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Letter to the Editor JAMA Pediatrics: Re: In Reply to Rubella and Zika Vaccine Research—A Cautionary Tale About Caution, by Lyerly et al. JAMA Pediatr. Published online June 26, 2017

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Lyerly et al refer to historical aspects of the rubella vaccination program as “a cautionary tale about caution” concerning Zika vaccine research.[1] The US rubella vaccination program has been a tale of appropriate caution and a remarkable success in rubella and congenital rubella syndrome (CRS) elimination[2]. We concur with the authors' assertion that safety studies in pregnant women are important and could have overcome the initial reluctance to give rubella vaccine to women of childbearing age (WCBA). However, points within the article warrant comment.

First, Lyerly suggests that the limited evidence that receipt of vaccine during pregnancy did not cause fetal harm when the US rubella vaccination program began in 1969 should have led to recommendations regarding vaccination of WCBA in the first decade of the vaccine use. Wild rubella virus was a known teratogen, and in 1969, it was known that rubella vaccine virus crossed the placenta[3]. The vaccine virus's teratogenic potential was not known. If the vaccine virus caused birth defects, and the focus for vaccination was WCBA, thousands of women unknowingly pregnant at the time of vaccination, especially in the first trimester, could have been at high risk of a newborn with birth defects. Over time, as evidence showed no risk to the fetus, recommendations regarding vaccination of non-pregnant WCBA were strengthened[4].

Secondly, Lyerly contends that the initial rubella immunization strategy was historically “ineffective” in reaching its goals. We contend that the initial goal of the program --- to protect WCBA by reducing exposure to disease[2] --- was appropriately cautious and effective, given the absence of data on risks of rubella vaccine in pregnancy and the recent memories of the thalidomide tragedy. By focusing the vaccination strategy on infants up to pre-pubertal children, where most disease occurred, the goal was to markedly reduce rubella transmission within the first few years and to reduce the burden of CRS *over time*, because fewer susceptible pregnant females would be exposed to wild virus.

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Conflicts of interest: none

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Finally, most of the vaccine candidates for Zika prevention are not live attenuated whole Zika viruses[5]. In contrast, rubella vaccines licensed in 1969 were live attenuated viruses that could have been teratogenic. Thus, some concerns about rubella may not apply to current vaccine candidates to prevent Zika infection. Nevertheless, the rubella experience highlights the importance of collecting vaccine safety data post-licensure when vaccination of pregnant women takes place, because women are vaccinated who are unknowingly pregnant.

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