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BRIEF REPORTS

Reducing Unintended Pregnancies as a Strategy to Avert Zika-Related Microcephaly Births in the United States: A Simulation Study

Katherine A. Ahrens[1] · Jennifer A. Hutcheon[2] · Loretta Gavin[1] · Susan Moskosky[1]

Abstract *Introduction* There is increasing evidence that infection with the Zika virus (ZIKV) during pregnancy can lead to severe brain abnormalities in infants exposed in utero. The objective of our analysis was to estimate the contribution of enhanced contraception access to averting ZIKV-related microcephaly births in the United States, alone and in combination with another possible strategy, anti-ZIKV vaccination. *Methods* We used Monte Carlo sampling techniques (n = 100,000 simulations) to estimate the number of microcephaly births expected under strategies of enhanced contraception only, vaccination only, both enhanced contraception and vaccination, and status quo (no intervention). Enhanced contraceptive access was assumed to reduce unintended pregnancy rates by 46% and anti-ZIKV vaccination was assumed to be 90% effective. Plausible values for effectiveness of enhanced contraceptive access, ZIKV cumulative incidence, ZIKV-related microcephaly risk, and anti-ZIKV vaccination parameters were derived from the literature or best available knowledge. *Results* Enhanced contraceptive access alone reduced the median number of ZIKV-related microcephaly births by 16% (95% simulation interval: 5, 23), while the anti-ZIKV

vaccine alone reduced these births by 9% (95% SI: 0, 18), 45% (95% SI: 36, 54), and 81% (95% SI: 71, 91), under conservative (10% vaccine uptake), moderate (50% vaccine uptake), and optimistic (90% vaccine uptake) scenarios, respectively. The reduction in ZIKV-related microcephaly births was always greater if both interventions were employed. *Discussion* Enhanced contraceptive access alone has the ability to produce a meaningful reduction in microcephaly births, and could provide an important adjuvant prevention strategy even following the development of a highly-effective anti-ZIKV vaccine.

✉ Katherine A. Ahrens
  kate.ahrens@hhs.gov

1 Department of Health and Human Services, Office of Population Affairs, Office of the Assistant Secretary for Health, 1101 Wootton Parkway, Suite 700, Rockville, MD 20852, USA

2 Department of Obstetrics and Gynaecology, University of British Columbia, Vancouver, Canada

Significance

What is already known on the subject? The role of enhanced contraceptive access in minimizing the number of Zika-related microcephaly births has received relatively little attention, despite the fact that approximately one-third of births in the US are unintended at the time of conception.

What this study adds? Using data simulations, we found that enhanced contraceptive access alone may have the ability to produce a meaningful reduction in microcephaly births, and could provide an important adjuvant prevention strategy even following the development of a highly-effective anti-Zika vaccine.

Introduction

There is increasing evidence that infection with Zika virus (ZIKV) during pregnancy can lead to structural anomalies

and functional disabilities in fetuses and infants exposed in utero, including severe brain abnormalities such as microcephaly (Rasmussen et al. 2016; Moore et al. 2016). Although there has been considerable discussion on the roles of vector control, vaccine development, and prevention of sexual transmission through condom use in preventing the spread of ZIKV (Frieden et al. 2016; Weaver et al. 2016), the role of enhanced contraceptive access in minimizing the number of infants born with ZIKV-related birth defects has received relatively little attention (Burke and Moreau 2016; Goldthwaite and Velasquez 2016; Dehlendorf et al. 2017). Approximately 45% of pregnancies and 35% of births in the United States are unintended at the time of conception (Finer and Zolna 2016; Martin et al. 2013), and offering women who do not want to become pregnant the full range of contraceptive methods, including long-acting, reversible contraception (LARCs; i.e., intrauterine devices, progestin implants), has been shown to be highly effective in reducing unintended pregnancy rates (Harper et al. 2015; Secura et al. 2014). Induced termination, while effective in reducing unplanned births in general, may be not be a feasible option for many women given how late ZIKV-related birth defects can be diagnosed in pregnancy (Aiken et al. 2016; Burke and Moreau 2016). Despite the evidence pointing to the important role of enhanced contraception access in preventing unintended pregnancies, the contribution of enhanced contraception access to ZIKV-related birth defect prevention has not yet been empirically evaluated.

This study aimed to quantify the number of ZIKV-related microcephaly births in the United States that might be averted through prevention of unintended pregnancy. Although ZIKV infection during pregnancy can result in a range of structural anomalies and functional disabilities (Moore et al. 2016; Brasil et al. 2016; Boulet et al. 2016; Cuevas et al. 2016), we focused on the specific birth defect of microcephaly because estimates of its prevalence at birth among women infected with ZIKV while pregnant are available (Johansson et al. 2016; Cauchemez et al. 2016; Ellington et al. 2016). To help contextualize the magnitude of any observed reductions in ZIKV-related microcephaly births, we compared these estimates to those expected under another strategy for mitigating adverse health outcomes given widespread local ZIKV transmission: the use of a yet to be commercially available anti-ZIKV vaccine. We estimate the number of ZIKV-related microcephaly births in the United States that would be expected to occur under 4 strategies: (1) the current rate of unintended pregnancies and no anti-ZIKV vaccine (status quo); (2) enhanced contraceptive access to reduce the rate of unintended pregnancies; (3) administration of an anti-ZIKV vaccine to reproductive aged women; and (4) enhanced contraception access in conjunction with an anti-ZIKV

vaccine. Understanding the reductions potentially achieved by these different strategies may help guide allocation of resources for reducing ZIKV-related microcephaly births.

Methods

We estimated the number of reproductive-aged women (15–44 years) residing in states with potential ZIKV-carrying mosquitoes using census population estimates for 2015 and compiled county-level data on the presence of *Aedes aegypti* and *Aedes albopictus* mosquitoes during 1995–2016 (Hahn et al. 2016; US Census Bureau). The following 11 states (plus the District of Columbia) had at least one *Aedes aegypti* mosquito, the primary vector for ZIKV, documented in at least one county for the years 2013, 2014, and 2015: Arizona, California, Florida, Georgia, Kansas, Kentucky, New Jersey, New Mexico, South Carolina, Texas, Virginia and the District of Columbia. Incidentally, these areas also had at least one report of *Aedes albopictus*, a secondary vector for ZIKV, in at least one county for 3 or more years during 1995–2016.

Estimates of the prevalence of microcephaly birth following ZIKV infection during pregnancy, anti-ZIKV vaccine effectiveness, and anti-ZIKV vaccine uptake were taken from the literature when published estimates were available (Web Table). When published estimates were unavailable, we used best available knowledge to derive a range of plausible values. Conservative (10%), moderate (50%), and optimistic (90%) anti-ZIKV vaccine uptake scenarios were evaluated; mean vaccine effectiveness was assumed to be 90%. Vaccine uptake was assumed to cover a sample of average-risk reproductive age women, in contrast to a vaccination campaign where only those at highest risk of ZIKV infection are vaccinated (e.g., ring vaccination). Given the uncertainty about how widespread ZIKV infection could be in the United States, we allowed the cumulative incidence of ZIKV infection to range from 0 to 100%. However, we highlighted low (5%), moderate (25%) and high cumulative incidence (50%) levels to direct attention to these three possibilities, as the incidence of ZIKV infection will most likely vary by ZIKV transmission patterns and how successful vector control and condom use promotion efforts are to reduce mosquito and sexual transmission, respectively.

Estimates of the number of unintended pregnancies and the proportion of unintended pregnancies resulting in a live birth were obtained from a recent analysis by Finer et al. using data from the National Survey of Family Growth, vital records, and surveys of abortion providers and patients (Martin et al. 2013; Finer and Zolna 2016). Enhanced contraceptive access was assumed to reduce unintended pregnancy rates by 46%, based on findings from a cluster

randomized trial in 40 reproductive health clinics across the United States evaluating the effect of evidence-based LARC training (Harper et al. 2015). Enhanced contraceptive access was assumed to be independent of anti-ZIKV vaccine uptake.

To estimate the number of ZIKV-related microcephaly births expected to occur during the first year of widespread local ZIKV transmission, we first estimated the number of reproductive-aged women expected to be exposed to ZIKV across the range of cumulative incidence assumptions. Second, we estimated the number of women whose ZIKV infection would be averted under the different vaccine uptake scenarios. Third, we estimated the number of intended and unintended pregnancies expected to occur and, of these, the fraction of unintended pregnancies, pregnancy losses and terminations, and births that would be averted with provision of enhanced contraception access. Finally, we estimated the number of resulting ZIKV-related microcephaly births among women with ZIKV infection during pregnancy.

We used Monte Carlo sampling techniques to randomly assign values based on normal distributions using published confidence intervals to define the parameter distributions when available. The median number of microcephaly births, along with the 95% simulation interval (based on the 2.5th and 97.5th simulation percentile values), was calculated from 100,000 simulations. We used SAS 9.4 statistical software to perform the simulations. No ethical approval of protocol was required for this simulated data analysis.

Results

Approximately 27.4 million reproductive-aged women were included in our study population. Assuming current pregnancy rates, no anti-ZIKV vaccine, and a ZIKV cumulative incidence of 25%, as Puerto Rico is expected to experience by year's end (Frieden et al. 2016), we estimated approximately 670,253 pregnancies (307,769 unintended and 362,484 intended) would occur to women infected with ZIKV. After accounting for pregnancy losses and terminations (239,376), these pregnancies would lead to approximately 430,877 births. The expected number of ZIKV-related microcephaly births would range from 4309 (assuming 1% microcephaly risk) to 56,014 (assuming 13% microcephaly risk) (Fig. 1).

Under the enhanced contraceptive access alone strategy, there would be decreases in the total number of pregnancies (528,679), pregnancy losses and terminations (167,016), and births (361,663), resulting in 16% [95% simulation interval (SI): 5, 23] fewer ZIKV-related microcephaly births compared with no intervention (3,617 and 47,016 assuming 1 and 13% microcephaly risk births,

respectively). Under the strategy of anti-ZIKV vaccination alone, assuming moderate vaccine uptake (50%), there would be 45% (95% SI: 36, 54) fewer ZIKV-related microcephaly births (2370 and 30,808, respectively). Under the scenario of both enhanced contraceptive access and anti-ZIKV vaccination with moderate uptake, there would be 54% (95% SI: 44, 62) fewer ZIKV-related microcephaly births (2,370 and 25,859, respectively).

A conservative vaccine uptake scenario (10%) resulted in only a 9% (95% SI: 0, 18) reduction in the number of ZIKV-related microcephaly births compared with no intervention, which was a smaller reduction than enhanced contraception access alone (Fig. 1), while an optimistic vaccine uptake scenario (90%) resulted in an 81% (95% SI: 71, 91) reduction. Both enhancing contraceptive access and administering an anti-ZIKV vaccine resulted in the fewest number of ZIKV-related microcephaly births, regardless of the vaccine uptake scenario. Varying the cumulative incidence of ZIKV infection changed the expected number of ZIKV-related microcephaly births, but the relative decreases in these births under the different control strategies compared with no intervention remained the same.

Discussion

Our findings suggest that enhancing contraceptive access, a readily available tool with a current policy environment supportive of removing cost barriers, may be an important strategy to reduce ZIKV-related microcephaly births (Fox and Barfield 2016; Burke and Moreau 2016; Goldthwaite and Velasquez 2016; Dehlendorf et al. 2017). Its potential contribution to ZIKV-related microcephaly prevention is particularly important given that the single vaccine to reach Phase I safety and immunogenicity human trials so far is not expected to be commercially available until at least 2018 (Clinicaltrials.gov 2016) and no clinically approved therapy is currently available for treating any type of flavivirus infection (Weaver et al. 2016). Further, any vaccine or therapy targeted for use in pregnant women would likely undergo additional testing, adding more time to the approval process (Weaver et al. 2016). As estimated lifetime costs associated with a single microcephaly birth are estimated to be between 1 and 10 million dollars (Freiden 2016; Li et al. 2017) and contraception is already cost-beneficial in terms of averting unintended pregnancies (Foster et al. 2013; Trussell et al. 2013), it is likely that enhanced contraception alone would be cost-beneficial in preventing ZIKV-related microcephaly births.

For our simulation, we based our parameter assumptions on either published estimates or on what we considered to be plausible values; however, these values may not be accurate given the scarcity of current knowledge on ZIKV.
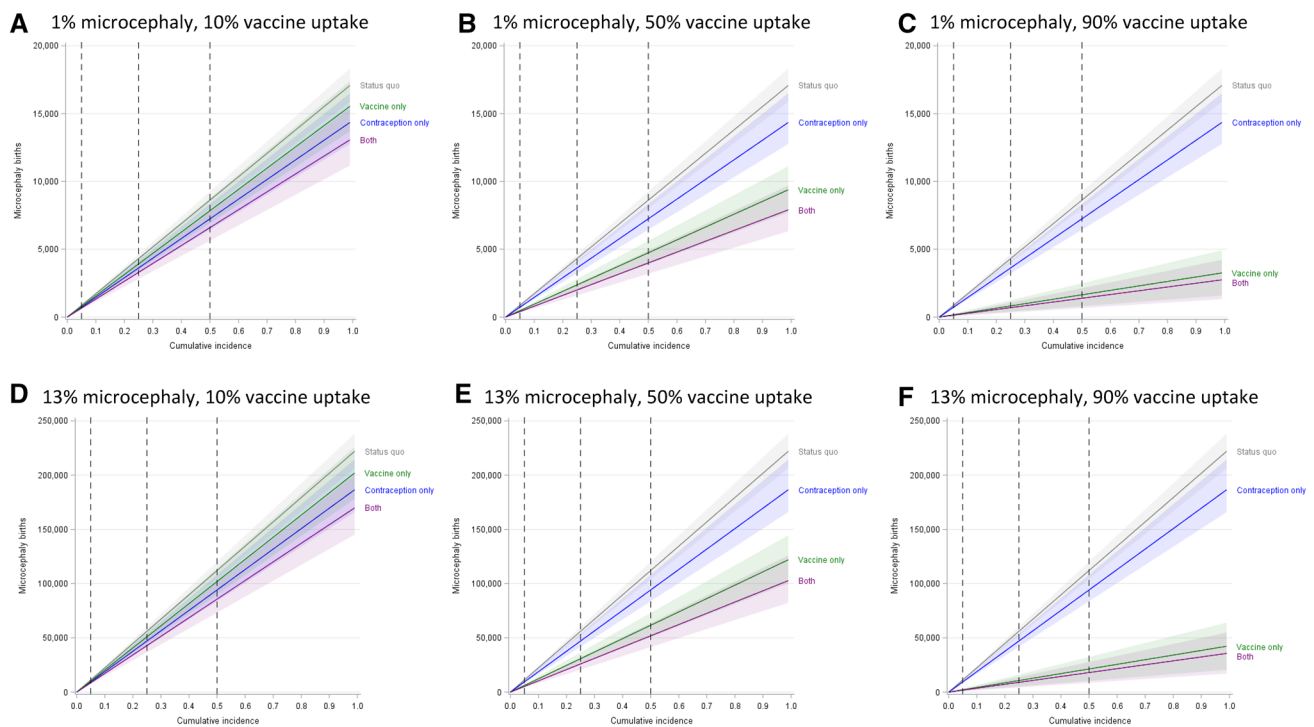
Fig. 1 Number of Zika-related microcephaly live births expected over the course of one year in 11 states (plus the District of Columbia) with potential Zika-carrying mosquitoes recently documented assuming: current unintended pregnancy rate and no anti-Zika virus vaccination (status quo), 46% reduction in unintended pregnancy rate only (contraception only), 90% effectiveness anti-Zika vaccination (vaccine only), and both 46% reduction in unintended pregnancy rate and anti-Zika vaccination (both). *Top row* (**a, b, c**) assumes 1% risk of microcephaly and bottom row (**d, e, f**) assumes 13% risk. From *left* to *right*, **a, d** assume 10% uptake of vaccine; **b, e** assumed 50% uptake; and panels **c** and **f** assume 90% uptake. *Solid lines* represent median number of expected microcephaly births and shaded bands represent the 95% simulation interval. *Dashed vertical line marks* cumulative incidence of Zika infection of 5, 25 and 50%. See text for details of simulation methods and further parameter assumptions

Some of our parameter assumptions may have led to an overestimation of the expected number of ZIKV-related microcephaly births. First, we may have overestimated the number of reproductive aged women at risk of encountering ZIKV-carrying mosquitoes by including states with documented presence of *Aedes aegypti* in the past 3 years; this may not be an accurate predictor of future risk of autochthonous ZIKV transmission, but alternative methods to define an at-risk population were either too broad or included states with travel-associated risk of ZIKV (Boulet et al. 2016; FDA 2016). Second, we applied first trimester risk of ZIKV-related microcephaly to all expected pregnancies in our study population, which could have overestimated the risk of microcephaly given that most studies to date have found the risk of ZIKV-related birth defects is highest for women infected during first trimester (Johansson et al. 2016; Pacheco et al. 2016; Honein et al. 2016). Yet there is evidence linking post-first trimester ZIKV infection to microcephaly (Brasil et al. 2016; Faria et al. 2016) and, for many areas included in our analysis, encounters with ZIKV carrying mosquitoes may be nearly year round. For example, Texas recently reported its first

autochthonous ZIKV transmission occurred in November, 2016 (New York Times). Third, we may have overestimated the proportion of ZIKV-affected pregnancies leading to live births as these pregnancies might be at higher risk of both pregnancy loss and induced termination compared to non ZIKV-affected pregnancies (Aiken et al. 2016); however, we are unaware of risk estimates for these outcomes from a representative sample of all women infected with ZIKV during pregnancy (Honein et al. 2016).

In contrast, our study could have also underestimated the risk of ZIKV-related microcephaly births. We applied national estimates for unintended pregnancy rates to the population included in our analysis, which most likely underestimated the actual number of unintended pregnancies because of the higher rates of unintended pregnancy in areas at higher risk of ZIKV (Burke and Moreau 2016; Dreweke 2016). Also, we chose to highlight the number of ZIKV-related microcephaly births assuming a cumulative incidence of 25%, which is the estimate for Puerto Rico by the end of 2016, but this may be an underestimate of the true attack rate once the ZIKV epidemic is over. Further, enhanced contraceptive access alone could be even more

effective than we assumed in our simulation if a higher reduction in unintended pregnancy rate following enhanced contraceptive access is applied (Secura et al. 2014) (Web Figure).

In addition, our analyses only estimated microcephaly births and did not include the broader array of structural anomalies and functional disabilities increasingly being recognized as being part of Congenital Zika Syndrome (CZS) (Moore et al. 2016; Weaver et al. 2016). In fact, microcephaly may not even be one of the diagnoses resulting from ZIKV infection, particularly for infants with brain atrophy compensated by ventricular size enlargement, leading to a head circumference in the normal range (Melo et al. 2016; Franca et al. 2016). However, microcephaly is a birth defect detectable in utero (SMFM 2016), apparent at birth, and has received considerable attention during the recent ZIKV outbreak in the Americas. Further, estimates of microcephaly prevalence at birth given population level Zika exposure are available (Ellington et al. 2016; Johansson et al. 2016; Cauchemez et al. 2016) while the prevalence of a broader array of anomalies and disabilities among average women infected with ZIKV during pregnancy is lacking (Brasil et al. 2016; Honein et al. 2016; Cuevas et al. 2016).

Nevertheless, our simulation study provides a basis for empirically evaluating two interventions to avert ZIKV-related birth defects in the United States, with a focus on microcephaly, and our findings regarding relative reductions should be robust given that ZIKV infection parameter errors would affect all intervention strategies equally.

While enhanced contraceptive access does not offer a solution for preventing ZIKV-related microcephaly births for women who do want to become pregnant, our analyses suggest that enhanced contraceptive access, which has received little discussion to date by public health agencies, has the potential to play an important role in prevention of ZIKV-related microcephaly for the large fraction of American women who do not want to become pregnant.

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