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Estimation of Hepatitis C Virus Infections Resulting From Vertical Transmission in Egypt

Lenka Benova,[1,2] Susanne F. Awad,[1] F. DeWolfe Miller,[3] and Laith J. Abu-Raddad[1,4,5]

Despite having the highest hepatitis C virus (HCV) prevalence in the world, the ongoing level of HCV incidence in Egypt and its drivers are poorly understood. Whereas HCV mother-to-child infection is a well-established transmission route, there are no estimates of HCV infections resulting from vertical transmission for any country, including Egypt. The aim of this study was to estimate the absolute number of new HCV infections resulting from vertical transmission in Egypt. We developed a conceptual framework of HCV vertical transmission, expressed in terms of a mathematical model and based on maternal HCV antibody and viremia. The mathematical model estimated the number of HCV vertical infections nationally and for six subnational areas. Applying two vertical transmission risk estimates to the 2008 Egyptian birth cohort, we estimated that between 3,080 and 5,167 HCV infections resulted from vertical transmission among children born in 2008. HCV vertical transmission may account for half of incident cases in the <5-year age group. Disproportionately higher proportions of vertical infections were estimated in Lower Rural and Upper Rural subnational areas. This geographical clustering was a result of higher-area-level HCV prevalence among women and higher fertility rates. *Conclusion:* Vertical transmission is one of the primary HCV infection routes among children <5 years in Egypt. The absolute number of vertical transmissions and the young age at infection highlight a public health concern. These findings also emphasize the need to quantify the relative contributions of other transmission routes to HCV incidence in Egypt. (HEPATOLOGY 2015;61:834–842)

Infection with the hepatitis C virus (HCV) affects 2%-3% of the world's population.[1] Egypt has the highest recorded prevalence of HCV in the world, reaching 14.7% for HCV-antibody (Ab) positivity among 15- to 59-year-olds in 2008.[2] The viremic population of Egypt was estimated at over 6 million in 2008.[3] This epidemic has been linked, in part, to a mass campaign of parenteral antischistosomal therapy in the 1950s-1980s, during which millions of people received intravenous treatment in rural community campaigns.[4-6] The current pattern of HCV prevalence is higher in rural areas, increases with age, and is higher in men compared to women.[2,7] Universal screening of blood and blood products was introduced in Egypt in June 1993.[8] However, nosocomial and other health care-related exposures remain associated with HCV among adults and children.[9-14] Parental, and especially the mother's, HCV serostatus, is an additional risk factor for prevalent HCV infection among children.[11,15,16]

Globally, vertical transmission appears to be the most important route of HCV transmission among children.[17] However, the contribution of vertical transmission to HCV incidence and its public health consequences remain unknown. Maternal human immunodeficiency virus (HIV) coinfection doubles the

Abbreviations: Ab, antibody; ASFR, age-specific fertility rate; CI, confidence interval; EDHS, Egypt Demographic and Health Survey; HCV, hepatitis C virus; $HCV^{+(-)}$, presence (absence) of HCV antibodies; HIV, human immunodeficiency virus; $RNA^{+(-)}$, presence (absence) of HCV viremia.

From the [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, United Kingdom; [3]Department of Tropical Medicine and Medical Microbiology and Pharmacology, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI; [4]Department of Healthcare Policy and Research, Weill Cornell Medical College, Cornell University, New York, NY; and [5]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA

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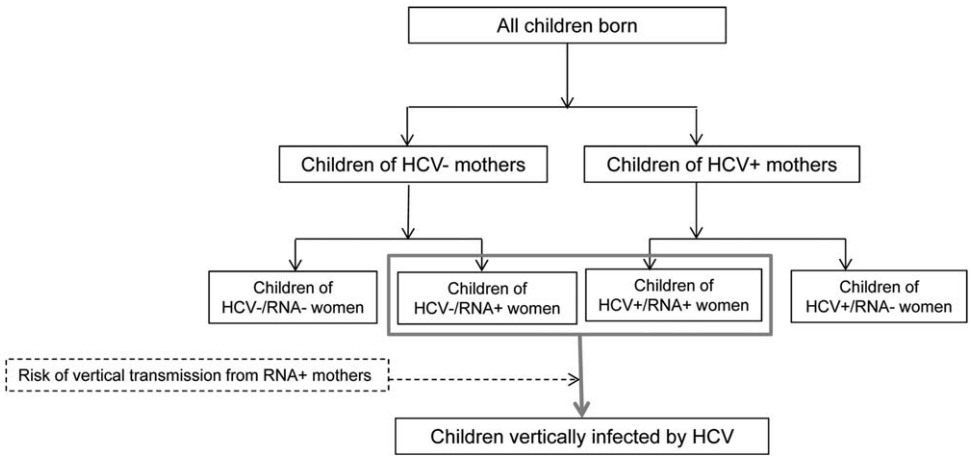

Fig. 1. Conceptual framework diagram.

odds of HCV vertical transmission,[18,19] but the mother's age, parity, HCV genotype, or breastfeeding do not appear to be associated with the risk of vertical infection.[20-26] There are no nationally representative estimates of HCV prevalence among children under 15 years of age in Egypt. However, a systematic review of HCV in Egypt identified six studies assessing HCV prevalence among school children between 1992 and 2005 and found a range of HCV-Ab-positive prevalence from 2.1% to 12.1%.[13] In a cohort followed from birth to 5 years of age in Lower Egypt, the estimated HCV incidence was significantly higher during the first year of life, compared to the 1- to 5-year age group (3.8 and 2.0 per 1,000 person-years, respectively).[27]

With over 80 million inhabitants, Egypt is the most populous Arab country and continues to experience high annual population growth (1.5%-1.9% in 2010-2015).[28] Despite a large reservoir of HCV infection in the adult population as well as a relatively high fertility rate, no published studies estimating the extent of vertical transmission in Egypt were identified. Though HCV prevalence among adults in Egypt is well characterized, the level of ongoing HCV incidence and relative contribution of various transmission routes remain uncertain and a subject of discussion.[29-32]

The first aim of this study was to develop a conceptual framework, expressed in terms of a mathematical model, for estimating HCV vertical transmission in settings of generalized HCV epidemics such as Egypt. The second and main aim of this study was to estimate the number of annual HCV infections resulting from vertical transmission in Egypt and assess its contribution to the overall HCV incidence in this country.

Materials and Methods

Conceptual Framework

We developed a framework to categorize children's vertical exposure to HCV according to maternal HCV status (Fig. 1). Conceptually, only the presence of maternal HCV viremia (RNA^+) constitutes exposure to vertical transmission. The existing estimates of HCV viremia prevalence from Egypt relied on procedures where HCV-RNA presence was only tested among individuals who first tested positive for HCV Abs (HCV^+). This procedure may have missed recently infected viremic individuals without detectable HCV Abs and misclassified them as HCV RNA^-. Therefore, we conceptually specified four categories of maternal HCV status and considered children born to HCV^+/RNA^+ and to HCV^-/RNA^+ women as vertically exposed.

Definition of Vertical Transmission

For the purpose of selecting vertical transmission risk estimates based on primary studies to use in our model, we defined vertically acquired HCV infection as the presence of HCV Abs at or beyond 18 months

Address reprint requests to: Lenka Benova, M.A., M.Sc., London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom. E-mail: lenka.benova@lshtm.ac.uk; fax: +44 (0)20 7436 5389 or Laith Abu-Raddad, Ph.D., Infectious Disease Epidemiology Group, Weill Cornell Medical College-Qatar, Qatar Foundation-Education City, P.O. Box 24144, Doha, Qatar. E-mail: lja2002@qatar-med.cornell.edu; fax: +43 (974) 4492 8333.

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of age and/or presence of HCV RNA on at least two separate occasions by 18 months of age, among infants vertically exposed to HCV.[33] We also applied published pooled estimates of the risk of vertical infection among exposed children.

Model Description

National Estimates. We constructed a mathematical model estimating the total number of children vertically infected with HCV in the 2008 annual birth cohort in Egypt. The population used in the model was stratified into groups according to maternal HCV status (HCV^+/RNA^+ and HCV^-/RNA^+) and maternal age group. The number of vertically infected children was modeled as a function of the number of women in reproductive age (by HCV status and age group), their age-specific fertility rates, risk of HCV vertical transmission, and risk of dying between birth and 18 months of age (Equation (1), Fig. 2). I^c is the absolute number of children born in 2008 who are alive and vertically infected with HCV at age 18 months. $\rho_{m_{HCV+/RNA+}\to c}$ and $\rho_{m_{HCV-/RNA+}\to c}$are the risks of vertical transmission to children born to HCV^+/RNA^+ women and HCV^-/RNA^+ women, respectively. The index i labels the i-age group (5-year age intervals) in the female population of reproductive age (15-49 years old). $B(i)$ is the total number of births to women in each age group, based on the number of women in each age group and the age-specific fertility rate in the age group. $I^{m_{HCV+}}(i)$is the prevalence of HCV^+ among currently married women in each age group. $p^{m_{RNA+}^{HCV+/}}(i)$ is the proportion of HCV^+ currently married women in each age group that is RNA^+. $f^{m_{RNA+}^{HCV-/}}$ is the fraction of mothers that are HCV^-, but RNA^+, as a proportion of the size of the HCV^+/RNA^+ group of women. We structured our model in terms of this fraction to utilize the best available direct empirical data to capture this contribution.[34] μ is the risk of dying between birth and 18 months of age. $X^{HCV+/RNA+}(i)$ and $X^{HCV-/RNA+}(i)$ are the number of children born to HCV^+/RNA^+ and HCV^-/RNA^+ mothers, respectively.

Subnational Estimates. To evaluate the geographical distribution of the total number of children vertically infected with HCV in Egypt, we calculated the number of children vertically infected with HCV for each of the six subnational areas in Egypt, by maternal HCV status and age group (Equation (2), Fig. 2). Here, $I^c_{area}$is the absolute number of children born in 2008 who are alive and vertically infected with HCV at age 18 months in an area, where (Equation (3), Fig. 2).

Parameterization

Demographic Estimates. The data sets available from the most recent Egypt Demographic and Health Survey (EDHS) in 2008 were used to calculate nationally and subnationally representative HCV biomarkers in the 15-59 age bracket. The 2008 EDHS report provided nationally and subnationally representative estimates of fertility.[2] The model of vertical transmission was based on the 2008 annual cohort of live births in Egypt (Table 1). The population of women ages 15-49 (in 5-year age groups) in 2008 was obtained from the United Nations population projections (medium variant projection),[28] and their distribution into the six subnational areas was based on the distribution of the total population in the most recent population census preceding the 2008 EDHS survey, conducted in 2006.[35] The six subnational areas are Urban governorates (Cairo, Alexandria, Suez, and Port Said), Lower Urban Egypt, Lower Rural Egypt, Upper Urban Egypt, Upper Rural Egypt, and Frontier governorates, as defined in the 2008 EDHS survey sampling strategy.[2]

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

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

$$\sum_{area=1}^{6} I^c_{area} = I^c \quad (3)$$

Fig. 2. Equations (1), (2), and (3).

Table 1. Fertility and Number of Live Births to Currently Married Women in Egypt in 2008, by Age Group

Age Group	Female Population (2008)*	ASFR†	Number of Births (2008)‡
15-19	3,934,839	50	196,742
20-24	3,967,574	169	670,520
25-29	3,422,792	185	633,217
30-34	2,695,181	122	328,812
35-39	2,270,714	59	133,972
40-44	2,132,325	17	36,250
45-49	1,959,858	2	3,920
Total	**20,383,283**		**2,003,432**

Sources of data:
*World Population Prospects: The 2010 Revision.
†Source: EDHS 2008 report (estimates of ASFR for the 36-month period preceding the survey).
‡Expected number of births, calculated by authors.

The 2008 EDHS was the source for the estimates of national and subnational age-specific fertility rates (ASFRs; number of live births per 1,000 women per year) in 5-year age groups (Table 2). We assumed nondifferential fertility and pregnancy outcomes by HCV status.[36] The risk of dying between birth and 18 months of age was calculated for Egypt overall and for each subnational area by taking the infant mortality rate (risk of dying in the first year of life, per 1,000 births) and adding the equivalent of 6 months of the child mortality rate (risk of dying between first and fifth birthdays, per 1,000 births), as provided by the 2008 EDHS for the 10-year period preceding the survey.[2] The resulting risk of dying between birth and 18 months of age, expressed as a proportion of births, ranged from a low of 1.53% in Lower Urban areas to a high of 3.95% in Upper Rural areas, with a national level of 2.92%. Owing to the mild progression of vertically acquired HCV among children, the risks of dying before 18 months of age were assumed not to differ between HCV-infected and uninfected children.[37]

Epidemiological Estimates. National prevalence of HCV-Ab positivity and the proportion of HCV-Ab-positive women with active HCV viremia were calculated for currently married women in 5-year age groups using EDHS 2008 data sets provided by MEASURE DHS (Demographic and Health Surveys), adjusting for complex survey design with the *svyset* command in Stata/SE software (version 12; StataCorp LP, College Station, TX). As shown in the conceptual framework, a proportion of HCV-Ab negative women may be RNA^+, reflecting early acute HCV infection.[38] The 2008 EDHS evaluated HCV viremia only among those who were HCV-Ab positive and would therefore not have identified such cases. Based on a study from Egypt, we estimated that the number of HCV^-/RNA^+ mothers was 3% of the number of HCV^+/RNA^+ mothers.[34]

The prevalence of HCV^+ and RNA^+ was estimated among currently married women in each subnational area, but because of limited sample size could not be estimated further within each age group. Therefore, the age-group estimates of HCV^+ prevalence and the proportion RNA^+ among HCV^+ within the six subnational areas were calculated by scaling the national estimates in each age group by a factor obtained by dividing the overall subnational area prevalence by the overall national prevalence. No separate estimates of vertical transmission by mother's HIV serostatus were produced given that the prevalence of HIV in Egypt is $<1\%$.[39-41]

Risk of Vertical Transmission. Two groups of vertically exposed children were identified in the conceptual framework according to maternal HCV status: HCV^+/RNA^+ and HCV^-/RNA^+. However, no risk estimates of vertical transmission from HCV^-/RNA^+ mothers were identified in the existing literature. Therefore, estimates capturing the risk of vertical transmission from HCV^+/RNA^+ were applied to births occurring to all viremic women, irrespective of HCV-Ab status. Two estimates of the risk were used separately in the mathematical model in order to obtain a credible range. Risk estimate A was based on a cohort study in Egypt, which estimated the vertical transmission risk at 3.5% (95% confidence interval

Table 2. National and Subnational Age-Specific Fertility Rates (Number of Live Births Per 1,000 Women Per Year) in 5-Year Age Groups Among Currently Married Women in Egypt

Subnational Area		Lower Urban	Lower Rural	Upper Urban	Upper Rural	Urban Govs	Frontier Govs	Egypt Overall
Age group, years	15-19	25	60	41	68	24	55	50
	20-24	142	191	130	204	127	160	169
	25-29	173	188	191	201	166	201	185
	30-34	114	101	154	140	119	147	122
	35-39	58	46	65	74	61	73	59
	40-44	5	10	10	32	23	23	17
	45-49	0	0	4	6	2	6	2

Source: EDHS 2008 report.
Abbreviation: Govs, governorates.

[CI]: 1.5-6.7).[42] Risk estimate B was from the most recent global systematic review and meta-analysis, which estimated the pooled risk of vertical transmission to children born to HIV-negative, HCV^+/RNA^+ mothers at 5.8% (95%CI: 4.2-7.8).[43]

Uncertainty Analyses

Uncertainty analyses were conducted for the national and subnational estimates of the number of children vertically infected by HCV. For this purpose, 20,000 runs of the model were implemented using Monte Carlo sampling from binomial probability distributions incorporating the sample sizes of the source studies for the following parameters: prevalence of HCV^+ among currently married women by age group ($I^{m_{HCV+}}(i)$); the proportions of HCV^+ currently married women in each age group that are RNA^+ ($p^{m_{HCV+/RNA+}}(i)$); and the two vertical transmission risk estimates (risk estimate A and risk estimate B). This set of new parameters was then used to calculate two estimates of the number of children infected, for risk estimate A and risk estimate B. Distributions for the estimated number of children infected were then generated and used to calculate the mean and associated 95% CI.

Contribution of Vertical Transmission to Incidence

Current HCV incidence in Egypt remains uncertain. Overall annual HCV incidence rate in published cohort studies in Egypt ranges between 0.8 and 6.8 per 1,000 person-years.[13] Based on analyses of these incidence studies and HCV prevalence age distribution, it is predicted that the annual national incidence is likely to exceed 100,000 cases.[29-31] In order to quantify the contribution of vertical transmission to the estimated number of annual incident HCV infections among children, we used two published estimates of HCV incidence. First, we used a nationally representative estimate of the average annual HCV incidence rate experienced by the living Egyptian cohort in the 0-5-year age group.[30] Second, we drew on a cohort study from Lower Egypt, a region with higher than national prevalence of HCV, which estimated HCV incidence in the first year of life at 3.8 per 1,000 person-years.[27]

Results

We estimated that the national prevalence of HCV^+ among 15- to 49-year-old currently married women was 11.7% (95% CI: 10.6-12.9). In this group, 59.9% were estimated to be viremic, resulting in HCV viremia prevalence of 7.0% (95% CI: 6.2-8.0). The prevalence of HCV-Ab positivity on the national level increased with women's age, ranging from approximately 5% among women of ages 15-29 to 24.1% in the age group 45-49 (Fig. 3). The highest prevalence of HCV-Ab positivity among currently married women was recorded in Lower Rural Egypt (14.9%) and lowest in Frontier governorates (2.4%). The proportion of HCV-Ab positive women who were viremic ranged from 54.5% in Urban governorates to 70.3% in Upper Urban Egypt (Table 3).

We estimated that in 2008, 20.3 million women aged 15-49 in Egypt gave birth to 2 million children. The estimated number of vertical HCV infections in this birth cohort reached 3,080 (95% CI: 1,146-5,465) based on risk estimate A and 5,167 (95% CI:

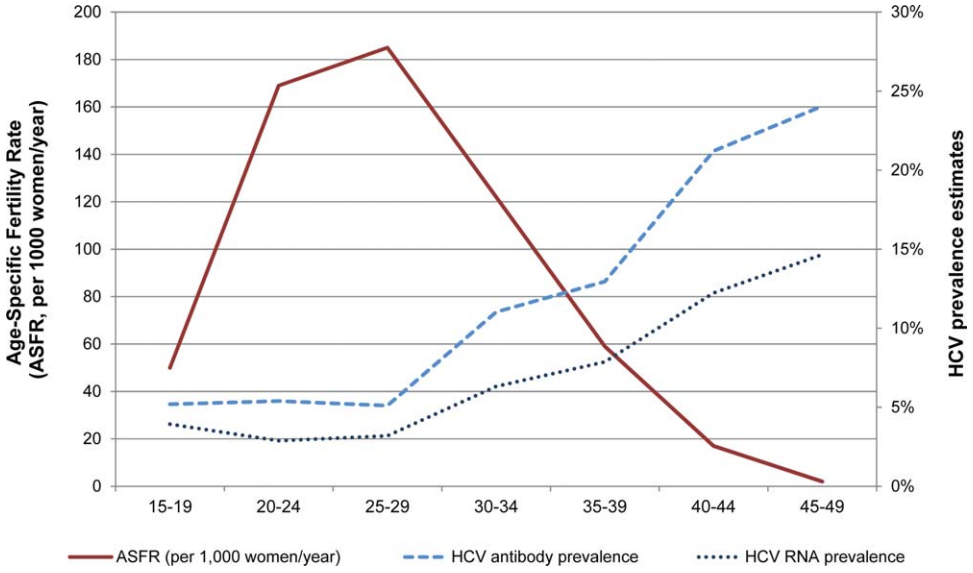

Fig. 3. Fertility rates and HCV biomarkers among currently married women in Egypt, by age group.

Table 3. Calculation of HCV$^+$ Prevalence and Proportion of HCV$^+$ That Are RNA$^+$ Among Currently Married Women, by Age Group and Subnational Area

Subnational Area	Indicator	Estimate (%)	95% CI	% RNA$^+$ (of HCV$^+$)	Factor (Regional/ National)	Age Group (Years) 15-19 (%)	20-24 (%)	25-29 (%)	30-34 (%)	35-39 (%)	40-44 (%)	45-49 (%)
Lower Urban	% HCV$^+$	8.2	5.7-11.7	57.3	0.70	3.6	3.8	3.6	7.7	9.1	14.9	16.9
	% RNA$^+$	4.7	3.0-7.2		0.96	72.5	51.1	59.9	54.8	58.2	55.2	58.3
Lower Rural	% HCV$^+$	14.9	12.8-17.3	58.3	1.27	6.6	6.9	6.5	14.0	16.6	27.0	30.7
	% RNA$^+$	8.7	7.1-10.6		0.97	73.6	52.0	60.8	55.7	59.1	56.1	59.3
Upper Urban	% HCV$^+$	6.9	4.4-10.7	70.3	0.59	3.1	3.2	3.0	6.5	7.7	12.5	14.2
	% RNA$^+$	4.9	3.0-7.7		1.17	88.9	62.7	73.4	67.2	71.3	67.7	71.5
Upper Rural	% HCV$^+$	13.9	11.8-16.3	65.8	1.19	6.2	6.4	6.1	13.1	15.4	25.2	28.6
	% RNA$^+$	9.1	7.4-11.2		1.10	83.1	58.7	68.7	62.9	66.7	63.3	66.9
Urban Govs	% HCV$^+$	7.1	4.8-10.3	54.5	0.61	3.2	3.3	3.1	6.7	7.9	12.9	14.6
	% RNA$^+$	3.9	2.4-6.3		0.91	68.9	48.6	56.9	52.1	55.3	52.5	55.5
Frontier Govs	% HCV$^+$	2.4	1.1-5.4	65.8	0.21	1.1	1.1	1.0	2.3	2.7	4.3	4.9
	% RNA$^+$	1.6	0.6-4.1		1.10	83.2	58.7	68.7	63.0	66.8	63.4	67.0
Egypt national	**% HCV$^+$**	**11.7**	**10.6-12.9**	**59.9**		**5.2**	**5.4**	**5.1**	**11.0**	**13.0**	**21.2**	**24.1**
	% RNA$^+$	**7.0**	**6.2-8.0**			**75.7**	**53.4**	**62.5**	**57.3**	**60.8**	**57.7**	**61.0**

% HCV$^+$ refers to proportion of all women with HCV Abs (HCV$^+$). % RNA$^+$ refers to proportion of all women with active infection (RNA$^+$). % RNA$^+$ (of HCV$^+$) refers to proportion of HCV$^+$ women with active infection (RNA$^+$). Source of estimates: EDHS 2008 data sets. Age group estimates within subnational areas were calculated by multiplying national estimates for each age group by the area factor.

Abbreviation: Govs, governorates.

3,954-6,544) based on risk estimate B (Fig. 4). The two subnational areas where the proportion of overall vertical infections was greater than the proportion of total births were Lower Rural (31.7% of births and 36.5% of vertical infections) and Upper Rural (26.6% of births and 34.4% of vertical infections), as shown in Fig. 5. The lowest proportion of all vertical infections was estimated to occur in Frontier governorates (0.9%).

Based on estimates of HCV incidence in Egypt of at least 100,000 new infections per year, vertical transmission accounts for 5% of the total HCV incidence in Egypt at most. However, based on the estimate of 10,000 annual incident cases in the 0-5-year age group, vertical transmission could account for between 31% and 52% of annual HCV infections in this age group. The estimate of HCV incidence in children <1 year from the cohort in Lower Egypt would result in 7,600 HCV infections in the 2008 birth cohort. Vertical transmission could thus account for 41%-68% of annual incident cases among children <1 year.

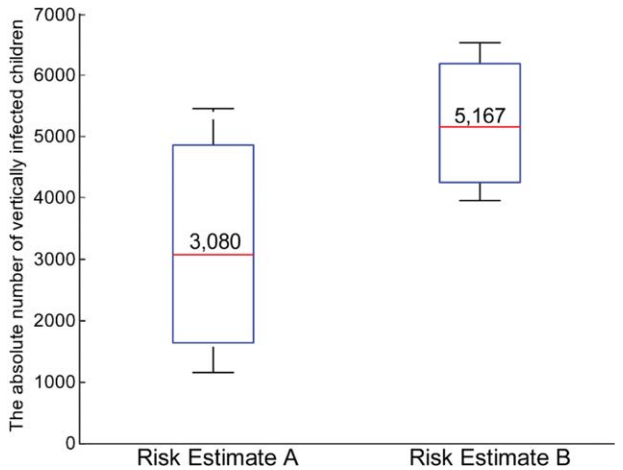

Fig. 4. Estimates of the number of children from the 2008 annual birth cohort vertically infected by HCV and alive at age 18 months (interquartile range and 95% CI).

Discussion

We modeled the number of HCV vertical infections based on demographic characteristics of the Egyptian population, epidemiological estimates of HCV prevalence among currently married women in reproductive age, and two separate robust estimates of the risk of HCV vertical transmission. The resulting estimates showed that between 3,000 and 5,000 children in the 2008 birth cohort were vertically infected with HCV. Lower Rural and Upper Rural subnational areas together contributed more than 7 in every 10 incident infections occurring through this mode of transmission in Egypt. This geographical clustering of HCV vertical infections was largely driven by the combination of higher HCV prevalence and higher fertility rates in these subnational areas.

The HCV epidemic in Egypt is of similar scale to the HIV epidemic in sub-Saharan Africa. In this context, all potential transmission routes need to be examined with the view of being addressed by public health interventions. The national estimate of HCV incidence

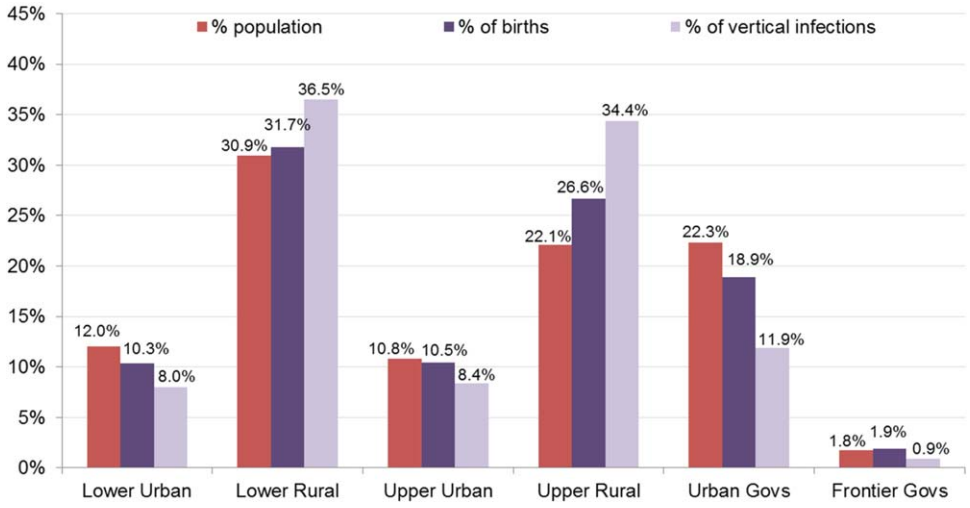

Fig. 5. Comparison of the proportions of total population, total births, and total number of vertical infections by subnational area.

in Egypt remains contentious, and the relative contributions of the transmission routes that drive this incidence are not well established. To our knowledge, this is the first published study to estimate the contribution of a specific HCV transmission route to HCV incidence in Egypt. Moreover, this research is also the first to estimate, for any country, the number of HCV infections resulting from vertical transmission. Our estimates of the absolute and relative contribution of vertical transmission to HCV incidence are essential for planning health service provision and development of appropriate interventions. Indirectly, but importantly, our findings show that transmission routes other than mother-to-child transmission contribute the bulk (>90%) of the overall HCV incidence in Egypt. The relative contribution of each of these remaining routes is yet to be quantified.

Our model relied on robust demographic estimates of the number of women in reproductive age and their fertility rates based on a nationally representative survey of birth history in the 36 months preceding data collection in 2008. HCV prevalence was obtained from the 2008 EDHS, which used third-generation HCV-Ab assay and confirmed all positive and retested 5% of negative samples. The quantitative RNA polymerase chain reaction test used in this survey would have been able to detect viral load at a lower limit of ~50 IU/mL. We assumed that children in the 2008 annual cohort were born to currently married women and calculated the HCV biomarker prevalence among women by age group accordingly. However, among currently married women selected for HCV testing, 7.3% had missing data for HCV biomarkers, mainly because of refusal to provide blood or absence at the time of blood sample collection.

The 2008 EDHS tested for HCV viremia only in the HCV-Ab-positive samples. Therefore, infections occurring several weeks before this serosurvey may have tested as HCV-Ab negative and been classified as HCV^{-}/RNA^{-} despite being viremic. We adjusted for this potential misclassification using the best available estimates from Egypt. To capture the potential variation in the estimates of vertical transmission risk, this study relied on two separate estimates, one based on data from Egypt and the other a result of a recent meta-analysis of high-quality global studies.[42,43] Both sources also provided estimates of vertical transmission risk to children born to HCV^{+}/RNA^{-} mothers and showed that the vertical transmission risk was 0%, in line with our conceptual framework. We defined vertically acquired HCV infection as the persistence of HCV Abs and/or continued presence of HCV RNA on at least two separate occasions by 18 months of age. Further spontaneous clearance may occur after this age, and our estimate of vertical infections could be higher than the eventual number of chronic HCV infections in the birth cohort.[44] Our assessment of the contribution of HCV vertical transmission to HCV incidence among the <5- and <1-year-old children was based on the two best sources of incidence estimates available for Egypt. However, given that both studies may have overestimated current HCV incidence for these age groups, the contribution of HCV vertical transmission to the total HCV incidence in the 0-5-year and <1-age groups, based on our results, may be underestimated.

Several potential steps to reducing the number of vertical HCV infections may exist. The current HCV treatment regimen of pegylated interferon and ribavirin is contraindicated during pregnancy,[38] and new drugs have not yet been

evaluated for use in pregnant women.[45,46] One potential intervention could offer HCV treatment to women before conception.[47] Whereas currently only 2% of women in Egypt report ever having been tested for HCV,[2] testing could be made available during premarital counseling and lead to treatment referral.[48] Children born to HCV-infected pregnant women could be clinically followed and treated at earlier stages of the disease. Whereas HCV treatment is currently not offered to children <2 years of age, 55%-93% of children in the 2-17 age group undergoing combination treatment achieve sustained viral response.[49]

In conclusion, we developed a conceptual framework of HCV vertical transmission, expressed in terms of a mathematical model, to estimate the number of HCV infections resulting from mother-to-child transmission in the 2008 birth cohort in Egypt. We estimated that between 3,000 and 5,000 children from this birth cohort were vertically infected by HCV. This represents approximately 5% of all incident HCV cases in Egypt, but may account for between one and two thirds of incident HCV in the 0-5-year age group. The absolute number of vertical transmissions is of public health importance, as is the young age at infection and resulting potential lifelong HCV infection and its clinical and social consequences. In light of the significance of vertical transmission as an HCV infection route among children in Egypt, we encourage further research to better understand this transmission route and assess potential interventions to prevent infection. Such research should be conducted in conjunction with studies estimating the relative contributions of other transmission routes to the overall HCV incidence in Egypt.

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References

1. Alter MJ. Epidemiology of hepatitis C virus infection. World J Gastroenterol 2007;13:2436-2441.
2. El-Zanaty F, Way A. Egypt Demographic and Health Survey 2008. Cairo: Ministry of Health, El-Zanaty and Associates, and Macro International; 2009.
3. Bruggmann P, Berg T, Ovrehus AL, Moreno C, Brandao Mello CE, Roudot-Thoraval F, et al. Historical epidemiology of hepatitis C virus (HCV) in selected countries. J Viral Hepat 2014;21(Suppl 1):5-33.
4. Strickland GT. Liver disease in Egypt: hepatitis C superseded schistosomiasis as a result of iatrogenic and biological factors. Hepatology 2006;43:915-922.
5. Deuffic-Burban S, Mohamed MK, Larouze B, Carrat F, Valleron AJ. Expected increase in hepatitis C-related mortality in Egypt due to pre-2000 infections. J Hepatol 2006;44:455-461.
6. Frank C, Mohamed MK, Strickland GT, Lavanchy D, Arthur RR, Magder LS, et al. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. Lancet 2000;355:887-891.
7. Cuadros DF, Branscum AJ, Miller FD, Abu-Raddad LJ. Spatial epidemiology of hepatitis C virus infection in Egypt: analyses and implications. Hepatology 2014;60:1150-1159.
8. National Committee for the Control of Viral Hepatitis. Egyptian National Control Strategy for Viral Hepatitis 2008-2012. Cairo: Arab Republic of Egypt, Ministry of Health and Population; 2008 (April).
9. Arafa N, El Hoseiny M, Rekacewicz C, Bakr I, El-Kafrawy S, El Daly M, et al. Changing pattern of hepatitis C virus spread in rural areas of Egypt. J Hepatol 2005;43:418-424.
10. Habib M, Mohamed MK, Abdel-Aziz F, Magder LS, Abdel-Hamid M, Gamil F, et al. Hepatitis C virus infection in a community in the Nile Delta: risk factors for seropositivity. Hepatology 2001;33:248-253.
11. Mohamed MK, Magder LS, Abdel-Hamid M, El-Daly M, Mikhail NN, Abdel-Aziz F, et al. Transmission of hepatitis C virus between parents and children. Am J Trop Med Hyg 2006;75:16-20.
12. Esmat G, Hashem M, El-Raziky M, El-Akel W, El-Naghy S, El-Koofy N, et al. Risk factors for hepatitis C virus acquisition and predictors of persistence among Egyptian children. Liver Int 2012;32:449-456.
13. Mohamoud YA, Mumtaz GR, Riome S, Miller D, Abu-Raddad LJ. The epidemiology of hepatitis C virus in Egypt: a systematic review and data synthesis. BMC Infect Dis 2013;13:288.
14. Mostafa A, Taylor SM, el-Daly M, el-Hoseiny M, Bakr I, Arafa N, et al. Is the hepatitis C virus epidemic over in Egypt? Incidence and risk factors of new hepatitis C virus infections. Liver Int 2010;30:560-566.
15. Mohamed MK, Abdel-Hamid M, Mikhail NN, Abdel-Aziz F, Medhat A, Magder LS, et al. Intrafamilial transmission of hepatitis C in Egypt. Hepatology 2005;42:683-687.
16. Plancoulaine S, Mohamed MK, Arafa N, Bakr I, Rekacewicz C, Tregouet DA, et al. Dissection of familial correlations in hepatitis C virus (HCV) seroprevalence suggests intrafamilial viral transmission and genetic predisposition to infection. Gut 2008;57:1268-1274.
17. Tovo PA, Lazier L, Versace A. Hepatitis B virus and hepatitis C virus infections in children. Curr Opin Infect Dis 2005;18:261-266.
18. Pappalardo BL. Influence of maternal human immunodeficiency virus (HIV) co-infection on vertical transmission of hepatitis C virus (HCV): a meta-analysis. Int J Epidemiol 2003;32:727-734.
19. Polis CB, Shah SN, Johnson KE, Gupta A. Impact of maternal HIV coinfection on the vertical transmission of hepatitis C virus: a meta-analysis. Clin Infect Dis 2007;44:1123-1131.
20. Syriopoulou V, Nikolopoulou G, Daikos GL, Theodoridou M, Pavlopoulou I, Nicolaidou P, Manolaki N. Mother to child transmission of hepatitis C virus: rate of infection and risk factors. Scand J Infect Dis 2005;37:350-353.
21. Mast EE, Hwang LY, Seto DS, Nolte FS, Nainan OV, Wurtzel H, Alter MJ. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. J Infect Dis 2005;192:1880-1889.
22. Resti M, Bortolotti F, Azzari C, Giacchino R, Zancan L, Gussetti N, Vierucci A. Transmission of hepatitis C virus from infected mother to offspring during subsequent pregnancies. J Pediatr Gastroenterol Nutr 2000;30:491-493.
23. Yeung LT, King SM, Roberts EA. Mother-to-infant transmission of hepatitis C virus. Hepatology 2001;34:223-229.
24. Shiraki K, Ohto H, Inaba N, Fujisawa T, Tajiri H, Kanzaki S, et al. Guidelines for care of pregnant women carrying hepatitis C virus and their infants. Pediatr Int 2008;50:138-140.
25. Bhola K, McGuire W. Does avoidance of breast feeding reduce mother-to-infant transmission of hepatitis C virus infection? Arch Dis Child 2007;92:365-366.
26. Cottrell EB, Chou R, Wasson N, Rahman B, Guise JM. Reducing risk for mother-to-infant transmission of hepatitis C virus: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2013;158:109-113.
27. Saleh DA, Shebl FM, El-Kamary SS, Magder LS, Allam A, Abdel-Hamid M, et al. Incidence and risk factors for community-acquired

hepatitis C infection from birth to 5 years of age in rural Egyptian children. Trans R Soc Trop Med Hyg 2010;104:357-363.
28. Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat. World Population Prospects: The 2010 Revision. New York: United Nations; 2011.
29. Lehman EM, Wilson ML. Epidemic hepatitis C virus infection in Egypt: estimates of past incidence and future morbidity and mortality. J Viral Hepat 2009;16:650-658.
30. Miller FD, Abu-Raddad LJ. Evidence of intense ongoing endemic transmission of hepatitis C virus in Egypt. Proc Natl Acad Sci U S A 2010;107:14757-14762.
31. Breban R, Doss W, Esmat G, Elsayed M, Hellard M, Ayscue P, et al. Towards realistic estimates of HCV incidence in Egypt. J Viral Hepat 2013;20:294-296.
32. Miller FD, Abu-Raddad LJ. Quantifying current hepatitis C virus incidence in Egypt. J Viral Hepat 2013;20:666-667.
33. Resti M, Bortolotti F, Vajro P, Maggiore G. Guidelines for the screening and follow-up of infants born to anti-HCV positive mothers. Dig Liver Dis 2003;35:453-457.
34. Saleh DA, Shebl F, Abdel-Hamid M, Narooz S, Mikhail N, El-Batanony M, et al. Incidence and risk factors for hepatitis C infection in a cohort of women in rural Egypt. Trans R Soc Trop Med Hyg 2008;102:921-928.
35. Central Agency for Public Mobilization and Statistics. Population in governorates (urban/rural) according to final results of 2006 population census. Cairo: CAPMAS; 2013.
36. Jabeen T, Cannon B, Hogan J, Crowley M, Devereux C, Fanning L, et al. Pregnancy and pregnancy outcome in hepatitis C type 1b. QJM 2000;93:597-601.
37. Zuccotti GV, Salvini F, Farina F, Agostoni C, Riva E, Giovannini M. Longitudinal long-term follow-up study of children with vertically acquired hepatitis C virus infection. J Int Med Res 2006;34:215-222.
38. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. HEPATOLOGY 2009;49:1335-1374.
39. Abu-Raddad LJ, Hilmi N, Mumtaz G, Benkirane M, Akala FA, Riedner G, et al. Epidemiology of HIV infection in the Middle East and North Africa. AIDS 2010;24(Suppl 2):S5-23.
40. National AIDS Program Egypt. Global AIDS response progress report 2012: Arab Republic of Egypt. Cairo: Ministry of Health; 2012.
41. Abu-Raddad L, Akala FA, Semini I, Riedner G, Wilson D, Tawil O. Characterizing the HIV/AIDS epidemic in the Middle East and North Africa: time for strategic action. Middle East and North Africa HIV/AIDS Epidemiology Synthesis Project. World Bank/UNAIDS/WHO Publication. Washington, DC: The World Bank Press; 2010.
42. Shebl FM, El-Kamary SS, Saleh DA, Abdel-Hamid M, Mikhail N, Allam A, et al. Prospective cohort study of mother-to-infant infection and clearance of hepatitis C in rural Egyptian villages. J Med Virol 2009;81:1024-1031.
43. Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C: systematic review and meta-analysis. Clin Infect Dis 2014;59:765-773.
44. Yeung LT, To T, King SM, Roberts EA. Spontaneous clearance of childhood hepatitis C virus infection. J Viral Hepat 2007;14:797-805.
45. Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet 2014;383:515-523.
46. Asselah T. Sofosbuvir for the treatment of hepatitis C virus. Expert Opin Pharmacother 2014;15:121-130.
47. Arshad M, El-Kamary SS, Jhaveri R. Hepatitis C virus infection during pregnancy and the newborn period—are they opportunities for treatment? J Viral Hepat 2011;18:229-236.
48. Pembrey L, Newell ML, Tovo PA. The management of HCV infected pregnant women and their children European paediatric HCV network. J Hepatol 2005;43:515-525.
49. Wirth S. Current treatment options and response rates in children with chronic hepatitis C. World J Gastroenterol 2012;18:99-104.