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Modelling the potential clinical and economic impact of universal antenatal hepatitis C (HCV) screening and providing treatment for pregnant women with HCV and their infants in Egypt: a cost-effectiveness study

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ABSTRACT

Backgrounds and aims Pregnant women and children are not included in Egypt's hepatitis C virus (HCV) elimination programmes. This study assesses the cost-effectiveness of several screening and treatment strategies for pregnant women and infants in Egypt.

Design A Markov model was developed to simulate the cascade of care and HCV disease progression among pregnant women and their infants according to different screening and treatment strategies, which included: targeted versus universal antenatal screening; treatment of women in pregnancy or deferred till after breast feeding; treatment of infected children at 3 years vs 12 years. Current practice is targeted antenatal screening with deferred treatment for the mother and child. We also explored prophylactic treatment after birth for children of diagnosed HCV-infected women. Discounted lifetime cost, life expectancy (LE) and disability-adjusted life-years (DALYs) were calculated separately for women and their infants, and then combined.

Results Current practice led to the highest cost (US$314.0), the lowest LE (46.3348 years) and the highest DALYs (0.0512 years) per mother–child pair. Universal screening and treatment during pregnancy followed by treatment of children at 3 years would be less expensive and more effective (cost saving) compared with current practice (US$219.3, 46.3525 and 0.0359 years). Prophylactic treatment at birth for infants born to HCV RNA-positive mothers would also be similarly cost saving, even with treatment uptake as low as 15% (US$218.6, 46.3525 and 0.0359 years). Findings were robust to reasonable changes in parameters.

Conclusion Universal screening and treatment of HCV in pregnancy, with treatment of infected infants at age 3 years is cost saving compared with current practice in the Egyptian setting.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While Egypt is making huge progress towards the elimination goal, to achieve elimination requires the treatment of all populations, including pregnant women and children aged ≤12 years who are currently excluded from the national test-and-treat programme.

WHAT THIS STUDY ADDS

⇒ In this context, a decision analysis model was designed to evaluate the long-term clinical impact and cost-effectiveness of different hepatitis C virus (HCV) screening and treatment strategies among pregnant women and their infants. We found that the current practice resulted in the highest cost, lowest life expectancy and highest disability-adjusted life-years per mother–child pair. In contrast, universal screening and treatment of women during pregnancy followed either by treatment of children at the age of 3 years or by prophylactic treatment at birth for infants born to HCV RNA-positive mothers would be cost saving compared with current practice.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights the need to ensure pregnant women and their children are not left behind the national elimination goals.

INTRODUCTION

In 2015, Egypt had the highest prevalence of hepatitis C virus (HCV) infection in the world, affecting approximately 7% of the population.[1 2] In response to the WHO HCV elimination targets, that is, a 90% reduction in incidence and a 65% reduction in

mortality by 2030 compared with a 2015 baseline,[3] the Egyptian government launched a large-scale HCV test-and-treat programme, following the increased availability of low-cost short-course direct acting antiviral (DAA) treatments which has >95% cure rate. This programme aimed to screen 62 million adults and 15 million adolescents by 2020. During 2018–2019, 49.6 million adults were screened and 2.2 million persons with HCV were referred for treatment with cure rate about 90%.[4] In addition, more than 3 million adolescents aged 15–18 years were screened, of whom 0.38% were HCV antibody positive. All of these were linked to care and 100% of HCV-RNA-positive cases were eligible for treatment.[5]

While Egypt is making huge progress towards the elimination goal, to achieve elimination requires the treatment of all populations, including pregnant women and children aged ≤12 years who are currently excluded from the national test-and-treat programme. In 2018–2019, there were an estimated 345 000 women of childbearing age (age 15–49 years) and 55 000 children aged ≤12 living with HCV in Egypt,[6 7] corresponding to HCV RNA prevalence rates of 1.38% and 0.20%, respectively. Even if the main route of acquisition for children is nosocomial,[5] the risk of vertical transmission of HCV is estimated at 5% and could be higher in the presence of certain maternal risk factors, such as HIV coinfection.[8–10] Current practice in Egypt is antenatal testing of HCV for women at high risk of HCV (history of blood transfusion and/or hepatitis), mainly focused on women with planned caesarean section (c-section). Women who are diagnosed with active HCV during pregnancy (confirmed with HCV RNA) are referred to start treatment after cessation of breast feeding (median duration of breast feeding is 17 months[1]). According to the national population-based screening programme in Egypt, all school children aged 12–18 years are offered HCV antibody screening. HCV antibody-positive children are referred for HCV RNA testing and if positive are offered DAA treatment.[11] The cost-effectiveness of universal antenatal screening for HCV has been demonstrated in some high-income countries,[12–14] with limited data from low-income and middle-income countries with a high HCV burden. It is important to note that DAAs are not currently approved for use during pregnancy, breast feeding or for young children aged <3 years. Nevertheless, treatment of HCV infection during pregnancy has become a realistic prospect, as DAAs are highly effective and treatment duration is relatively short,[15] and one small phase II single-arm clinical trial in nine pregnant women with HCV in the USA showed high efficacy and no safety concerns although for the small sample size.[16] There are also emerging data on off-label use of DAA in pregnancy in India, again with high cure rates, no safety concern but small sample size.[17 18]

This study aims to assess the potential clinical and economic impact of alternative HCV screening and treatment strategies for both pregnant women and children with HCV versus current practice, in the Egyptian setting.

MATERIAL AND METHODS

Study design overview

We designed a decision analysis model to evaluate the long-term clinical impact and cost-effectiveness of different HCV screening and treatment strategies among pregnant women and their infants building on previously published antenatal model of short-term HCV maternal and paediatric outcomes (at delivery)[19] with two post-delivery models, one among women, the other among their infants. We explored eighteen different potential screening and treatment strategies as compared with current practice. The strategies are composed of three components, detailed in table 1: (a) antenatal screening for HCV: current practice screening of women at high risk of HCV focused on those with planned c-section OR WHO recommended targeted screening based on a broader risk factors for HCV in addition to current practice screening OR universal screening of all pregnant women; (b) treatment of HCV-RNA positive pregnant women: deferred treatment to after delivery and cessation of breast feeding OR targeted early treatment during pregnancy of women with risk factors for HCV vertical transmission only OR offer early treatment during pregnancy in all women with HCV RNA; (c) treatment of HCV-RNA positive children: from 12 years (after HCV screening as part of the national elimination campaign) OR early treatment of children from 3 years old according to WHO recommendations (after early screening for HCV in infants born to women diagnosed with HCV RNA positive).

Lifetime horizons of the mother and their children were considered. Long-term model outcomes were calculated separately for mother and child and combined per mother–child pair including life expectancy (LE, in years), disability-adjusted life-years (DALYs, in years) and lifetime HCV-related healthcare cost (in 2023 US dollars, US$1=30.9 Egyptian pounds). LE, DALYs and cost are calculated from start of pregnancy for women (at the age of 30 years) and from birth for children. The incremental cost-effectiveness ratio (ICER) between two strategies was defined as the additional combined cost for mother and infant of a specific strategy compared with the next least expensive strategy, divided by its additional clinical benefit (LE gained or DALYs averted). As a result, such ICER can be interpreted as dollars per life-year gained or per DALY averted. Strategies were considered inefficient and excluded from ICER calculations if they resulted in higher costs but less (or equal) benefit, or had a higher ICER than a more effective strategy (ie, dominated strategies). We used the gross domestic product (GDP) per capita (US$4295 in 2022) for interpreting the ICER, following the WHO's Commission on Macroeconomics and Health[20]: interventions that have an ICER of less than three times GDP per capita are considered cost-effective (ie, willingness to pay (WTP) of US$12 885), and those that have an ICER of less than one times GDP per capita as very cost-effective (ie, a WTP of US$4295). As the threshold of US$12 885 can be considered too high and

Table 1 Screening and treatment strategies evaluated in the cost-effectiveness model

Strategy brief description	Maternal screening	Maternal treatment	Infant treatment*
$S_{Targeted}$-$T_{Deferred}$-T_{12}	Mainly focused on women with planned caesarean section	Defer treatment for HCV RNA-positive women to after delivery and cessation of breast feeding	Treatment from 12 years of HCV RNA-positive children‡
$S_{Risk\text{-}based}$-$T_{Deferred}$-T_{12}	Risk-based screening (WHO recommendations)†		
$S_{Universal}$-$T_{Deferred}$-T_{12}	Universal screening during pregnancy		
$S_{Targeted}$-$T_{Targeted}$-T_{12}	Mainly focused on women with planned caesarean section	Targeted early treatment during pregnancy for HCV RNA-positive women with ≥1 risk factor for HCV vertical transmission§	
$S_{Risk\text{-}based}$-$T_{Targeted}$-T_{12}	Risk-based screening (WHO recommendations)†		
$S_{Universal}$-$T_{Targeted}$-T_{12}	Universal screening during pregnancy		
$S_{Targeted}$-$T_{Universal}$-T_{12}	Mainly focused on women with planned caesarean section	Early treatment during pregnancy for all HCV-RNA positive women	
$S_{Risk\text{-}based}$-$T_{Universal}$-T_{12}	Risk-based screening (WHO recommendations)†		
$S_{Universal}$-$T_{Universal}$-T_{12}	Universal screening during pregnancy		
$S_{Targeted}$-$T_{Deferred}$-T_{3}	Mainly focused on women with planned caesarean section	Defer treatment for HCV RNA-positive women to after delivery and cessation of breast feeding	Early treatment for HCV RNA-positive infants from 3 years old¶ (WHO recommendations)
$S_{Risk\text{-}based}$-$T_{Deferred}$-T_{3}	Risk-based screening (WHO recommendations)†		
$S_{Universal}$-$T_{Deferred}$-T_{3}	Universal screening during pregnancy		
$S_{Targeted}$-$T_{Targeted}$-T_{3}	Mainly focused on women with planned caesarean-section	Targeted early treatment during pregnancy for HCV RNA-positive women with ≥1 risk factor for HCV vertical transmission§	
$S_{Risk\text{-}based}$-$T_{Targeted}$-T_{3}	Risk-based screening (WHO recommendations)†		
$S_{Universal}$-$T_{Targeted}$-T_{3}	Universal screening during pregnancy		
$S_{Targeted}$-$T_{Universal}$-T_{3}	Mainly focused on women with planned caesarean section	Early treatment during pregnancy for all HCV-RNA positive women	
$S_{Risk\text{-}based}$-$T_{Universal}$-T_{3}	Risk-based screening (WHO recommendations)†		
$S_{Universal}$-$T_{Universal}$-T_{3}	Universal screening during pregnancy		

*Infants born to women diagnosed as HCV RNA-positive during pregnancy will be eligible for HCV screening during the first year of life. All children (irrespective of maternal diagnosis and HCV status) are offered screening at age 12 years.
†Based on HCV infection risk factors: Persons who have received medical or dental interventions in healthcare settings where infection control practices are substandard, persons who have received blood transfusions prior to the time when serological testing of blood donors for HCV was initiated or in countries where serological testing of blood donations for HCV is not routinely performed, people who inject drugs, persons who have had tattoos, body piercing or scarification procedures done where infection control practices are substandard, children born to mothers infected with HCV, persons with HIV infection, persons who use/have used intranasal drugs, prisoners and previously incarcerated persons.
‡After HCV screening as part of the national elimination campaign.
§Risk factors for HCV vertical transmission: presence of HIV unsuppressed infection and/or high HCV viral load (≥6 log IU/mL).
¶Treatment is offered after early screening for HCV-exposed infants born to women diagnosed with HCV RNA positive during pregnancy; children who are HCV RNA positive and not treated at age 3 will be offered treatment at age 12.
HCV, hepatitis C virus.

contestable, we interpreted our results according to both thresholds. We considered an intervention cost saving if it resulted in lower costs and higher benefit than other interventions.

All LE, DALYs and costs were discounted at 3.5% per year.[21] We adopted a healthcare system perspective as the focus is only on the production of healthcare and not on global care (which includes informal caregivers).

Model structure

Two population-specific (maternal and paediatric) HCV postdelivery Markov-based models were developed and simulated the trajectory of a cohort of pregnant women and their newborns until maternal and child death (figure 1 and online supplemental figure S1).

The three simulation models are described in detail in online supplemental information and in previous

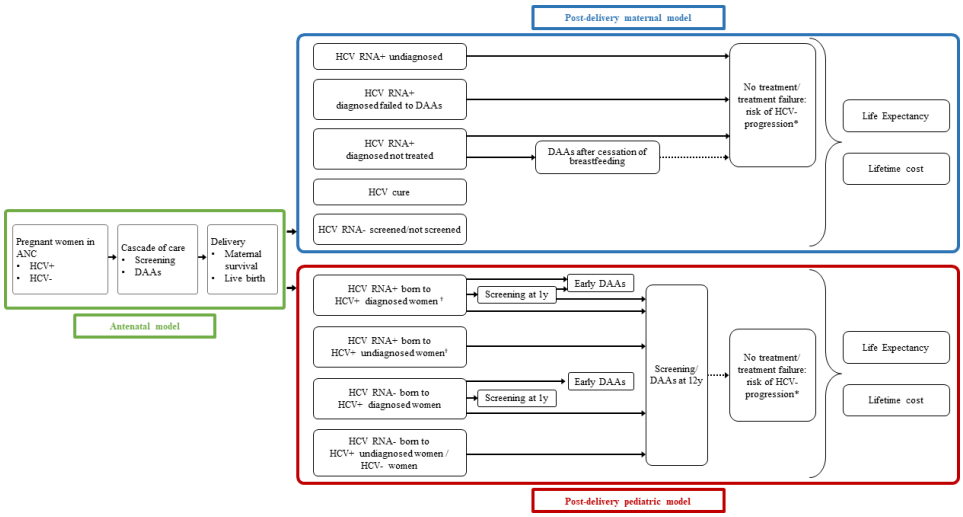

Figure 1 Model structure. The antenatal model provides the postdelivery distribution of mothers and their infants regarding their HCV status.[19] Postdelivery maternal and paediatric models allow assessment of lifetime costs and life expectancies based on the postdelivery cascade of care.*The risk of HCV progression in post-delivery maternal and pediatric models is related to the model of chronic hepatitis C progression presented in online supplemental figure S1.†During the first 5 years of life, children with HCV RNA positive status have an annual probability of clearing HCV infection. DAA, direct acting antiviral; HCV, hepatitis C virus.

publications.[19 22] Briefly, the first part of the postdelivery models stratifies mother and child populations according to their characteristics at delivery: women are categorised based on their HCV RNA status (±), HCV diagnosis status (yes/no) and their HCV treatment during pregnancy status (untreated/treated and cured/treated and not cured); infants are categorised based on their HCV RNA status (±) and whether their mother is diagnosed HCV RNA-positive or not. This stratification varied according to the different strategies from the antenatal model. Moreover, to take into account the eligibility and timing of treatment initiation for women, the model was also stratified by whether or not they breastfeed, and the duration of breast feeding. Then for each profile of individuals, the Markov-chain simulated the possible interventions (screening, offer of treatment, uptake of treatment), depending on women or children subpopulation and the strategy assessed and progression through liver disease stages. At the Markov node, we categorised HCV-RNA positive women into fibrosis stages according to available data,[23] while all HCV RNA-positive infants (assume all due to vertical transmission) are initially assigned to the undiagnosed F0 fibrosis state at time of birth with an annual probability of disease progression while untreated.

The Markov cycle for both the maternal and paediatric model is 1 year. Pregnant women enter the model at the start of pregnancy, children enter at birth. Pregnant women have a probability of being diagnosed with HCV and linked to care. In the paediatric model, this is only among children born to women diagnosed with HCV in pregnancy. For all there is a probability of screening from age 12 as part of the national programme. During the first 5 years of life, children with HCV RNA positive status have an annual probability of clearing HCV infection.[24] HCV RNA-positive maternal and paediatric populations have an annual risk of disease progression (details in online supplemental figure S1). Among those in care there is an annual risk of loss to follow-up and among the strategies where treatment is offered—a probability of uptake of treatment and being cured.

Model inputs

Study population

The study population consisted of a cohort of pregnant women and their infants. Values for the model parameters are given in online supplemental table S1. According to our previous modelling study, 1.33% of pregnant women were HCV RNA-positive at entry into antenatal care[19]: 0.78% undiagnosed, 0.55% diagnosed and untreated, 0% diagnosed with treatment failure, 0% HCV cure in $S_{Targeted}$-$T_{Deferred}$- regardless of infant component, compared with 0.16%, 0.26%, 0.05% and 0.87%, respectively, in $S_{Universal}$-$T_{Universal}$- regardless of infant component. It should be noted that we assumed an 88% uptake of screening during pregnancy in the universal strategy based on an acceptability study conducted among pregnant and postpartum women in Egypt.[25]

For the strategies with deferred maternal treatment until after delivery and cessation of breast feeding, we assumed 97% of women in Egypt breastfeed at delivery, reducing to 89% at 1 year and 31% at 2 years based on national estimates.[1] We assumed that no women continued breast feeding after 3 years.

According to our previous modelling study,[19] the proportion of HCV RNA-positive infants at delivery decreased from 0.116% for strategies deferring treatment of women to after delivery and breastfeeding cessation to 0.06% for universal treatment of women during pregnancy (online supplemental table S1). Among

them, between 41% and 85% were born to diagnosed HCV RNA-positive mothers, depending on the strategy. Among HCV RNA-negative infants at delivery, between 0.43% and 0.96% were born to diagnosed HCV RNA-positive mothers (online supplemental table S1).

Finally, HCV RNA-positive women were distributed into disease stages at time of entry to the model (at start of pregnancy): 27% in F0, 27% in F1, 10% in F2, 17% in F3 and 19% in F4 (online supplemental information).[23]

HCV progression, retention in care, HCV screening and treatment

Online supplemental table S1 also presents all input parameters and assumptions. Parameters values of the progression models and assumption regarding retention in care are detailed in online supplemental information.[26–33] The assumptions for uptake of HCV screening and treatment are based on the opinion of the Egyptian professors of this study except for the uptake of treatment of women after breastfeeding cessation (68.4%) which was based on a retrospective cohort study conducted at university hospital for delivery in 2018.[34] Although the national programme concerns the screening and treatment of adolescents between 12 and 18 years of age, we applied it to all children at the age of 12.

Adapted DAAs combination are chosen for each subpopulation according to the current practice[4] or the WHO recommendations.[35] Sustained virological response (SVR) is derived from local published data for women after breastfeeding cessation and children at the age of 12 years[5] and from clinical trial for children at the age of 3 years.[36] Annual probabilities of HCV clearance according to age were calculated from Ades *et al*'s study[24] and detailed in online supplemental table S1.

Cost data

We considered direct medical lifetime costs associated with HCV screening, HCV disease care and treatment (online supplemental table S1). Cost of HCV screening included the test for HCV antibodies, and when positive, the test for HCV-RNA.[4] Based on the antenatal model,[19] we calculated the costs of screening and treatment of women during pregnancy (online supplemental information). We estimated cost related to health condition, death and treatment initiation from local data.[37 38] Regarding treatment costs, drug costs for 12 weeks course were estimated depending on the appropriate DAA combination: US$85 for Sofosbuvir/Daclatasvir (SOF/DAC), US$116 for Sofosbuvir/Ledipasvir (SOF/LED) and US$381 for Sofosbuvir/Velpatasvir (SOF/VEL).[4 5 39]

DALYs data

DALYs are the sum of years of life lost due to disease (YLL) and years of life spent in the disease state weighted to disability weight. We used the LE projected by the model for an HCV-free population (38.9 years for pregnant women aged 30, 67.3 for girls and 65.5 for boys at birth) to calculate YLL. We obtained disability weights for each health state from the GBD 2019 (online supplemental table S1).[40]

Sensitivity analysis

An extensive sensitivity analysis was conducted to evaluate the impact of assumptions or uncertainties around the data and to determine the robustness of our overall conclusions. We first performed a deterministic univariate sensitivity analysis on lifetime cost, LE and DALYs for the most efficient or cost-saving strategy. We varied the value of each parameter from the lower to the upper bound of its uncertainty interval based on the literature or, if not available, set to plausible range (online supplemental table S1).

We also explored the impact of the variation of the initial distribution in fibrosis stages for women at entry to model with a less (35%%–35%-10%%–15%–5%) or more (20%%–20%-15%%–20%–25%) severe distribution compared with baseline.[23] We also varied the discounting rate at 2% and 6%.[21]

Second, we performed two probabilistic sensitivity analyses, simultaneously varying the 20 most influential parameters on lifetime cost and LY on the one hand and on lifetime cost and DALY on the other hand, identified in the univariate analysis, using appropriate probability distributions across 10 000 simulations (online supplemental table S2).

Finally, we performed an exploratory analysis where prophylactic treatment using DAAs were offered soon after birth for infants born to mother diagnosed HCV RNA-positive at entry into antenatal care irrespective of maternal DAA treatment status during pregnancy.[41 42] For that we considered a treatment uptake range between 15% and 25% and assumed the same data regarding the DAAs combination, cost and SVR as treating children at the age 3 years.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Baseline analysis

Table 2 provides the base-case cost-effectiveness analysis for combined outcomes per mother–infant pair. $S_{Universal}$-$T_{Universal}$-T_3 resulted in the lowest discounted lifetime cost (US$219.3), the highest discounted LE (46.3525 years) and the lowest discounted DALYs (0.0359), and was therefore cost saving compared with other strategies which are all dominated.

Projected maternal and paediatric outcomes are presented in online supplemental table S3 according to each strategy. Maternal lifetime costs from pregnancy were US$580.1 (undiscounted) and US$290.6 (discounted) with current practice ($S_{Targeted}$-$T_{Deferred}$-regardless of infants' component). These costs decreased to US$394.5 (undiscounted) and US$197.1 (discounted)

Table 2 Base-case cost-effectiveness analysis of strategies $S_{Universal}$-$T_{Universal}$-T_3 to $S_{Targeted}$-$T_{Deferred}$-T_{12}: combined outcomes per mother–infant pair

Strategy*	Lifetime cost† (US$)	Life expectancy† (years)	DALYs	ICER (US$/ years)
$S_{Universal}$-$T_{Universal}$-T_3	219.3	46.3525	0.0359	Cost saving
$S_{Universal}$-$T_{Universal}$-T_{12}	219.6	46.3525	0.0359	Dominated
$S_{Risk\text{-}based}$-$T_{Universal}$-T_3	225.7	46.3511	0.0370	Dominated
$S_{Risk\text{-}based}$-$T_{Universal}$-T_{12}	226.0	46.3511	0.0371	Dominated
$S_{Universal}$-$T_{Targeted}$-T_3	231.4	46.3500	0.0386	Dominated
$S_{Universal}$-$T_{Targeted}$-T_{12}	231.8	46.3499	0.0386	Dominated
$S_{Universal}$-$T_{Deferred}$-T_3	238.6	46.3489	0.0397	Dominated
$S_{Risk\text{-}based}$-$T_{Targeted}$-T_3	238.9	46.3486	0.0397	Dominated
$S_{Universal}$-$T_{Deferred}$-T_{12}	239.2	46.3488	0.0398	Dominated
$S_{Risk\text{-}based}$-$T_{Targeted}$-T_{12}	239.3	46.3485	0.0398	Dominated
$S_{Risk\text{-}based}$-$T_{Deferred}$-T_3	245.8	46.3475	0.0408	Dominated
$S_{Risk\text{-}based}$-$T_{Deferred}$-T_{12}	246.4	46.3475	0.0409	Dominated
$S_{Targeted}$-$T_{Universal}$-T_3	302.5	46.3367	0.0493	Dominated
$S_{Targeted}$-$T_{Universal}$-T_{12}	302.6	46.3367	0.0493	Dominated
$S_{Targeted}$-$T_{Targeted}$-T_3	311.2	46.3353	0.0508	Dominated
$S_{Targeted}$-$T_{Targeted}$-T_{12}	311.3	46.3352	0.0508	Dominated
$S_{Targeted}$-$T_{Deferred}$-T_3	313.7	46.3349	0.0512	Dominated
$S_{Targeted}$-$T_{Deferred}$-T_{12}	314.0	46.3348	0.0512	Dominated

*First component corresponds to antenatal screening for HCV (S): $S_{Targeted}$=current practice screening of women at high risk of HCV focused on those with planned c-section; $S_{Risk\text{-}based}$=WHO recommended targeted screening based on a broader risk factors for HCV in addition to current practice screening; $S_{Universal}$=universal screening of all pregnant women; Second component corresponds to treatment of HCV-RNA positive pregnant women (T): $T_{Deferred}$ = deferred treatment to after delivery and cessation of breast feeding; $T_{Targeted}$=targeted early treatment during pregnancy of women with risk factors for HCV vertical transmission only; $T_{Universal}$=offer early treatment during pregnancy in all women with HCV RNA; Third component corresponds to treatment of HCV-RNA positive children (T): T_{12}=from 12 years (after HCV screening as part of the national elimination campaign); T_3=early treatment of children from 3 years old according to WHO recommendations (after early screening for HCV in infants born to women diagnosed with HCV RNA positive);
†Discounted; maternal outcomes are calculated from pregnancy (at the age of 30 years); paediatric outcomes are calculated from birth.
DALY, disability-adjusted life-year; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; LE, life expectancy.

with $S_{Universal}$-$T_{Universal}$. Maternal LE was 38.7284 (undiscounted) and 20.8644 (discounted) years from pregnancy with current practice ($S_{Targeted}$-$T_{Deferred}$- regardless of infants' component), and increased to 38.7752 (undiscounted) and 20.8820 (discounted) years from pregnancy with $S_{Universal}$-$T_{Universal}$. Conversely, maternal DALY was 0.1164 (undiscounted) and 0.0511 (discounted) years from pregnancy with current practice ($S_{Targeted}$-$T_{Deferred}$- regardless of infants' component), and decreased to 0.0789 (undiscounted) and 0.0359 (discounted) years from pregnancy with $S_{Universal}$-$T_{Universal}$.

Regarding paediatric outcomes (online supplemental table S3), current practice ($S_{Targeted}$-$T_{Deferred}$-T_{12}) was the most expensive (US$169.7 when undiscounted, US$23.4 when discounted) and the least effective (66.3465 and 0.0007 undiscounted years and 25.4704 and 0.0001 discounted years, respectively, for LE and DALYs from birth), whereas $S_{Universal}$-$T_{Universal}$-T_3 was the least expensive (US$167.4 when undiscounted, US$22.2 when discounted) and the most effective (66.3471 and 0.0002 undiscounted years and 25.4705 and $<10^{-4}$ discounted years, respectively, for LE and DALYs from birth).

Sensitivity analysis

Figure 2 illustrates the results of deterministic sensitivity analysis for the 20 most influential parameters on projected lifetime costs, LE and DALYs per mother–infant pair for $S_{Universal}$-$T_{Universal}$-T_3. Overall, with the exception of the discount rate variation, the impact was moderate on lifetime costs and DALYs (maximum 8% and 16% relative variation, that is, US$18 and 0.0038 years per mother–infant pair) and very low on LE (<0.02% relative variation, ie, 0.0056 year per mother–infant pair). First, varying the proportion of F4 in HCV RNA-positive women, annual cost associated with death and annual cost associated with fibrosis stage F4 by ±20% have an impact on the outcomes without affecting our main conclusion: $S_{Universal}$-$T_{Universal}$-T_3 was still cost saving and dominated all others strategies (online supplemental tables S4–S6). Second, when we varied the initial

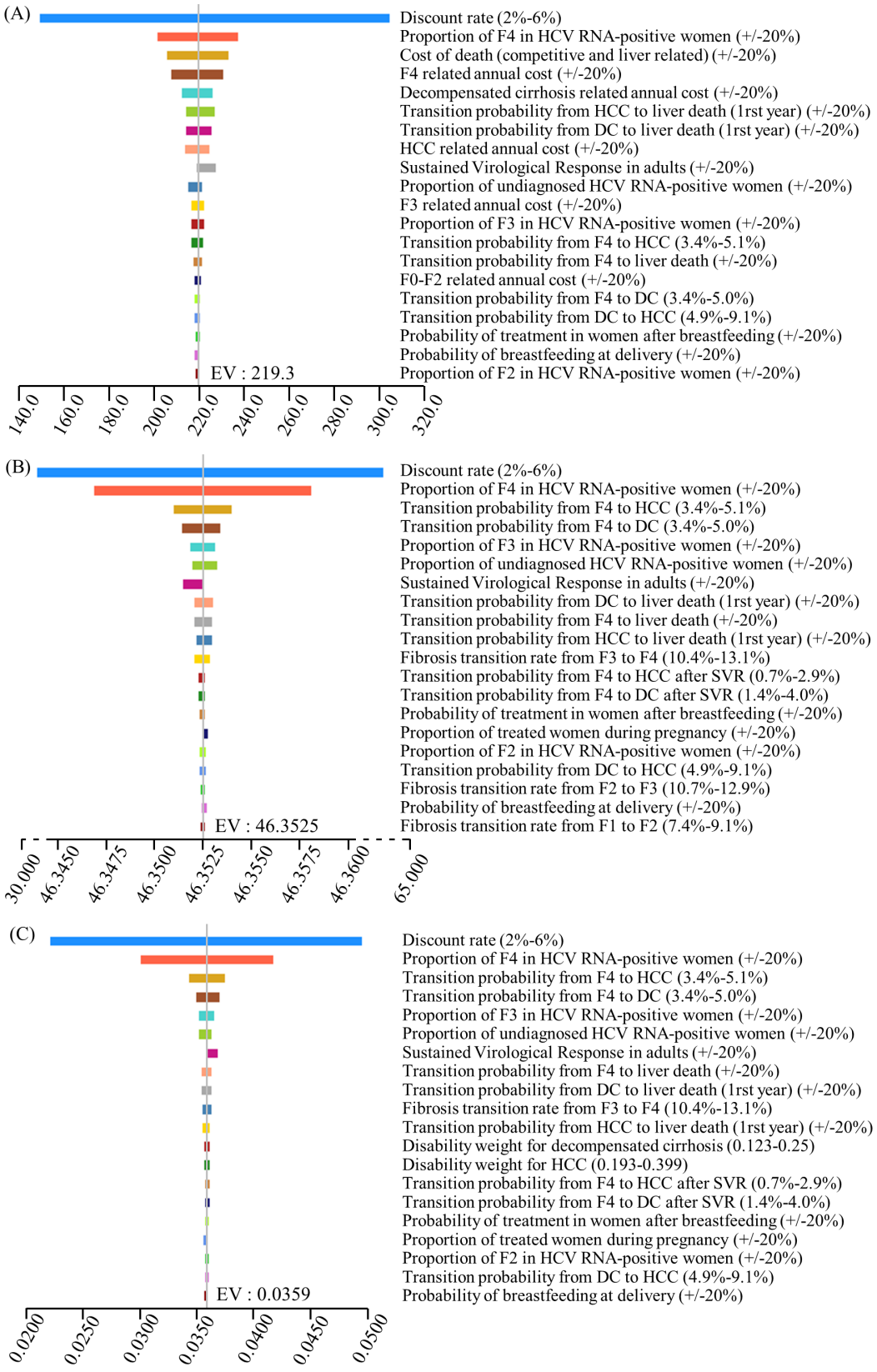

Figure 2 Univariate sensitivity analysis performed on the two outcomes for strategy ($S_{Universal}$-$T_{Universal}$-T_3): mother–infant pair combined HCV-related lifetime costs (A), life expectancy (B, C) disability-adjusted life-years (DALYs). The tornado diagram summarises univariate deterministic sensitivity analysis to explore the robustness of the two outcomes according to uncertainty of parameters. The bars represent the range in outcomes if the model's parameters varied across their plausible ranges. The vertical line in the middle denotes the base case (EV), that is, mother–infant pair combined HCV-related lifetime costs at US$219.3, life expectancy at 46.3525 years and DALYS at 0.0359 years. The horizontal bars were sorted according to the magnitude of variation of the outcomes. DC, Decompensated Cirrhosis; HCC, Hepatocellular Carcinoma;HCV, hepatitis C virus.

fibrosis distribution of women, a less severe distribution decreased lifetime costs (US$152.1 vs US$219.3 in base case), increased LE (46.3736 years vs 46.3525 years in base case) and decreased DALYs (0.0141 vs 0.0359) per mother–infant pair in $S_{Universal}$-$T_{Universal}$-T_3 (online supplemental table S7). On the contrary, a more severe distribution resulted in higher lifetime costs (US$251.3), lower LE (46.3427 years) and higher DALYs (0.0460) per mother–infant pair in $S_{Universal}$-$T_{Universal}$-T_3 (online supplemental table S7). However, our main results remained unchanged. Third, varying the discounting rate between 2% and 6% varied the three outcomes between 32% and 39% relative change, but our conclusions remained unchanged (online supplemental table S8). Finally, the impact of variation in other parameters was less (<5% relative change) and also did not affect the main conclusions (not shown); $S_{Universal}$-$T_{Universal}$-T_3 was still cost saving and dominated all others strategies.

Using probabilistic sensitivity analysis, we showed that ($S_{Universal}$-$T_{Universal}$-T_3) remained the optimal strategy regardless of WTP, and was cost saving in at least 87% of simulations at both one-time GDP per capita and three times GDP per capita WTP (figure 3A,B).

Finally, the exploratory analysis combining universal screening and treatment of women during pregnancy with a prophylactic treatment at birth for all infants born to mother diagnosed with HCV RNA-positive was cost saving compared with all strategies when assuming the same cost of DAA treatment as children at the age 3 and treatment uptake between 15% and 25% (online supplemental table S8). This conclusion remained unchanged when increasing the cost of DAA for the prophylactic treatment by 10 times (not shown).

DISCUSSION

This study evaluated the effectiveness, cost and cost-effectiveness of different HCV screening and treatment of pregnant women and their infants in Egypt. First, current practice, that is, $S_{Targeted}$-$T_{Deferred}$-T_{12}, was the most expensive in terms of mother–infant pair combined HCV-related lifetime costs and the less effective in terms of mother–infant pair combined LE. Second, $S_{Universal}$-$T_{Universal}$-T_3 is a cost-saving strategy compared with current practice and to all alternative strategies, leading to the lowest mother–infant pair combined HCV-related lifetime costs and highest mother–infant pair combined LE. Finally, combining universal screening and treatment of women during pregnancy with a hypothetical prophylactic treatment of all HCV exposed infants at birth may be cost saving compared with current strategy. These findings were consistent when considering plausible variation range of all parameters in sensitivity analyses, even for the prophylactic scenario where uncertainties about cost, effectiveness and duration of prophylactic treatment are greater.

Our modelled results are largely based on estimates obtained in our previously published study.[19] This pregnancy-specific study (short-term analysis) showed that universal screening and treatment of all pregnant women with HCV during their pregnancy would result in the largest number of women being diagnosed during pregnancy and cured by delivery, with a 50% decrease in the proportion of infants infected compared with current practice.[19] Our long-term analysis showed that in addition to the short-term clinical benefit for mothers and their children, $S_{Universal}$-$T_{Universal}$-T_3 is the most effective strategy over the long term and is even cost saving. This is true not only for the mother–infant pair combined outcome but also the separate maternal and paediatric outcomes. It is important to emphasise that the estimated costs and LE are an average of all pregnant women and their children, that is, those with and without HCV, explaining that the variations are small from one strategy to another. However, if we look more specifically at the HCV RNA-positive maternal and paediatric populations that will benefit from the strategies, $S_{Universal}$-$T_{Universal}$-T_3 would decrease maternal and paediatric lifetime costs by 38% and 24%, respectively, increase LE by 7.8% and 0.2%, respectively, and decreased DALYs by 30% and 42%, respectively, compared with current practice (online supplemental table S9). The small increase of LE for children between strategies is explained because of the small proportion of children remaining HCV RNA-positive, due to spontaneous HCV clearance during the first 5 years and the high proportion of treated children at 12 years for all strategies, thanks to the national elimination campaign. On the contrary, the gain in cost for children is substantial, −5% in the study population and −24% in the HCV RNA-positive population, $S_{Universal}$-$T_{Universal}$-T_3 avoiding costs related to HCV health condition thanks to early HCV cure.

We also confirm in this work that $S_{Targeted}$-$T_{Deferred}$-T_{12} is the least effective, as highly targeted screening of HCV resulted in the highest proportion of women with HCV remaining undiagnosed at delivery (0.78%) in comparison with the WHO targeted approach and universal screening (0.22%–0.16%). Subsequently, the proportion of infants infected with HCV was highest with current practice compared with the other strategies (0.116% vs 0.094%–0.06%); among infants infected with HCV, the proportion of those born to undiagnosed mothers—and therefore not targeted by postnatal screening—is also the highest (59% vs 15%–24%). One of the new results of this study is to show that the current practice strategy is also the most expensive. This is based on two elements: the availability of low costs of HCV tests and generic treatments in a short-time frame, while the costs of managing HCV disease are high, especially when complications such as DC and HCC occur. Varying these costs by ±20% in sensitivity analysis, did not change our conclusions.

Moreover, if infant-appropriate DAA formulations become available, safe and with a similar cost to DAAs for children aged 3 years, the exploratory scenario of prophylactic treatment at birth of all infants born to mothers diagnosed as HCV RNA-positive combined with

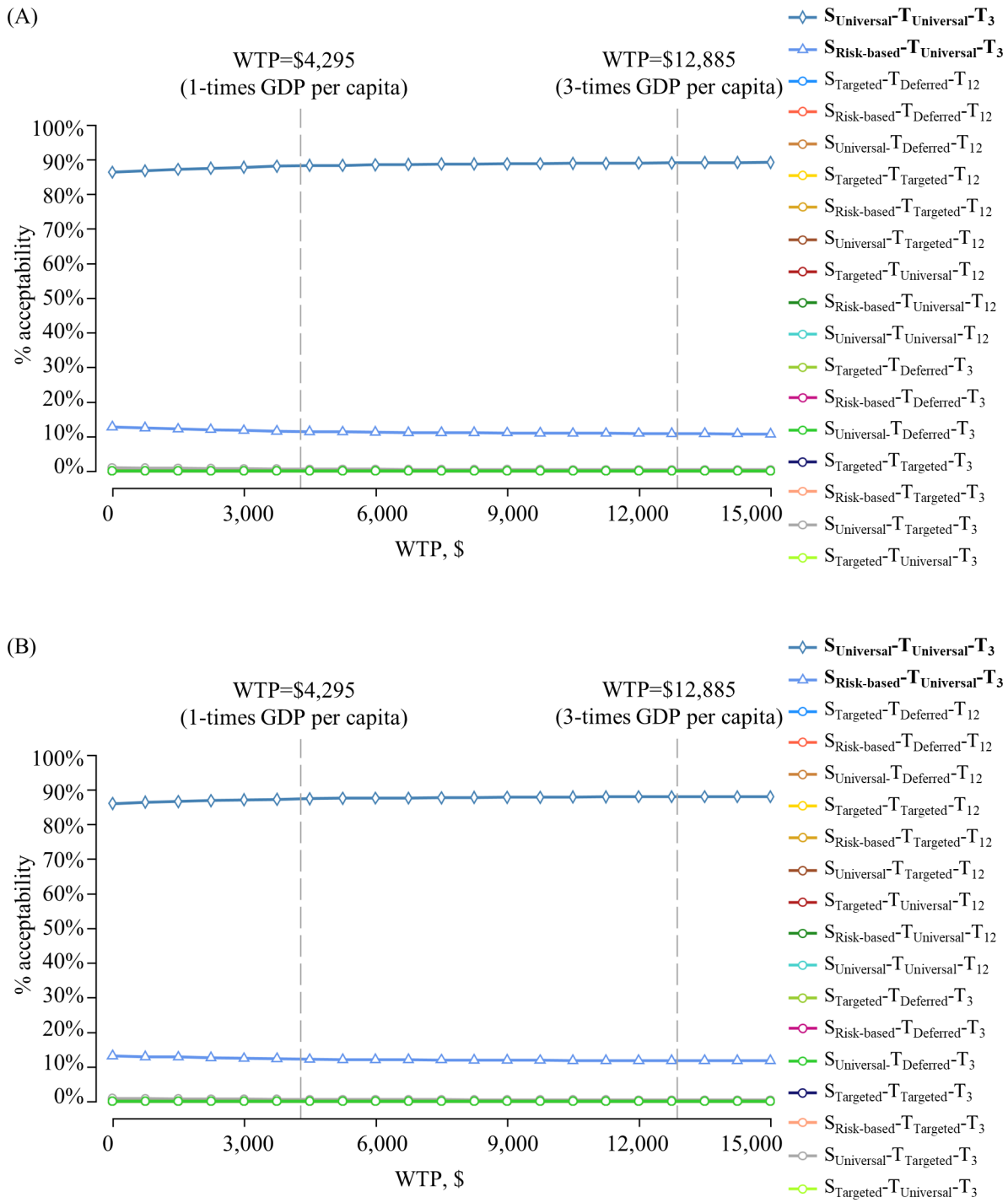

Figure 3 Results from the probabilistic sensitivity analysis. The acceptability curve depicts the probability that a given strategy is cost-effective as a function of the WTP across all simulations of the probabilistic sensitivity analysis. With the exception of $S_{Universal}$-$T_{Universal}$-T_3 and $S_{Risk\text{-}based}$-$T_{Universal}$-T_3 strategies (in bold), the other strategies overlap. GDP, gross domestic product; WTP, willingness to pay.

screening and treatment of the mother during pregnancy would be the least expensive and most effective strategy. Taking into account HCV spontaneous clearance up to the age of 5 years, one downside is the probability of overtreatment to those not infected or likely to clear. However, high rates of loss of follow-up when delaying HCV RNA testing infants at the WHO-recommended 18 months of age have been reported in previous studies[24] as a factor to support early treatment after birth for infants. Moreover, there is evidence that in patients without HCV infection who received a heart or lung transplant from donors with hepatitis C viraemia, pre-emptive treatment with DAAs, initiated within a few hours after transplantation, prevented the development of HCV infection.[41] These findings support the idea that early DAAs after potential vertical transmission could prevent it.[42]

We have previously demonstrated the importance of pregnancy as a unique opportunity to test and treat women at childbearing age when they are engaged with healthcare providers notably for surveillance even if Egypt is announced as the country that eliminated HCV.[19] In this work, we also demonstrated that postpartum period, thanks to the paediatric vaccination schedule during first years after delivery, is an opportunity to treat not only infants early after birth or at the age of 3 years but also their mothers after delivery and breastfeeding cessation. Nevertheless, the linkage to HCV programmes and Maternal and Child Health centre clinics remains essential for better follow-up and uptake of the treatment.

Our results are in line with previous studies in some high-income countries showing the cost-effectiveness of universal antenatal screening for HCV.[13 14] Although universal hepatitis C screening is already recommended in the USA,[43] this study is one of the first to assess the cost-effectiveness of different HCV screening and treatment strategies considering both the prenatal and postpartum periods. Apart from hepatitis C, Ciaranello *et al* projected clinical impact, costs and cost-effectiveness of WHO-recommended treatment strategies for prevention of mother to child HIV transmission in Zimbabwe.[44] They demonstrated the cost-effectiveness of a strategy in which all HIV-infected pregnant women and their infected children would initiate lifelong antiretroviral treatment, regardless of CD4 count.

Future areas of research include a budgetary impact analysis of adding HCV screening and treatment to existing antenatal and postnatal care policies across different settings. More broadly, it would be important to assess the budgetary impact of incorporating HCV to the WHO's recommendation for triple elimination of HIV, HBV and syphilis through screening and treatment in pregnancy.[45]

This study has some limitations. First, we used a mathematical model relying on input data from multiple sources. In the absence of real data, our baseline analysis was based on assumptions for HCV screening and treatment uptake, in particular for infants. However, varying these assumptions in sensitivity analysis does not change our conclusions. Second, we considered the same rates of fibrosis progression in children as in adults. Indeed, there are few data available in the paediatric population, and those available may be overestimated due to the estimation method. These estimates are obtained from the transitions and the time elapsed between fibrosis stages. However, in children, this time is necessarily shorter, leading to much higher rates of fibrosis than in adults.[26] Consequently, we made the choice to apply the rates of fibrosis progression estimated in the general population to the paediatric population after ensuring that our conclusions did not vary (not shown). This assumption of a slower progression is conservative since it favours late screening and treatment strategies. Third, in the absence of utility scores associated with quality of life among HCV-infected children and no recent data in adults in the Egyptian setting,[37] we did not perform cost per QALY analyses. As an alternative, we used DALYs, which is the preferred measure of health in resource-limited settings.[46] Indeed, while there is no database providing QALYs for all diseases and for each country, the GBD Disability Burden Survey provides a common data source for assessing the value of different health conditions.[40] Thus, we supplemented the cost-effectiveness analysis based on LE with a cost–utility analysis based on DALYs. The results of the two analyses lead to the same conclusion. This has also been the choice in the case of cost-effectiveness of strategies for prevention of mother-to-child HIV transmission.[44] Fourth, our modelling was unable to quantify reinfection rate in adult women and the percentage of intrafamily transmission of HCV. Fifth, our results relied on the costs of DAAs from recent published studies that may have decreased given the dynamics of elimination in progress in Egypt. However, the $S_{Universal}$-$T_{Universal}$-T_3 would be all the more cost saving. Similarly, with dramatic decreasing numbers of patients, companies may change producing medications to adapt to market demand. However, we also evaluated our strategies considering DAA combination of SOF/DAC also for children, and our conclusion remained unchanged (online supplemental table S10). Finally, this work was based on Egyptian data—as much as possible—and on the Egyptian health system but can be adapted to other countries with a high HCV prevalence.

In conclusion, the universal screening and treatment during pregnancy strategy was shown to be cost-effective as compared with current practice, based on the assumption that it is safe to use during pregnancy. More data on this are urgently needed to ensure pregnant women and their children are not left behind the national elimination goals.

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