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Rubella and Zika Vaccine Research—A Cautionary Tale About Caution

Anne Drapkin Lyerly, MD, MA,
Center for Bioethics and Department of Social Medicine, University of North Carolina at Chapel Hill, Chapel Hill

Samantha G. Robin, BS, and
School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill

Elana Jaffe, BA
Center for Bioethics and Department of Social Medicine, University of North Carolina at Chapel Hill, Chapel Hill

Overview

The public health response to the Zika crisis has evoked debate and critique, although there has been at least 1 clear success: rapid progress toward a vaccine, with phase 2 testing starting in early 2017, just a year after the Public Health Emergency of International Concern was declared.

Among the challenges of developing a vaccine to prevent Zika infection during pregnancy are ethically complex questions about the appropriate role of pregnant women in the vaccine development agenda. Though ideally women will be vaccinated before conceiving, inadvertent vaccination during pregnancy is unavoidable when women of childbearing age are targeted. Vaccination during pregnancy may also be beneficial because the risks of Zika infection persist through gestation.[1] Both underscore the importance of developing an approach that meets the needs of those most at risk: pregnant women and their offspring.

To some extent, the timing is auspicious. Vaccination during pregnancy is increasingly accepted and endorsed—the Advisory Committee for Immunization Practices recommends pertussis and inactivated influenza vaccines for all pregnant women. However, certain vaccines are contraindicated—notably, live attenuated vaccines such as measles, mumps, and

Corresponding Author: Anne Drapkin Lyerly, MD, MA, CB 7240, 333 MacNider, 333 South Columbia St, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7240 (alyerly@email.unc.edu).

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rubella and varicella.[2] Further, research with pregnant women is now widely recognized as ethically permissible, considerable challenges notwithstanding.

To better understand Zika's challenges, some have looked to rubella, an illness associated with a severe congenital syndrome. While its eradication in the Americas is often lauded as a success story, for pregnancy and vaccination, rubella provides a cautionary tale.

Lessons of Rubella

A live attenuated rubella vaccine was developed in 1969 and included in the measles, mumps, and rubella vaccine in 1971. The initial US strategy reflected considerable concerns about potential risks of vaccinating pregnant women and women who might become pregnant. While studies indicated that the vaccine could cross the placenta, there was no evidence that it caused fetal harm. Still, concern abounded, stoked by the thalidomide tragedy of the 1950s, and ensuing public mistrust in the pharmaceutical industry. the United States adopted a strategy of "vaccinating around" pregnant women by vaccinating preschool -and elementary school–aged children to reduce viral reservoirs, induce lasting immunity, and protect pregnant women through reduced exposure to wild-type virus.

Unfortunately, this initial approach did not achieve its prevention goals. Surveillance data through the 1970s showed that although rubella cases had declined by more than 70%, there was no significant reduction among individuals who were 15 years or older, the primary child-bearing population.[3] Between 1975 and 1979, reported cases among this population increased by 28.6%.[4] Notably, Centers for Disease Control and Prevention data did "not indicate a substantial decline in the rate at which infants (were) born with congenital rubella syndrome (CRS)."

As these failings became evident, public health officials called for a strategic shift. In 1977, the Centers for Disease Control and Prevention recommended vaccinating women of childbearing age, noting that "it has become increasingly apparent that there is little risk to the fetus from rubella vaccine virus."[5] The incidence of reported CRS declined and has remained virtually undetectable in the United States since 1985.[3]

While rubella prevalence waned, concern about the safety of vaccination during pregnancy persisted. The Centers for Disease Control and Prevention maintained a nearly 20-year registry and among 321 inadvertently vaccinated pregnant women found no cases of malformations compatible with CRS.[3] In 1990, they advised that "the risk of vaccine-associated defects is negligible and should not ordinarily be a reason to consider interruption of pregnancy,"[3] although the vaccine remains contraindicated in pregnancy because of the theoretical risk of transmission of the vaccine virus to the fetus. In the meantime, an estimated 40% to 50% of women inadvertently vaccinated during pregnancy terminated their pregnancies, and terminations continued past the 1990s.[6]

Thus rubella offers a cautionary tale—about caution. An abundance of caution about vaccinating pregnant women led to a campaign that failed to significantly reduce CRS rates in the first decade of vaccine use. In the interim, many children were born with CRS because their mothers were not candidates for vaccination before or during pregnancy. Hundreds of

pregnancies were electively terminated because of theoretical risks and the absence of data on vaccine safety during pregnancy.

What are the lessons? First, when caution leads to the development of an ineffective vaccination approach, that caution must be tempered and the strategy changed. Rubella illuminated the “paradoxical effect,” in which incomplete vaccination coverage can lead to an increased teratogenic burden. Metcalf and Barrett[7] explain, “Vaccination tends to increase the average age of infection by making the infection rare; if coverage has not sufficiently reduced incidence to offset this increase, the outcome can be an increase in the burden of CRS.” The initial strategy targeting children was associated with more infections among women of childbearing age, for whom risks were most immediate and relevant. The lesson has been credited with significantly shaping public health approaches to vaccination, and is reflected in the World Health Organization Target Product Profile for Zika, in which the immunization of women of childbearing age is characterized as “of highest priority.” Models suggest that this approach is more likely to result in the effective prevention of Zika-related birth defects than observed initially for rubella.[7]

But there is a deeper lesson: efforts to prevent harm can put in harm’s way the very population cautious policies are meant to protect. We see this too often: a reluctance to conduct research with pregnant women means that the uncertain risk of medications and vaccines is transferred to the clinical setting where pregnant women take on unknown risks for themselves and their offspring.

Rubella’s third lesson speaks more directly to research ethics. For rubella, the absence of safety data for pregnancy led to decades of uncertainty among pregnant women who were inadvertently vaccinated and terminations of wanted pregnancies that might have been avoided with more clarity about vaccine-associated risks. To some extent, prioritizing the development of a vaccine platform with a track record of safety during pregnancy will alleviate these concerns. Among the leading candidates is an inactivated Zika vaccine, a platform widely considered safe during pregnancy. Still, live attenuated vaccines—generally contraindicated in pregnancy because of theoretical risks, as is the case for rubella—are among the most advanced in the vaccine pipeline. Other platforms that do not entail theoretical risks but have not previously been used during pregnancy (eg, deoxyribonucleic acid) are also under study. Going forward, it is imperative to ethically and efficiently gather safety data on the range of vaccines to which pregnant women will be intentionally or inadvertently exposed.

There are many factors that create a reluctance to conduct studies with pregnant women, including ethical complexities, legal barriers, and misplaced incentives, which must be addressed. Institutional review boards and researchers need an ethical frame work with which to navigate these complexities and guide decisions about such studies.[8] The rubella story is a reminder of the importance of attending to the risk tradeoffs that research in pregnancy inevitably involves. A narrow focus on avoiding risk in studies in fact leaves pregnant women in harm’s way without data to inform health care decisions.[9] Pregnant women will be exposed to Zika vaccines whether or not they are intentionally enrolled in trials or trial designs capture data specific to pregnancy.

Conclusions

The rubella story and the ongoing Zika crisis remind us that justice in research requires not just the protection of participants from research harm but also access to the benefits that responsible research can provide. Unquestionably, caution is needed when developing vaccination strategies to be used in populations that may include pregnant women. But an overabundance of caution can, paradoxically, shift risks to those whom we most hope to protect.

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