[17] and may be mediated by peripheral blood mononuclear cell infection.[18] There is some evidence that female children may be at higher risk of vertical infection.[19]_ENREF_14 Other factors, such as mother's age, parity, HCV genotype and breastfeeding do not appear to be associated with the

risk.[14, 20-24] While there is some evidence that prolonged rupture of membranes may increase vertical transmission risk,[24] caesarean section is not currently recommended as a risk-reducing intervention.[25]

The objective of this systematic review is to provide an updated global estimate of the proportion of infants who contract HCV through vertical transmission by identifying all relevant published studies. We produce pooled estimates of vertical transmission risk separately by maternal HIV co-infection and identify potential sources of between-study heterogeneity. The review benefits from over a decade of new evidence, and is important not only for primary research of potential interventions, but also essential for understanding and communicating the extent of this risk in clinical settings.

Methodology

Conceptual framework

In order to account for the importance of maternal HCV viraemia in determining the risk of vertical transmission, we developed a conceptual framework capturing the different types of vertical transmission risk estimates, based on presence of maternal HCV antibody and viraemia (Figure 1). This review focused on quantifying the vertical transmission risk to children of HCV-antibody positive and RNA-positive women (Pathway C).We also present a narrative summary of included estimates assessing Pathway A (children of HCV-antibody positive women irrespective of RNA status) and Pathway B (children of HCV-antibody positive but RNA-negative women).

Data sources and search strategy

The search was conducted on May 2, 2013 using PubMed and Embase databases, combining text and MeSH terms (including all subheadings) for vertical transmission of HCV (Supplementary Material 1). No time or language limitations were applied. Two authors (LB and YM) independently screened titles and abstracts to identify relevant studies. Differences between screeners were reconciled. Reference lists of identified systematic reviews were screened for additional studies. This review is reported according to the PRISMA guidelines (Supplementary material 2).[26]

Study selection

Two authors (LB and YM) independently screened all full text articles. Studies were included if the full-text version was available or if the abstract provided minimum information for inclusion. Articles must have analysed primary data to estimate the risk of vertical transmission (case-control studies were excluded), while specifying the age(s) of children at which HCV infection status was determined. Only studies using 2nd or later generation tests for determining HCV-antibody presence were included due to the limited sensitivity and specificity of first generation assays.[27, 28] If no information about the type of antibody test was provided, studies analyzing data collected before the year 1993 were excluded. If neither the HCV antibody test type nor the year of data collection were reported, we included studies published after 2003 in order to allow for a 10-year interval between the beginning of 2nd generation test availability and publication of findings.

Risk estimates of vertical transmission (datapoints) reported by studies were included if they assessed transmission risk among vertically exposed children (from HCV-antibody positive women). We excluded datapoints in which HIV status among the sample of mothers was mixed (combined groups of HIV-positive and HIV-negative mothers) or unknown (women were not

tested for HIV or HIV status not reported by the study), and studies with sample sizes of fewer than 11 children assessed for infection at follow-up. Clearance of viraemia among children with transient RNA positivity occurs at the median age of 15 months,[29, 30] while 95% of children diagnosed as uninfected lose maternal antibodies by 12 months of age.[31] In addition to circulating HCV viraemia, the presence of HCV antibodies at or beyond 18 months of age has been used as a surrogate measure of infection.[32] Therefore, only datapoints which assessed HCV vertical transmission risk in samples of children followed to age 18 months or older were included. If a study presented more than one datapoint derived from the same sample of children, the datapoint with the longest follow-up time was used.

Data extraction

Extraction of information about included datapoints was conducted using a structured form by one author (LB) and checked by a second (YM) in a random sample of 20% of studies. Two authors (LB and YM) independently repeated the extraction of all Pathway C datapoints. Extracted information included study type, year(s) and location of data collection, sample recruitment method, number of women included in the study, number of live births, age at assessment of children's HCV infection status and definition of HCV infection among children, as well as the number of children followed up and the number considered infected, separately by maternal HIV serostatus. The corresponding author of one study describing a Pathway C risk estimate was successfully contacted to confirm information.

Analysis

Meta-analysis of the proportion of infants diagnosed with HCV at the age of 18 months or older born to HCV-antibody positive and RNA-positive women (Pathway C) was carried out using Stata/SEv13 and R2.15.3, separately by mother's HIV status. The risk of HCV vertical transmission among children was calculated as the proportion of the number of children

diagnosed with HCV divided by the number of children assessed at follow-up. The variance of the raw proportions was stabilized using the Freeman-Tukey type arcsine square-root transformation.[33] Estimates were pooled using a DerSimonian-Laird random effects model.[34] Inverse variance weighting was used in pooled analysis. The I^2 value was calculated as a measure of heterogeneity, or the proportion of between-study variation in the risk estimate of vertical transmission due to differences between the studies and not chance.[35]

A meta-regression was conducted to identify sources of between-study heterogeneity in the risk of vertical HCV transmission. Eight potential sources of heterogeneity were specified *a priori*. Four of these factors related to vertical transmission or its ascertainment: maternal HIV status (positive/negative), type of women enrolled in the sample (random selection or routine screening during pregnancy or delivery/risk groups such as people who inject drugs and women previously diagnosed with HCV), age of children at ascertainment of HCV status (18-23 months/24-36 months/>36 months), and whether the definition of HCV infection in children included two or more positive RNA tests or persistent viraemia (yes/no and unclear). The remaining four factors related to characteristics of studies: sample size of children at the time of HCV diagnosis (10-49/50+), study design (prospective/retrospective), median year of study after 2000 (yes/no) and any loss to follow-up of enrolled infants in the study between birth and HCV diagnosis (yes/no). A multivariable meta-regression model was built by adding each variable sequentially starting with the variable which showed the strongest association with the vertical transmission of HCV in univariate analysis; a variable remained in the multivariable model if it was independently associated with the prevalence of vertical HCV transmission at $p \leq 0.10$.

Results

The search strategy identified 1792 potentially relevant studies and one additional reference was found by screening reference lists. From the 298 studies screened in full-text, 109 studies were included and 331 datapoints were identified (Figure 2). Application of inclusion criteria to datapoints resulted in the exclusion of 261 datapoints, the majority of which assessed children younger than 18 months. We also excluded four datapoints evaluating HCV infection status among vertically unexposed children (born to HCV-antibody negative women); none reported any cases of HCV infection.[36-39] All three conceptually defined vertical transmission risk pathways were captured by the 70 datapoints included in this review.

Among HCV-antibody positive and RNA-positive women (Pathway C), 25 datapoints extracted from 20 studies were included. The age of children at follow-up was between 18 and 23 months of age in 14 datapoints, 24 to 36 months in nine datapoints and 36-72 months in two datapoints. All 25 datapoints measured maternal HCV antibody and viraemia during pregnancy or at delivery. Four studies used RNA presence as the sole marker of infection in children; the remaining 21 studies used both HCV-antibody and RNA presence (two of these required presence of both, 19 the presence of either). Four studies defined HCV infection in children based on one RNA positive test and 19 required two or more RNA tests or persistent RNA positivity during follow-up. The estimates of HCV vertical transmission from HIV-negative women ranged from 1.1% to 10.7%, and among HIV-positive women from 4.2% to 28.5%. Meta-analysis of the 17 estimates among children born to HIV-negative women showed that the pooled risk of vertical HCV infection was 5.8% (95% confidence interval [CI]: 4.2%-7.8%), displayed in Figure 3. Based on eight datapoints, children born to HIV-positive women had a 10.8% (95%CI: 7.6%-15.2%) risk of HCV vertical transmission. There was some evidence of between-study heterogeneity among studies of HIV-negative women (I^2=45.9%, p=0.02), but not among HIV-positive women (I^2=28.8%, p=0.20).

In univariate meta-regression, only mother's HIV status (p=0.02) and sample size (p=0.03) influenced the between-study variation in the risk of vertical HCV transmission (Table 1). In a multivariable model, maternal HIV status (p=0.002), definition of HCV infection (p=0.03), age of child at HCV infection determination (p=0.01), selection of women (p=0.07), and loss to follow-up (p=0.08) were independently associated with variation in the risk of vertical transmission, together explaining 51.3% of the between-study heterogeneity. The higher odds of vertical transmission among samples of HIV-positive women compared to HIV-negative women (odds ratio 2.56, 95%CI: 1.50-4.43) supported separating the categories in meta-analysis. Additionally, the odds was higher in samples of children older than 36 months compared to children assessed at ages 18-23 months, and marginally lower among samples of mothers identified in screening compared to pre-identified or high risk group samples. Compared to studies requiring two or more positive RNA tests to diagnose HCV infection among children, the odds of vertical infection reported by studies using only one RNA positive test was 2.10 times higher (95%CI: 1.08-4.08).

Vertical transmission risk to children of HCV-antibody positive mothers irrespective of HCV viraemia (Pathway A) was described by 13 datapoints among HIV-positive mothers (range of estimates: 0.0% to 27.3%) and 17 datapoints among HIV-negative mothers (range of estimates: 4.5% to 40.0%). Among the 15 datapoints describing HCV vertical transmission in children born to HCV-antibody positive but RNA-negative women (Pathway B), only one case of a child diagnosed with vertically-acquired HCV infection was identified among the total of 473 children followed up by the studies._ENREF_41_ENREF_41

Discussion

This systematic review included over a decade of new evidence to construct pooled estimates of vertical HCV transmission risk; 17 of the 25 included datapoints were extracted from studies published since the last review in 2001. Our meta-analysis estimated the risk of HCV vertical transmission from HCV-antibody positive and HCV-RNA positive women who are HIV-negative at 5.8% (17 estimates, 95%CI: 4.2-7.8%) and among HIV-positive women at 10.8% (8 estimates, 95% CI: 7.6%-15.2%). The risk to children born to HCV-antibody positive RNA-negative mothers was negligible; the diagnosis of HCV in one child born to a non-viraemic woman was potentially related to intermittent maternal viraemia or laboratory error. If pregnant women were correctly classified as HCV-antibody negative, vertical transmission to their children should not occur in the absence of HCV viraemia. The available evidence, while limited to four studies, showed this to be the case.

The meta-regression technique allowed us to assess the influence of differences between studies. We found that the risk of HCV vertical transmission among children born to HIV-positive women was greater than double compared to those born to HIV-negative women. This finding is similar to previous studies, which suggested that the primary biological mechanism of this association is related to higher HCV viral load among women with HIV co-infection.[16, 40]
A large majority of the included Pathway C datapoints used a combination of HCV-antibody positivity and RNA positivity for diagnosis of HCV among children. However, limited HCV antibody clearance may occur after the age of 18 months and in the absence of viraemia may reflect late clearance of maternal antibodies or cleared infection.[32] The risk of vertical HCV infection derived from samples of older children was expected to be lower compared to younger children, in the absence of non-vertical HCV transmission. Our analysis showed that risk estimates of vertical HCV infection increased with higher age at HCV status determination, although this result was largely based on two estimates published by the same study.

A previous systematic review found that HCV vertical transmission risk to children born to HCV-antibody positive women was higher in studies requiring a minimum of two positive HCV-RNA results compared to studies with one or more positive RNA tests (7.1% and 3.9%, respectively), a result the authors attributed to variable study methods.[14]_ENREF_40_ENREF_48 While their pooled risk estimates cannot be directly compared with our analysis of a subset of children born to HCV-antibody positive and RNA-positive women, our results showed that the risk of HCV infection in children was lower when the more rigorous definition was applied, as would be expected when applying more stringent criteria.

Half of the between-study variation of all estimates in HCV-antibody positive RNA-positive women was explained by the adjusted meta-regression model. Additional methodological and/or biological sources of heterogeneity may therefore exist. The type of women enrolled into studies carried a marginal independent effect on the risk of vertical transmission. The categories capturing women's selection (routinely screened vs. pre-identified based on risk factors) may have acted as proxies for more specific mechanisms of association, such as history of injecting drug use. While these other mechanisms could explain the effect observed, their assessment was not possible due to inconsistent reporting by studies. The marginally higher risk among studies reporting any loss to follow-up of children may be explained by higher likelihood of remaining in observation for children with early HCV-RNA positivity, who are also more likely to be diagnosed with infection. Potential selection bias may have originated from low enrollment rates in studies, but this factor was not consistently reported in studies and therefore not included in the meta-regression.

We identified potential sources of heterogeneity prior to conducting meta-regression in order to reduce the likelihood of identifying spurious associations. However, the results of the meta-

regression should be interpreted with caution. Only 25 datapoints capturing risk of vertical transmission from HCV-antibody positive and RNA-positive women were included in the meta-regression, resulting in small numbers of studies in some categories. The meta-regression results may be subject to residual confounding and the associations identified on the level of studies may not operate in the same direction or magnitude on the individual-level. Another limitation of this study includes a search strategy focused on two databases of published literature and it is possible that unpublished studies of HCV vertical transmission were not identified. We excluded 13 studies from non-English language journals on the basis of unavailability of full-text. During full-text screening, we may have excluded some valid estimates because the HCV-antibody test generation was not specified. However, the number of such studies was small and their absence unlikely to have significantly biased the results.

The body of evidence assessing risk factors of HCV vertical transmission, including this systematic review, is based solely on observational studies. No interventions during pregnancy or at the time of delivery have been demonstrated to reduce the risk.[24] The current treatment regimen of pegylated interferon and ribavirin is contraindicated during pregnancy[13] and new treatments have not yet been evaluated for use in pregnant women.[41, 42] The proportion of datapoints from low- and middle-income countries was considerably lower among included datapoints (4%, 3/70) compared to all identified datapoints (18%, 60/331). More rigorous primary research from different contexts is needed to identify remaining sources of heterogeneity, such as delay in HIV diagnosis and treatment.

This systematic review provided updated pooled estimates of HCV vertical transmission risk. We developed a conceptual framework to identify transmission pathways based on maternal HCV antibody and viraemia. In line with previous evidence, we showed that vertical transmission risk appeared limited to infants of viraemic mothers, where it ranged between 5.8%

and 10.8% depending on maternal HIV co-infection. This study highlighted the importance of using a standard definition of HCV infection in vertically exposed children. Additional risk factors warrant further examination in primary research, namely maternal HIV treatment and HCV genotype. Such research would contribute to quantifying the contribution of HCV vertical transmission to HCV incidence in high-burden countries and in high-risk populations globally. In summary, more than one in every 20 children delivered by women chronically infected by HCV is vertically infected. These updated estimates can serve as a basis for decision-making in research into risk-reducing measures as well as inform clinical case-management.

Notes

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Disclosures

The authors have no reported conflicts of interest.

Authors' contributions

LB and LJA-R conceptualized the study, LB and YAM conducted the literature search, screened references and extracted data. LB YAM and CC conducted data analysis, and wrote the first draft of the article. All authors contributed to the interpretation of findings and drafting of the manuscript.

List of Abbreviations

CI confidence interval

HCV hepatitis C virus

HIV human immunodeficiency virus

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Table 1: Meta-regression model

		Number of datasets	Univariable		Multivariable[2]	
			OR (95% CI)	P-value	AOR[1] (95% CI)	P-value
Mother's HIV status	HIV negative	17	1		1	
	HIV positive	8	2.12 (1.14-3.94)	0.02	2.56 (1.50-4.43)	0.002
Definition of infection includes two or more positive RNA tests	Yes	21	1		1	
	No	4	1.61 (0.68-3.84)	0.26	2.10 (1.08-4.08)	0.03
Selection of mothers	Routine screening	14	1		1	
	Pre-identified/risk factors	11	1.21 (0.63-2.33)	0.55	1.82 (0.95-3.48)	0.07
Age of child at determination of HCV status	18-23 months	14	1		1	
	24-36 months	9	0.85 (0.44-1.64)		1.62 (0.81-3.26)	
	>36 months	2	2.76 (0.87-8.80)	0.15	4.99 (1.91-13.06)	0.01
Sample size of children assessed at follow-up	11-49	12	1			
	50+	13	0.52 (0.29-0.93)	0.03	-	
Study design	Prospective	21	1			
	Retrospective	4	1.24 (0.51-3.02)	0.61	-	
Median year of study after 2000	No	20	1			
	Yes	5	1.35 (0.54-3.39)	0.50	-	
Loss to follow-up between birth and HCV status determination	No	21	1		1	
	Yes	4	1.56 (0.66-3.73)	0.30	1.88 (0.91-3.85)	0.08

[1] Adjusted odds ratio. [2] Total between-study variation explained by final multivariable model: 51.3%.

Figure legends

Figure 1. Conceptual framework for categorizing study estimates of HCV vertical transmission risk

Figure 2. Study selection for inclusion in the systematic review and meta-analysis

Figure 3. Pooled estimates of risk of HCV vertical transmission among children 18 months and older born to HCV-antibody positive and RNA-positive mothers, by maternal HIV serostatus

Figure 3 references

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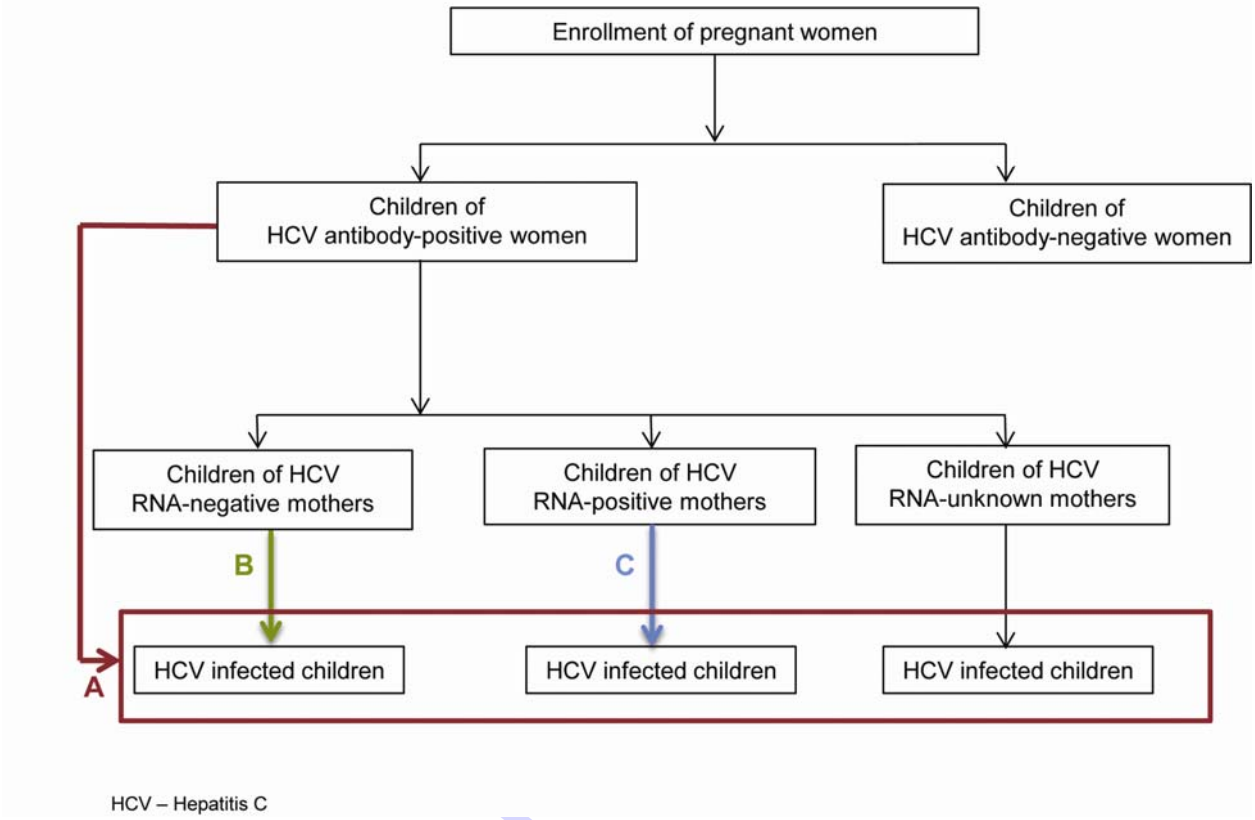
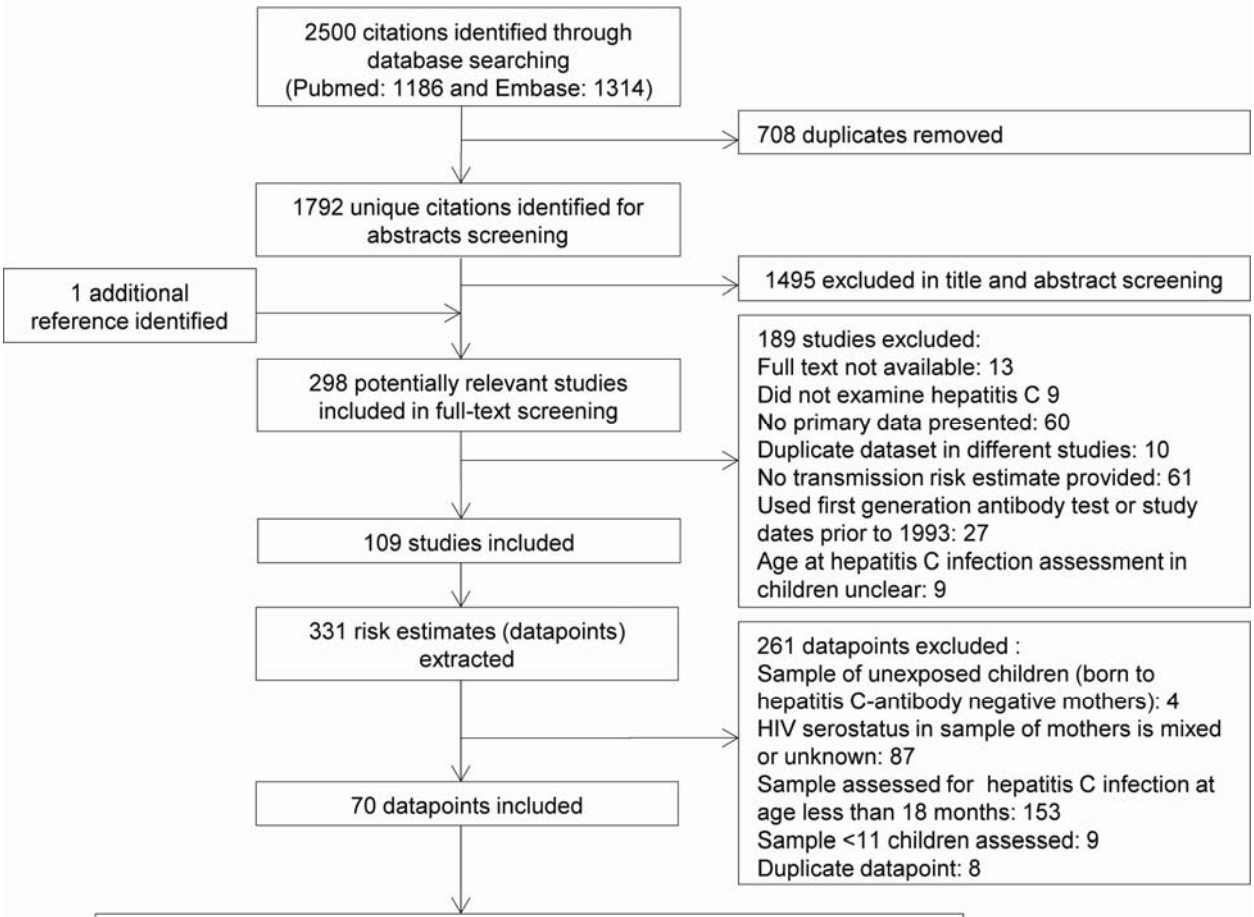
Figure 1.



HCV – Hepatitis C

Figure 2.



	Total	Pathway A	Pathway B	Pathway C
Number of datapoints	70	30	15	25
Maternal HIV status				
HIV-negative	46	17	12	17
HIV-positive	24	13	3	8
Country income level				
Low/middle	3	1	1	1
High	67	29	14	24
Study type				
Prospective	62	26	15	21
Retrospective	8	4	0	4

Pathway A describes vertical transmission from all HCV-antibody positive women, Pathway B from HCV-antibody-positive RNA-negative women and Pathway C from HCV-antibody-positive RNA-positive women. Country income level categories were based on World Bank classification.

Figure 3. Pooled estimates of risk of HCV vertical transmission among children 18 months and older born to HCV-antibody positive and RNA-positive mothers, by maternal HIV serostatus