SPONTANEOUS CLEARANCE OF VERTICALLY ACQUIRED HEPATITIS C INFECTION: IMPLICATIONS FOR TESTING AND TREATMENT

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Summary: Based on the largest purely prospective dataset assembled so far, 66% (50-82) of confirmed vertically acquired HCV clears spontaneously by age 5 years, rather than the 25-40% assumed in guidelines.

Abstract

Background. Current guidelines recommend that infants born to women with hepatitis C (HCV) viremia are screened for HCV antibody at age 18 months, and if positive, referred for RNA testing at 3 years to confirm chronic infection. This policy is based in part on analyses suggesting 25%-40% of vertically acquired HCV infections clear spontaneously within 4-5 years.

Methods. Data on 179 infants with HCV RNA and/or anti-HCV evidence of vertically acquired infection in three prospective European cohorts were investigated. Ages at clearance of infection were estimated taking account of interval censoring and delayed entry. We also investigated clearance in initially HCV RNA negative infants in whom RNA was not detectable until after 6 weeks.

Results. Clearance rates are initially high then decline slowly. Apparently, many infections clear before they can be confirmed. An estimated 65.9% (50.1-81.6) of confirmed infections cleared by 5 years, at a median 12.4 (7.1-18.9) months. If treatment began at age 6 months, 18 months or 3 years, at least 59.0% (42.0-76.9), 39.7% (17.9-65.9), and 20.9% (4.6-44.8) of those treated would clear without treatment. In seven (6.6%) confirmed infections, RNA was not detectable until after 6 weeks, and in 2 (1.9%) not until after 6 months. However, all such cases subsequently cleared.

Conclusions. Most confirmed infection clears by age 3 years. Treatment before age 3, if it was available, would avoid loss to follow-up, but would result in substantial over-treatment.

Keywords: Hepatitis C virus; HCV; vertical transmission; spontaneous clearance; over-treatment

The development of highly effective direct acting antiviral (DAA) treatment for HCV [1, 2] has raised the possibility that vertically acquired infection, which occurs in 5%-6% of deliveries to HCV RNA positive mono-infected women [3, 4], could be prevented or treated [5]. Screening of women in pregnancy, followed by treatment in late pregnancy or postnatally, as well as treatment of infected infants, have both been considered [2, 6], and could contribute substantially to the WHO targets to eliminate HCV by the year 2030 [7]. However, treatment in pregnancy is not currently recommended in spite of good safety profiles [8]. DAA treatment in children is approved from age 3 years in the European Union and the USA, and WHO recommendations for lower and middle income countries (LMICs) are under review [9-12]. Work on pediatric formulations and pharmacokinetic studies is ongoing.

Diagnosis of HCV infection in infants exposed in utero is based largely on the presence of HCV antibodies (anti-HCV) at 18 months [10-13]. Those who are anti-HCV positive are referred for RNA testing at age 3 years to confirm chronic infection [10].

The policy of deferred testing and treatment is supported by the assumption in recent reviews and guidelines that 25%-40% of vertical infections clear spontaneously by age 5 years [10-12, 14].However, little attention has been given to the precise timing of clearance during infancy. The literature (see Supplementary materials for a review) includes studies of infants tested at delivery (Supplementary Table S1), and studies in which children have not been tested regularly from birth and which may miss early clearance Supplementary Tables S2, S3). In some studiesinfants were recruited retrospectively and inclusion depended on a period of sustained follow-up, potentially resulting in selective inclusion of non-clearers. The 25%-40% clearance estimate derives from the European Pediatric HCV Network (EPHN) study [15], which included 40% retrospectively recruited children.

In addition, previous estimates have not taken account of interval censoring or left truncation in the data. Interval censoring refers to the fact that the age at clearance is never observed, only the ages at the last positive HCV RNA test and the first negative one. Left truncation, also known as "delayed entry", occurs if the first HCV RNA positive is not at or shortly after delivery: this would result in early clearance being missed. Failure to account for either of these features will tend to underestimate clearance and produce a biased picture of its timing.

To better inform guidance on testing and treatment, we therefore sought to obtain unbiased estimates of both the extent and timing of spontaneous clearance of confirmed infection by using a large, purely prospective dataset of infants born to HCV infected women, followed from birth, using statistical methods appropriate for the interval censored and left-truncated data.

We also investigated clearance of viremia, which includes both confirmed infection and cases where evidence for vertically-acquired HCV is based on a single positive RNA result. Previous authors [16] have referred to the latter as transient infections.

Finally, only about 40% of vertical infections can be detected at delivery, but most are HCV RNA positive by 4 to 8 weeks [17, 18]. However, the literature contains numerous reports of infected infants who remain HCV RNA negative for several months [19, 20]. This complicates management of infants at risk of vertical infection. Accordingly, we investigated the frequency of late appearance of detectable RNA in infected infants, and clearance in this group.

METHODS

Sources of data

We approached the investigators of 21 published prospective studies which followed over 100 HCV-infected pregnant women and their infants. Three agreed to contribute patient-level data: the European Pediatric HCV Network (EPHN) [3, 17, 21]; the British Pediatric Surveillance Unit (BPSU) study, including data from three maternity hospitals in Dublin [22]; the ALHICE study (Alpes-Maritimes, Languedoc, Haute Garonne Infection C chez l'Enfant) [23]. The risk factor distributions, periods of recruitment, and follow-up schedules are summarized in Supplementary Table S4. All infants followed up in these cohorts who met the definition of either confirmed infection or viremia (see below) were included in this analysis. The Faculty of Health Sciences Research Ethics Committee, University of Bristol, approved these analyses of historic data.

Definitions of infection and clearance

Confirmed infection: detection of RNA on at least two occasions, or of anti-HCV after 18 months. *Viremia:* as for confirmed infection, but only one positive RNA required. Confirmed infections are therefore included in viremias. C*learance:* To qualify as a clearer the child's last RNA test, or in the absence of an RNA test, the last HCV antibody test, had to be negative. In view of the high negative predictive value of these tests [24, 25] only a single marker of clearance was required, either a negative RNA or a negative anti-HCV test. Clearance was considered to have occurred before the date of the first of two consecutive negative markers, and after the immediately preceding positive RNA test. If there was only one (final) marker of clearance, it was considered to have occurred before that marker. Observations were subject to delayed entry: infants were not considered at risk of clearance until after their first positive HCV RNA test.

A two-marker criterion of clearance was included as a sensitivity analysis, in which the single (final) HCV RNA negative was considered as a censored observation rather than as a clearance. See Supplementary material for further details and supporting information.

Statistical methods

Restricted cubic spline time-to-event ("survival") models [26] were fitted with clearance as the end-point, taking interval censoring and delayed entry into account. Cubic splines are flexible models that can fit data smoothly, with the maximum number of "bends" controlled by the user. We allowed for clearance rates with up to two turning points (i.e. rising initially then falling, or vice versa). More complex patterns were considered implausible. Estimation was carried out by Bayesian Markov Chain Monte Carlo. Because spline models can be unstable, three commonly used parametric models (Weibull, lognormal and log-logistic) with additional cure parameters were used as sensitivity analyses. Further details of models and program code are shown in Supplementary materials.

Based on the estimated clearance curve for confirmed infection, we calculated the proportion of *all* infected children who would be potentially "over-treated" if treatment was begun at 6, 18, or 36 months in the sense that they would have cleared spontaneously in the absence of treatment (Public Health perspective). We also calculated the proportion of *treated* infections that would have cleared anyway if treatment began at those ages (Clinical perspective). These calculations assumed that there was no further clearance after age 5 years (See Supplementary materials).

Finally, we identified infants with at least one positive RNA test, but whose first RNA test was negative. Those who met the definition of confirmed infection, and who were still RNA negative until after 6 weeks of age, were selected for a record review.

RESULTS

Age at testing and clearance and numbers at risk

106 infants met the definition of confirmed infection, of whom 36 cleared; 179 were viremic at some point (including those with confirmed infection), of whom 87 cleared. Only 25 (26.4%) of the 106 confirmed infections and 55 (30.7%) of the 179 with viremia, were tested in the first 3 days of life, of whom 9 (36.0%) and 23 (41.8%) respectively were positive. The median age at the first HCV RNA positive test was 2.9 months in the confirmed infection cohort, and 2.6 months in all those with viremia. Median ages at the first test were 1.0 months and 0.9 months respectively.

Table 1 documents the ages at which children entered the risk set (the age of their first positive HCV RNA test), alongside the approximate age at clearance, age at loss to follow-up (censoring), and the numbers at risk at each age. Illustrating the delayed entry, the number at risk increases initially as more children are tested and enter the risk set. Note that only 54.8% of those with confirmed infection had entered the risk set by age 3 months, and only 57.5% of those with viremia.

Time to clearance of infection

57.3% (44.7-69.9) of those with confirmed infection cleared by 3 years and 65.9% (50.1-81.6) by five years (Figure 1, panel A). Among those who clear in 5 years the median age at clearance is 12.4 months (7.1-18.9). Viremia cleared very rapidly, mostly within three months (Figure 1, panel A), with 79.6% (95%CrI: 69.0-89.7) clearing by 12 months, and 90.6% (83.5-95.9) by 5 years. The rate at which clearance occurs, the risk per month, declines markedly over time (Figure 1 Panel B, note the log scale) although the rate of decline is less with confirmed infection.

Risk of "over-treatment"

Table 2 considers scenarios with treatment administered at different ages. Taking a public health perspective, and assuming no further clearance after age 5, 12.8% (3.8-23.1) of *all* confirmed infections would be over-treated if treatment was begun at 36 months (Table 2), compared to 33.6% at 18 months, and 74.3% at 6 months. Taking a clinical perspective, if treatment began at age 36 months, 20.9% (4.6-44.8) of *remaining* infections – i.e. of the infections that would be actually treated – would be expected to clear without treatment, compared to 39.7% at 18 months and 59.0% at 6 months.

Time to detectable RNA

A record review of the 7 babies (6.6% of the 106) who were initially HCV RNA negative and in whom confirmed infection was not detected until after 6 weeks is shown in Table 3. In most cases there were more than 2 positives, and more than 2 final negative tests, so it is unlikely that either the diagnosis of infection or of clearance are due to diagnostic errors. However, in 5/7 cases there was only a single initial negative test over 6 weeks, and there is a possibility these were false negatives.

In 4 cases, RNA was not detected until after negative findings at age 3 months, and in 2 cases after 6 months. However, all 7 cases eventually became RNA negative between 12 and 44 months, 6 meeting the criteria for confirmed clearance. Two, however, were anti-HCV positive at 17.9 and 44 months respectively and had experienced ALT levels over 80 IU/l. The risk factors for the 7 infants were unremarkable; 3/7 (43%) had breastfed, compared to 28% in the whole EPHN cohort (Supplementary Table S4).

Sensitivity analyses

For both confirmed infection and for viremia, there were no material differences between the preferred cubic spline model and the three parametric survival models in either model fit, median time to clearance, or estimated age at clearance (Supplementary Tables S5, S6). Two of the three parametric models, the lognormal and log-logistic, allow clearance rates to either rise initially then fall, or to fall continuously. For the confirmed infection dataset both these parametric models fitted a clearance rate with a brief initial rise, confirming what was seen with the spline model (Figure 1 Panel B).

Of the 36 infants clearing on a one-marker criterion, 27 cleared on the stricter two-marker definition. As expected, somewhat less clearance was observed with the two-marker criterion, but there was little impact on estimated risks of "over-treatment" if treatment was given at age 36 months.

DISCUSSION

Based on data from three cohort studies following prospectively recruited vertically infected infants from birth, we estimate that 57.3% (44.7-69.9) of confirmed infection clears by age 3 years, and 65.9% (50.1-81.6) by 5 years. These estimates are substantially higher than the 25-40% clearance rates that are commonly cited [5, 12, 27], which are partly based on datasets in which infants have either not been tested and followed from birth, and which have therefore missed cases of early clearance, or studies which have included retrospectively recruited infants. Studies in which clinics are asked to both retrospectively include children and then follow them prospectively may be especially vulnerable to bias, unless they include all those who have already been discharged or otherwise lost to follow-up at the time the clinic joins the study.

Our finding that 90.6% (95%CrI 83.5-95.9) of vertically acquired viremia clears by 5 years, mostly before 3 months, is entirely consistent with studies in which children are tested at birth and in which a single RNA test is taken as indicative of potential infection (Supplementary Table S1). In the largest study of this sort [16] 75% had cleared by 1.8 years, and all those who were RNA positive at delivery – nearly 30% of the total infected – had cleared by 4 months. This illustrates how, by taking delayed entry into account, our analysis is able to recover estimates that are similar to these studies, even though testing at delivery was infrequent in our dataset.

Current guidance recommends testing for HCV antibodies at 18 months and referral of positives for RNA testing at 3 years to confirm chronic infection prior to treatment [10]. A focus on treatment of chronic infection is reasonable at this time when no treatments are available under age 3. However, this strategy may not be sustainable longer term. Loss to follow-up between 50% and 80% has been reported in a number of US studies [28-30], with less than 50% of children followed to 18 months [31]. Higher follow-up rates should be achievable in well-resourced countries with centralized health systems, but follow-up to even 6 months may be seen as ambitious in lower and middle income countries, where delayed treatment may in many cases result in no treatment, with an attendant risk of liver disease and onward transmission [5].

Earlier treatment, were it to become available, could avoid much of the loss to follow-up, but our results show that this would be at the cost of a substantial degree of over-treatment. Assuming no further clearance after age 5 years, we projected that 33.6% *all* confirmed infections, and 39.7% of all *treated* infections, would clear spontaneously if treatment was administered at age 18 months, and 74.3% and 59.0% at age 6 months. These figures compare to 12.8% and 20.9% over-treatment at the currently recommended age of 3 years. However, if safe, affordable, and effective treatment before age 3 years was available, the

additional over-treatment might be considered a price worth paying to avoid risking loss to follow-up and no treatment.

The extent of over-treatment will be greater if further clearance occurs after age 5 years. Clinic-based studies (Supplementary Table S3) suggest 2.3%-29% clearance after 5 years but these estimates cannot be relied on for reasons given above. More data on rates of clearance after age 3 years would be valuable as the credible intervals on our estimates are wide.

Another reason why delayed treatment is preferred is the difficulty of early diagnosis. While HCV RNA results between 2 and 6 months correlate well with antibody at 18 months [10], it has been reported that 11% (5%-20%) of infected children do not become HCV RNA positive until after age 3 months [22], and there are isolated reports of late-appearing RNA throughout the literature [19, 20], and even *re*-appearance of infection after apparent clearance [16, 32]. In our study 7 of 106 confirmed infected babies were still RNA negative after 6 weeks, including 2 after 6 months. Although it is reassuring that all these cases eventually cleared, this is a too small sample to justify early diagnosis based on HCV RNA. If earlier diagnosis is to be considered, sufficient time must be allowed for all vertical infections to either clear or to become manifest.

Given the risk of over-treatment, and the difficulties surrounding diagnosis and follow-up, treatment in pregnancy to prevent transmission in pregnancy may be a better strategy than treatment of pediatric infection. However, infants born to mothers treated in pregnancy will still require follow-up and testing, at least until the efficacy of treatment in pregnancy is established.

Although this is the largest purely prospective dataset assembled to date, there are important limitations. Foremost is the historical nature of our dataset, collected between 1994 and 2004, when HCV RNA testing was less accurate and less standardized, so that it was not possible to

use quantitative RNA results. This emphasizes the need for additional data. A further difficulty is that confirmed infection is not a well-defined construct: estimates of both the VT rate and the extent of clearance both depend on the precise details of the definition and on the intensity of the follow-up schedule, as noted previously [16, 19]: more frequent testing will result in higher VT rates and more clearance. However, the frequency of testing after delivery in our data approximates the schedule that might be expected in contemporary trials. The pattern of clearance reported here underscores the need to estimate vertical transmission rates "net" of clearance at different ages. This is the subject of a companion paper based on the same three cohorts.

The significance of a single positive virological marker that clears in the first 3 months is unclear. If these are true infections, as opposed to non-replicating viral fragments, then the underlying vertical transmission and spontaneous clearance rates are both very much higher than has been thought. Our results and methods may also be relevant to other vertically acquired infections such as hepatitis B, where there are similar complexities introduced by early clearance of virological markers in the exposed newborn [33, 34].

This paper has clarified the extent of spontaneous clearance and has thrown new light on its timing. It has set out for the first time the statistical and study design considerations required to obtain unbiased estimates, and has introduced methods for estimating of the extent of potential over-treatment. However, our estimates are relatively uncertain and more accurate information on both vertical transmission, clearance rates, and time to detectable RNA is needed. For this we must await large-scale randomized trials of early treatment or treatment in pregnancy. In the meantime, routine testing of anti-HCV in antenatal or neonatal samples, now recommended in the USA [35] and shown to be cost-effective at a prevalence of 0.07% [36], would allow HCV RNA positive infants to be identified and followed until treatment is available.

Notes

Author contributions AEA conceived and carried out the analyses with the assistance of FG. AEA wrote the first and subsequent drafts of the paper. KS carried out the literature search and review. AEA, AJ, JC, and DMG were co-investigators on the HCVAVERT project, and AJ was the principal investigator. EC was a researcher on the HCVAVERT project. LP, EM-B, DMG and KB were senior or principal investigators on the 3 contributing studies: EPHN (European Pediatric HCV Network); ALHICE (Alpes-Maritimes, Languedoc, Haute Garonne Infection C chez l'Enfant); BPSU (British Pediatric Surveillance Unit). GI provided clinical input on hepatology and management of pediatric HCV. Curation of the original data files available to the project was the responsibility of LP and CT (EPHN), DMG, JC and KB (BPSU), and EM-B (ALHICE). Subsequent data processing was by FG and AEA. All authors critically reviewed and revised drafts as necessary, and approved the final version for submission.

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Potential conflict of interest CT is a member of the Infectious Disease in Pregnancy Screening Programme Advisory Board, Public Health England and reports grants or contracts from European Commission, Child Health CIO, Public Health England, Penta Foundation, and ViiV Healthcare via Penta Foundation all paid to the institution outside of the submitted work and payment or honoraria from ViiV Healthcare paid to self. EC reports grants or contracts from ViiV Healthcare to the institution via the Penta Foundation outside of the submitted work. IJC reports Medical Research Council Global Health Trials Development grant and Gilead HCV Elimination competitive grant both paid to the institution and outside of the submitted work. No other author had conflicts to disclose.

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Table 1. Age at first test, age at clearance, and number at risk of clearance for confirmed infection and viremia.

Age band	Confirmed infection				Viraemia			
	First tested HCV RNA positive (cumulative % of 106)	Number cleared [1] (% of 36)	Number lost to follow-up (% of 70)	Number at risk [2]	First tested HCV RNA positive (cumulative % of 179)	Number cleared[1] (% of 87)	Number lost to follow-up (% of 92)	Number at risk [2]
0 - 3d	9 (8.5)	0 (0)	0 (0)	9	23 (12.8)	0 (0)	4 (4.3)	23
3d - 6w	26 (33.0)	0 (0)	1 (1.4)	35	45 (38.0)	5 (5.7)	2 (2.2)	64
6w - 3m	22 (53.8)	1 (2.8)	0 (0)	56	35 (57.5)	7 (8.0)	5 (5.4)	92
3m - 6m	26 (78.3)	7 (19.4)	10 (14.3)	81	44 (82.1)	28 (23.0)	17 (18.5)	124
6m-12m	14 (91.5)	7 (19.4)	13 (18.6)	78	22 (94.4)	22 (25.3)	17 (18.5)	101
12m-24m	6 (97.2)	16 (44.4)	22 (31.4)	64	6 (97.8)	20 (23.0)	21 (22.8)	68
24m-36m	3 (100)	3 (8.3)	14 (20.0)	29	4 (100)	3 (3.4)	16 (17.4)	31
36m-60m	0 (100)	2 (5.6)	8 (11.4)	12	0 (100)	2 (2.3)	8 (8.7)	12
>60m	0 (100)	0 (0)	2 (2.9)	2	0 (100)	0 (0)	2 (2.2)	2
TOTAL	106	36	70		179	87	92	

[1] The numbers shown cleared no later than in the period indicated, but may have cleared in an earlier period, depending on when they were first tested positive.

[2] The numbers at risk include those who have entered the risk set, minus those who have cleared or were lost to follow-up in previous time periods.

Table 2. Projected proportion "over-treated" in that they would be expected to clear without treatment. (A) Public Health perspective: estimated proportion of *all confirmed infections* that would be potentially over-treated, if treatment began at each age. (B) Clinical perspective: estimated proportion of *remaining confirmed infections* over-treated at each age.

Age at treatment, months	**Percent of all infections that will clear without treatment (95% CrI)**	**Percent of all remaining infections that will clear without treatment (95% CrI)**
6	74.3 (54.3-87.6)	59.0 (42.0-76.9)
18	33.6 (17.0-51.8)	39.7 (17.9-65.9)
36	12.8 (3.8-23.1)	20.9 (4.6-44.8)

Table 3. Record review of 7 infants meeting the definition for Confirmed Infection (at least two positive RNA tests) who were initially RNA negative, and who remained RNA -ve until after 6 weeks. Ages in months

Case	Age last RNA –ve	No. of initial RNA -ves > 6w	Age first RNA +ve	Number of RNA +ves	Age last RNA+ve	Number of final RNA -ves	Age last antibody +ve	Age first antibody -ve	Ever breastfed	Mode of delivery	Mother HIV	Mother PCR	Infant HIV	Highest ALT, IU / L	Hepatomegaly
1	2.7	1	6.4	2	9.7	3	9.7	14.1	Yes	EC-S	Neg	Pos	No	40-80	No
2	2.7	1	15.0	2	17.9	2	2.7	23.9	Yes	EC-S	Neg	Neg	No	40-80	No
3	3.0	2	6.0	3	18.0	3	6.0	11.8	Yes	Other	Neg	Pos	No	40-80	No
4	6.1	1	8.8	4	44.0	1	44.0	-	No	EC-S	Neg	NK	No	>80	Yes
5	6.8	2	10.5	3	32.4	3	10.5	14.4	No	Other	Neg	Pos	No	<40	No
6	1.9	1	5.8	5	12.3	2	1.9	5.75	No	EC-S	Neg	NK	No	<40	No
7	1.7	1	1.9	3	25.9	4	17.9	-	No	Other	Neg	Pos	No	>80	No

EC-S: Elective Caesarean Section. NK: not known

Figure Captions

Figure 1. Panel A: Proportion remaining infected by age (months) with 95% credible error bars. **Panel B**: Rate of clearance per month with 95% credible error bars on a log scale. Solid line confirmed infection, dotted line viremia.

Figure 1