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Estimate of vertical transmission of Hepatitis C virus in Pakistan in 2007 and 2012 birth cohorts

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Summary

Despite a combination of high Hepatitis C virus (HCV) prevalence, a large adult population and high fertility, no published estimates of the scale and contribution of vertical transmission to HCV incidence in Pakistan exist. The objective of this study was to estimate the number of new HCV infections occurring in Pakistan as a result of vertical transmission. We adapted a published mathematical model based on HCV antibody and viraemia prevalence, fertility rates, risk of HCV vertical transmission and children mortality rates to estimate the number of infections in the 2007 and 2012 birth cohorts nationally and in four subnational regions. We estimated that 19 708 (95% uncertainty interval [UI]: 15 941-23 819) children were vertically infected by HCV in 2007 and 21 676 (95% UI: 17 498-26 126) in 2012. The majority of these cases (72.9% and 72.5% in 2007 and 2012, respectively) occurred in Punjab. We estimated that vertical transmission as a mode of exposure accounted for a quarter of HCV infections among children under 5 years of age (25.2% in 2007 and 24.0% in 2012). **Conclusion:** Our results showed that one in 260 children born in Pakistan in 2007 and 2012 acquired HCV vertically. While currently no interventions during pregnancy and childbirth are recommended to reduce this risk, prevention, testing and treatment strategies should be considered to reduce the burden of vertical HCV infections among young children. Other routes of transmission appear to contribute the majority of HCV infections among children and must also be clarified and urgently addressed.

KEYWORDS
infant, infectious disease transmission, mother-to-child transmission, pregnancy, transmission routes

1 | INTRODUCTION

Pakistan is a country with one of the highest adult prevalence of Hepatitis C virus (HCV) in the world.[1] A recent systematic review estimated a high overall prevalence of serological evidence of HCV infection (HCV antibody [HCV-Ab] positivity) at >5% among the general adult (15 years and older) population, but noted higher levels in poorer rural and peri-urban areas, and among high-risk populations, such as intravenous drug users, multitransfused patients, prisoners and dialysis patients.[2] The most common HCV genotype in Pakistan appears to be 3,[3] but genotype 2 is also widespread in some provinces.[2,4,5] Pakistan has the second largest adult viraemic population in the world at about seven million,[1,6] the vast majority of which remains undiagnosed.[7,8] Its population of 189 million (2015) is expected to grow by more than 1.7% annually by 2025,[9] due to a relatively high total fertility rate (3.8 per woman in 2012).[10] The combination of high HCV prevalence, a large affected adult population and high fertility draws

Abbreviations: ASFR, age-specific fertility rates; CI, confidence interval; DHS, Demographic and Health Surveys; HCV, Hepatitis C virus; HIV, human immunodeficiency virus; NWFP, North-West Frontier Province; UI, uncertainty interval.

focus to the potentially important scale and contribution of vertical transmission to the HCV epidemic in Pakistan.

Six studies (none nationally representative) assessed HCV-Ab prevalence among pregnant women and found that it ranged from 1.8% to 8.6% with a mean of 4.5%, similar to the level in the general population.[2] Only one of these studies, conducted in Karachi, assessed present HCV infection (HCV RNA positivity) among HCV-Ab-positive women (79.7%),[11] comparable to population-level viraemia prevalence among HCV-Ab+ cases globally.[1,8,12-14] Nosocomial transmission appears to be the most important contributor to the ongoing epidemic, and particularly so among women.[2,15,16] Factors found to be associated with HCV-Ab positivity among pregnant women included history of blood transfusion, therapeutic injection use, surgery and sharing household items.[17-19] Additionally, dental procedures and dilatation and curettage, low socio-economic status (including low education and rural residence) and older age were identified as associated with HCV-Ab positivity among females.[20-24]

The most recent population-based nationally representative prevalence survey in Pakistan conducted between July 2007 and May 2008 showed overall HCV-Ab prevalence of 4.9% (95% CI: 4.7-5.1), with no statistically significant difference between the sexes.[25] Regional prevalence varied from a high of 6.7% (95% CI: 6.4-7.0) in Punjab to 1.1% in (95% CI: 0.9-1.3) in the North-West Frontier Province (NWFP).[25] Prevalence among children under 5 years in this survey was found to be 1.9%, meaning that based on a population of 24.7 million children in this age group in 2015,[9] nearly half a million children might currently be HCV-Ab+. A study among 1- to 15-year-olds in Karachi found that, strikingly, none of the assessed nosocomial exposures were significantly associated with HCV infection.[26] While there is no estimate of what proportion of infections among Pakistani children might be a result of vertical transmission, globally, vertical transmission is thought to be the most important HCV infection route among young children.[27-29]

The main objective of this study is to estimate the number of annual HCV infections resulting from vertical transmission in Pakistan. The secondary objective is to estimate the proportion of HCV infections among children that arose as a result of vertical transmission.

2 | MATERIALS AND METHODS

2.1 | Model

We based our model on a previously published conceptual framework and modelling approach, where children born to HCV RNA+ women are exposed to the risk of vertical transmission,[30] with minor simplifications to reflect the nature of the data available for Pakistan. We estimated the number of children infected vertically by HCV in Pakistan, in the annual cohorts born in 2007 and in 2012, nationally and for each region. These specific years were chosen based on availability of population-based nationally representative demographic estimates (note next subsection for further details) that are temporally closest to Pakistan's national HCV-Ab prevalence survey in 2007-2008.[25] The estimated number of vertical transmissions was a function of number of women in reproductive age (15-49 years), their age-specific fertility rates (ASFR, in 5-year age groups), HCV-Ab prevalence rates among women by age group, proportion of HCV-Ab+ women estimated to be RNA+, the risk of HCV vertical transmission and the risk of dying between birth and 18 months of age (age at which vertically acquired HCV can be confirmed), in 2007 and 2012, as expressed in Equation 1:

$$I^c = \sum_{i=1}^{N}\left(\rho_{m_{\mathrm{HCV+/RNA+}}\rightarrow c}\underbrace{B(i)I^{m_{\mathrm{HCV+}}}(i)p^{m_{\mathrm{HCV+/RNA+}}}(i)}_{X^{\mathrm{HCV+/RNA+}}(i)}\right)-\mu\sum_{i=1}^{N}B(i) \quad (1)$$

In this equation, I^c is the absolute number of vertically infected children in a given year, and $\rho_{m_{\mathrm{HCV+/RNA+}}\rightarrow c}$ is the risk of vertical transmission to children born to HCV-Ab+/RNA+ women. The index i labels the i-age group (5-year age intervals) in the female population of reproductive age (15-49 years old) in a given year. $B(i)$ is the total annual number of births to women in each age group, based on the number of women in each age group and the ASFR in the age group. $I^{m_{\mathrm{HCV+}}}(i)$ is the prevalence of HCV-Ab+ among currently married women in each age group. $p^{m_{\mathrm{RNA+}}^{\mathrm{HCV+/}}}(i)$ is the proportion of HCV-Ab+ currently married women in each age group that is RNA+. $X^{\mathrm{HCV+/RNA+}}(i)$ is the number of children born to HCV-Ab+/RNA+ mothers in a given year. Last, μ is the risk of dying between birth and 18 months of age.

Subnational estimates were calculated for four regions (Sindh, Punjab, Balochistan and NWFP) to assess the geographical distribution of the burden of vertical transmission of HCV (Equation 2). In this equation, I^c_{area} is the number of children born in a given annual cohort who are alive and vertically infected with HCV at age 18 months, and where $\sum_{\mathrm{area}=1}^{4} I^c_{\mathrm{area}} = I^c$.

$$I^c_{\mathrm{area}} = \sum_{i=1}^{N}\left(\rho_{m_{\mathrm{RNA+}}^{\mathrm{HCV+/}}\rightarrow c}\underbrace{B_{\mathrm{area}}(i)I^{m_{\mathrm{HCV+}}}_{\mathrm{area}}(i)p^{m_{\mathrm{RNA+}}^{\mathrm{HCV+/}}}_{\mathrm{area}}(i)}_{X^{\mathrm{HCV+/RNA+}}_{\mathrm{area}}(i)}\right)-\mu_{\mathrm{area}}\sum_{i=1}^{N}B_{\mathrm{area}}(i) \quad (2)$$

The estimates for each region were divided into those occurring in urban and rural areas.

2.2 | Parameters

2.2.1 | Demographic estimates

The demographic estimates are based on the population-based nationally representative Demographic and Health Surveys (DHS), conducted in 2006-2007 and 2012-2013.[10,31] The number of children alive at 18 months of age from the 2007 to 2012 birth cohorts, for Pakistan overall and for each of the four regions, was estimated. It was based on the number of women in reproductive age (in 5-year age groups from 15 to 49 years) in 2007 and 2012, obtained from the United Nations medium variant population projections,[9] and their distribution in the four regions and urban and rural areas within each region, based on the most recent population census from 1998.[32] The ASFRs were obtained from the DHS reports for both years (Table

S1). We estimated the proportion of HCV-infected infants from both birth cohorts alive at 18 months of age by combining the infant mortality rate per 1000 live births (0-11 months) with six months' (one-eighth) equivalent of the child mortality rate per 1000 live births (12-60 months) estimated on both DHS surveys. The resulting mortality estimates, for Pakistan as a whole, were 8.03% (2007) and 7.61% (2012).

2.2.2 | Epidemiological estimates

The HCV-Ab prevalence as measured in the 2007-2008 national survey was applied to both birth cohorts. The prevalence estimates were available disaggregated by age group or by province or by marital status, but not by all three population characteristics.[25] HCV-Ab prevalence among all women was estimated for four age groups (5-19, 20-29, 30-39 and 40-49). We used these estimates to model a linear regression estimating prevalence and 95% confidence interval (CI) for each one-year age group and calculating an average for each 5-year age group between ages 15 and 49. We then scaled the estimates for each of the seven 5-year age groups to reflect the 60% higher prevalence found on the survey among women who are at risk of conception and birth (currently married women aged 20-49), and to estimate the HCV-Ab prevalence for each age group by region (Figure 1, Table 1).

As HCV RNA positivity was not measured in the national survey, we used estimates of the percentage of HCV-Ab+ women with RNA+ estimated from a survey of pregnant women in Karachi.[11] This percentage was not available by women's age group, and one estimate (79.7%) was thus applied to all age groups. The risk of vertical transmission, diagnosed at 18 months of age, was estimated based on a recent meta-analysis at 5.8% (95% CI: 4.2-7.8).[33] The one study of risk of vertical transmission conducted in Pakistan did not significantly differ from this estimate of risk (3.9% [95% CI: 0.6-7.2], according to the above definition).[34] The risk of vertical transmission used is for children of human immunodeficiency virus (HIV) negative women, as HIV prevalence in Pakistan was very low at <0.1% according to 2013 estimates for adults aged 15-49.[35]

2.2.3 | Uncertainty analyses

Uncertainty analyses were performed to specify the ranges of uncertainty in the national and regional estimates for the number of children vertically infected by HCV with respect to variations in the structural parameters of the model. The parameters that were varied included the following: prevalence of HCV-Ab among currently married women by age group ($I^{m_{HCV+}}(i)$), the proportion of HCV-Ab+ currently married women that are RNA+ ($p^{m}{}_{RNA+}^{HCV+/}(i)$) and the risk of vertical transmission to children born to HCV-Ab+/RNA+ women ($\rho_{m_{HCV+/RNA+}\rightarrow c}$). We implemented 20 000 runs of the model using Monte Carlo sampling from binomial probability distributions incorporating the sample sizes of the source studies for the parameters of the model. Distributions for the estimated number of children infected were then generated and used to determine the mean values and associated 95% uncertainty intervals (UIs).

2.3 | Contribution of vertical transmission to incidence among children

We were unable to identify any study estimating incidence of HCV or risk factors for HCV infection among children in Pakistan. In order to assess the contribution of vertical transmission to the burden of HCV infection among children, we used our estimate of the number of annual HCV cases resulting from vertical transmission, multiplied by five and expressed these as a percentage of all HCV-Ab+ cases among children under 5 years. We calculated the expected total number of HCV-Ab+ cases among children under 5 years in Pakistan using the

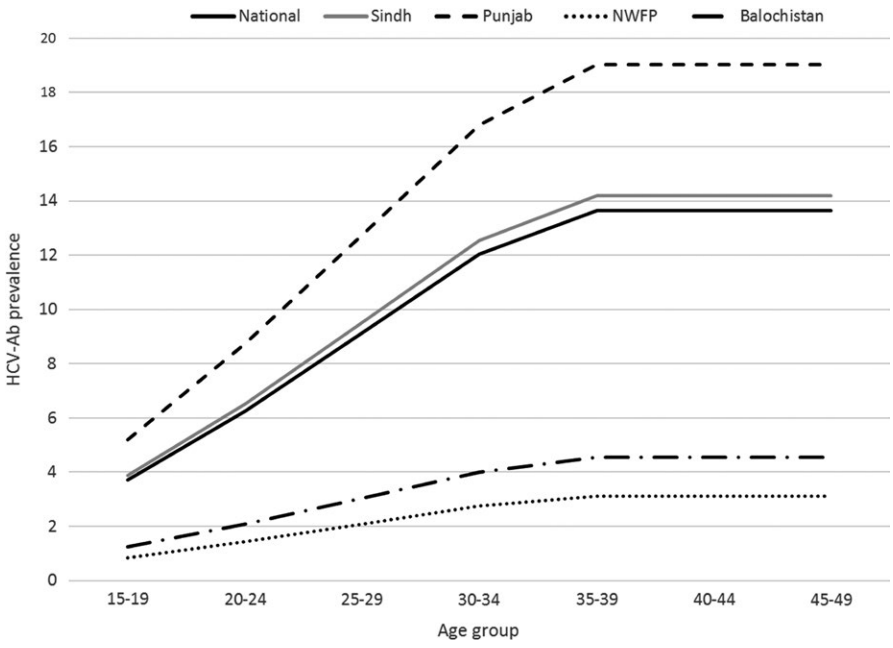

FIGURE 1 Estimates of HCV-Ab prevalence among currently married women 15-49 yr of age in Pakistan, nationally and by region, by age group
NWFP, North-West Frontier Province.
Source: Pakistan Medical Research Council, *Prevalence of Hepatitis B&C in Pakistan*. Pakistan Medical Research Council: Islamabad, Pakistan

TABLE 1 Estimates of HCV-Ab prevalence among currently married women 15-49 yr of age in Pakistan in 2007-2008, nationally and by region, by age group

Age group	National			Sindh			Punjab			NWFP			Balochistan		
	Estimate	LCI	UCI	Estimate	LCI	UCI	Estimate	LCI	UCI	Estimate	LCI	UCI	Estimate	LCI	UCI
15-19	3.72	3.10	4.31	3.87	2.96	4.82	5.19	4.27	6.08	0.85	0.55	1.18	1.24	0.76	1.77
20-24	6.26	5.29	7.27	6.52	5.05	8.12	8.73	7.29	10.26	1.43	0.94	1.99	2.09	1.29	2.99
25-29	9.14	7.78	10.55	9.52	7.43	11.79	12.76	10.72	14.90	2.10	1.38	2.90	3.05	1.90	4.35
30-34	12.03	10.27	13.73	12.53	9.81	15.34	16.79	14.15	19.38	2.76	1.83	3.77	4.01	2.51	5.65
35-39	13.64	11.51	15.30	14.20	11.00	17.10	19.03	15.86	21.60	3.12	2.05	4.20	4.55	2.81	6.30
40-44	13.64	11.51	15.30	14.20	11.00	17.10	19.03	15.86	21.60	3.12	2.05	4.20	4.55	2.81	6.30
45-49	13.64	11.51	15.30	14.20	11.00	17.10	19.03	15.86	21.60	3.12	2.05	4.20	4.55	2.81	6.30

NWFP, North-West Frontier Province.

Source: Pakistan Medical Research Council, *Prevalence of Hepatitis B&C in Pakistan*. Pakistan Medical Research Council: Islamabad, Pakistan. Estimates shown were used in models for both 2007 and 2012. Scaled to achieve estimates of prevalence among currently married women, by 5-year age groups and for each region.

United Nations population projections for the years 2007 and 2012,[9] and HCV-Ab prevalence and 95% CI in this age group from the HCV 2007-2008 national survey.[25] The uncertainty intervals for the estimated proportions of HCV-Ab+ cases among children under 5 years of age due to vertical transmission in 2007 and 2012 were calculated using the 95% CI of HCV-Ab prevalence and 95% UIs of the estimated numbers of vertical transmissions.

3 | RESULTS

We estimated that in 2007, a total of 5.1 million live births occurred to women aged 15-49. By the time, this annual birth cohort reached the age of 18 months, the number of children alive with vertically transmitted HCV was estimated at 19 708 (95% UI: 15 941-23 819). The number of births in 2012 was estimated at 5.6 million, and the resulting number of vertically transmitted HCV cases was 21 676 (95% UI: 17 498-26 126).

The majority of these vertically transmitted cases (65.1% and 65.0% in 2007 and 2012, respectively) occurred in rural areas, reflecting the population distribution (Figure 2). Nearly three-quarters of all cases (72.9% and 72.5% in 2007 and 2012, respectively) occurred in Punjab, which was also the only region where the proportion of overall vertical infections was greater than the proportion of total births (Figure 3). The lowest proportion of all vertical infections in Pakistan was estimated to occur in Balochistan (<2% of vertical infections in both annual cohorts).

Based on the population of children under 5 years and HCV-Ab prevalence in this age group from the 2007 to 2008 national survey, we estimated that a total of 391 084 (95% CI: 308 751-473 418) children were HCV-Ab+ in 2007 and 451 074 (95% CI: 356 111-546 036) in 2012. Vertical transmission as a mode of exposure therefore accounted for approximately a quarter of HCV infections in this age group in both years (25.2% [UI 16.8%-38.6%] in 2007 and 24.0% [UI 16.0%-36.7%] in 2012).

4 | DISCUSSION

This is the first study to estimate the absolute number and the contribution of vertical transmission to HCV prevalence among children in Pakistan, one of the countries most affected by HCV. To produce our estimates, we adapted a published methodology and used quality epidemiological and demographic input data. We found that ~20 000 children acquire HCV annually as a result of vertical transmission. While fewer than 60% of Pakistan's population lives in Punjab, this region accounted for three-quarters of HCV vertical transmissions due to the highest HCV prevalence among the four regions examined. Under the assumption that the prevalence of HCV among women of reproductive age remained similar to the levels measured on the 2007-2008 national survey, vertical transmission would have produced nearly 150 thousand new HCV cases in Pakistan in the 9 years between 2007 and 2015.

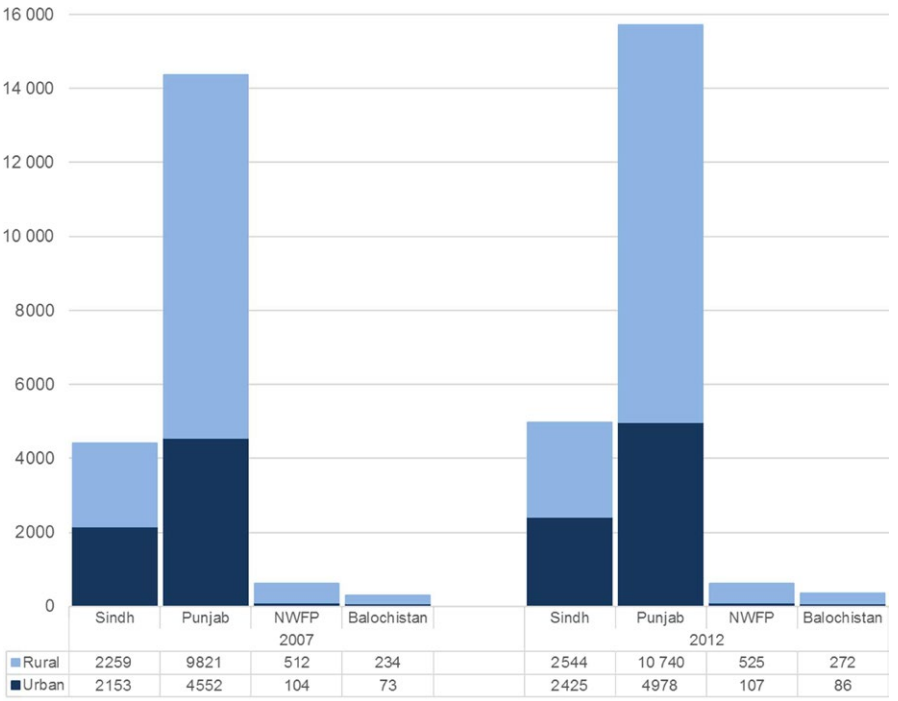

FIGURE 2 Estimated number of vertical HCV infections by annual birth cohort and region (urban and rural), 2007 and 2012. NWFP, North-West Frontier Province

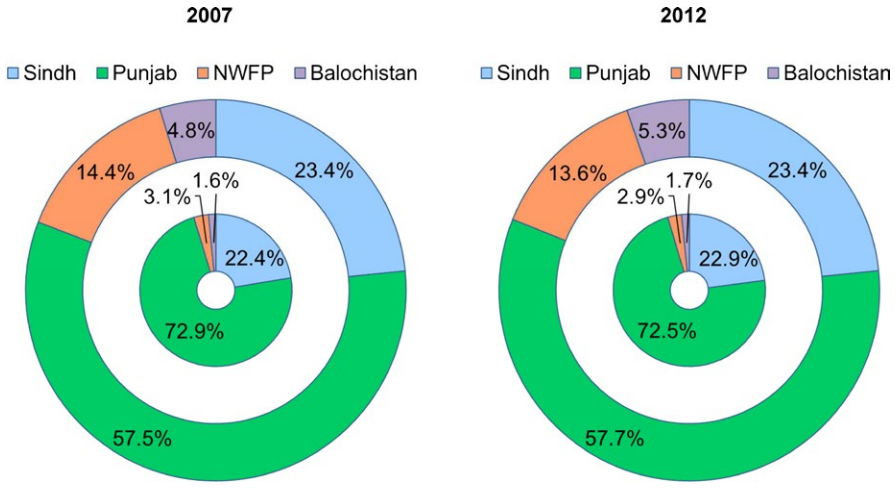

FIGURE 3 Estimated percentages of all births in Pakistan (outer circle) and percentages of vertical HCV infections in Pakistan (inner circle) by region, 2007 and 2012. Outer circles represent the distribution of all births in Pakistan and the inner circles the distribution of vertical HCV infection in Pakistan by region. NWFP, North-West Frontier Province

Vertical transmission of HCV infection was estimated recently for Egypt.[30] While Egypt appears to have the highest HCV prevalence worldwide,[12,13,36] our estimate of the number of HCV vertical transmission cases in Pakistan is fourfold higher than that in Egypt. The larger population size in Pakistan (189 million vs 92 million in Egypt in 2015[9]) explains a large part of this difference. Unlike in Egypt, where men have a higher HCV prevalence, difference between the sexes is not significant in Pakistan.[25] The fact that two regions with the largest populations (Punjab and Sindh) also have the highest HCV-Ab prevalence creates a combination of demographic and epidemiological factors resulting in a large burden of vertical HCV infections. Lastly, women of reproductive age who are 30 years old and above, who have the highest prevalence of HCV-Ab (particularly in the two most populous regions), also have unusually high fertility levels (ASFRs 32%-75% higher than in Egypt, depending on age group).

Our study has several limitations, pertaining primarily to the unavailability of raw data on HCV-Ab prevalence, which would have enabled us to calculate prevalence disaggregated by sex, age group, marital status, region and urban/rural residence. To deal with this issue, we scaled the prevalence for currently married women and by region and interpolated prevalence for the 5-year age groups in order to correspond with demographic estimates of fertility. As disaggregated data were not available, we used HCV prevalence in each region for both urban and rural areas within regions. The risk of vertical transmission might also differ in urban and rural areas; some of these differentials might be due to variable proportions of births occurring in healthcare versus home setting and related infection control practices. We applied the same risk of vertical transmission for both area types as we were unable to find rigorous studies assessing the extent and mechanisms of this differential in low- and middle-income countries.

Similarly, we were unable to identify studies estimating the specific effect of HCV infection on women's fertility or the risk of mortality for infants between 12 and 18 months of age; we applied nondifferential population-representative estimates in our model.

Second, some women with recent infection might be at risk of transmitting the virus (HCV RNA positive) but not yet have developed HCV antibodies, and thus would not be reflected in the HCV-Ab prevalence estimates. However, this number is likely to be negligible and was excluded from the model as we had not identified any study measuring HCV-Ab-/RNA+ prevalence among women in Pakistan. Third, nationally representative estimate for HCV-Ab prevalence was available only for 1 year, 2007-2008, and prevalence could have changed since then. We assumed stable prevalence since 2007-2008. The increase in the estimated number of vertical infections and slight changes in the regional distribution of vertical infections are therefore solely due to population dynamics (population numbers, distribution and fertility rates) rather than due to a combination of population dynamics and infection dynamics. Fourth, neither the 2007-2008 HCV national survey nor the 2006-2007 and 2012-2013 DHS covered some remote or disputed regions of Pakistan (Federally Administered Tribal Area and Jammu/Kashmir). However, these areas account for <3% of Pakistan's population, [31,32] and it is therefore unlikely that our estimates' accuracy was significantly compromised by this omission. Last, further clearance of HCV viraemia might occur among vertically infected children beyond the age of 18 months, and studies have noted higher clearance for HCV transmitted vertically compared to other routes.[37,38] Our results might therefore have slightly overestimated the true burden of vertically transmitted HCV in Pakistan.

While children with vertically acquired HCV appear to have mild disease progression,[39] no interventions during pregnancy or childbirth are currently recommended for the prevention of HCV vertical transmission.[37] Population-level strategies to prevent vertical infections in Pakistan might include addressing HCV transmission routes affecting girls and women in reproductive age, HCV testing and linkage to post-pregnancy treatment, and reducing unmet need for modern family planning methods which could help reduce unwanted pregnancies among HCV-Ab+ women.[10] While the safety of direct-acting antivirals (DAAs) administration during pregnancy has not yet been established, there is optimism about this possibility, unlike the older ribavirin-containing therapies. Encouragingly, generic DAA production has already started in Pakistan with prospects for reducing the cost of a treatment regimen to as little as $100. With such vastly reduced treatment costs, an important consideration in cost-effectiveness analyses is that undiagnosed and untreated HCV infection expose chronically vertically infected children to long periods of chronic illness and sequelae that can be a far more financially and socially expensive burden than the cost of treatment.

In conclusion, our results showed that one in 260 children born in Pakistan in the two annual birth cohorts assessed in this study acquired HCV vertically. This ratio reached one in 205 in Punjab, the worst affected region. While we showed that vertical transmission in the high HCV prevalence and high fertility context of Pakistan is an issue of public health importance, this should not detract from other efforts to identify and reduce other HCV transmission routes which, according to our estimates, appear to constitute the majority of HCV infections among children under 5 years of age.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

LB and LJA-R conceptualized and designed the study. LB and SFA conducted the analysis and wrote the first draft of the manuscript. All authors contributed to interpreting the results and writing of the manuscript, and approved the final draft.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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