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## Zika and the Regulatory Regime for Licensing Vaccines for Use During Pregnancy

*Sam Halabi\**

### I. INTRODUCTION

Microcephaly and other severe fetal brain defects (congenital Zika syndrome) caused by the Zika virus have prompted an urgent effort to develop and license a safe and efficacious vaccine.<sup>1</sup> Yet, that effort has run up against one of the most formidable barriers in vaccine research: pregnant women are almost always excluded from clinical trials for fear that the intervention may harm the fetus.<sup>2</sup> This article analyzes the existing regulatory framework for vaccines intended for use during pregnancy in an effort to identify ways the process may be reconsidered in light of recent public health emergencies that had a disproportionate effect on pregnant women.

Despite those recent public health emergencies and the routine administration of immunizations like diphtheria, pertussis, and tetanus to pregnant women, there is no vaccine licensed for use during pregnancy in the United States.<sup>3</sup> The regulatory review normally required by the U.S. Food and Drug Administration (“FDA”) for new drugs and biologic products (including vaccines) demands substantial evidence as to safety, purity, and potency both generally and for subpopulations designated on a product’s label. However, vaccines routinely administered during pregnancy are permitted through an alternative post hoc system that does not rely on the gold standard of double-blind, placebo controlled trials.<sup>4</sup> Under that alternative, the FDA defers to the U.S. Centers for Disease Control and

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1. Erika Check Hayden, *The Race is on to Develop Zika Vaccine*, NATURE (March 28, 2016), <http://www.nature.com/news/the-race-is-on-to-develop-zika-vaccine-1.19634>.

2. Mary C. Blehar et al., *Enrolling Pregnant Women: Issues in Clinical Research*, 23 WOMEN’S HEALTH ISSUES e39, e40 (2013).

3. Getta K. Swamy & R. Phillips Heine, *Vaccinations for Pregnant Women*, OBSTETRICS & GYNECOLOGY 1, 10 (2015).

4. Jeffery N. Roberts & Marion F. Gruber, *Regulatory Considerations in the Clinical Development of Vaccines Indicated for Use During Pregnancy*, 33 VACCINE 966, 967 (2015).

Prevention’s Advisory Committee for Immunization Practices (“ACIP”), the World Health Organization’s Strategic Advisory Group of Experts on Immunization, and other national immunization technical advisory groups.<sup>5</sup> Where those organizations recommend specific immunizations for pregnant women, the FDA does not consider the use inconsistent with the product’s labeling or “off-label”.<sup>6</sup>

This article situates the Zika threat in the context of the regulatory approval process for vaccines intended for use during pregnancy. In doing so, it suggests that the discrepancy between the review process overseen by the FDA and the alternative (but prevailing) process managed by national immunization technical advisory groups (ACIP, physician organizations, etc.) must be resolved as emerging viral threats pose specialized risks to pregnant women and their unborn children.

Part II provides a brief history of Zika and its emergence as a viral threat uniquely dangerous to pregnant women. Part III explains the regulatory complexities surrounding the licensing of vaccines intended for pregnancy. Lastly, part IV analyzes the disruptions the current regulatory system causes to the research, development, and approval process for vaccines intended for pregnant women.

## II. THE ZIKA THREAT

### *A. The Zika Disease Profile*

The Zika virus is a flavivirus related to yellow fever, dengue, West Nile, and Japanese encephalitis viruses.<sup>7</sup> It was discovered in Uganda in 1947 during the course of mosquito and primate surveillance.<sup>8</sup> The virus has historically circulated in wild primates and arboreal mosquitoes and rarely caused “recognized spillover” infections in humans.<sup>9</sup> However, between 2008 and 2016, both the number of geographic locations affected by Zika and the prevalence in those locations have increased, showing the worldwide spread of the virus.<sup>10</sup> By 2008, the virus had affected populations

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5. The Advisory Committee on Immunization Practices (ACIP), *Questions and Answers*, ACIP, <https://www.cdc.gov/vaccines/hcp/conversations/downloads/vacsafe-acip-color-office.pdf> (last reviewed Apr. 15, 2016).

6. Roberts & Gruber, *supra* note 4, at 966–67.

7. Edward B. Hayes, *Zika Virus Outside Africa*, 15 EMERGING INFECTIOUS DISEASES 1347, 1347 (2009).

8. G.W.A. Dick, S.F. Kitchen & A.J. Haddow, *Zika Virus (I). Isolations and Serological Specificity*, 46 TRANSACTIONS ROYAL SOC’Y TROPICAL MED. & HYGIENE 509, 509–11 (1952).

9. Anthony S. Fauci & David M. Morens, *Zika Virus in the Americas – Yet Another Arbovirus Threat*, 374 NEW ENG. J. MED. 601, 601 (2016).

10. Charleen McNeill et al., *Zika: What Providers Need to Know*, 12 J. NURSE PRAC. 359, 360 (2016).

sporadically in Africa and Asia for half a century.<sup>11</sup> Now, more than 60 countries and territories have continuing transmission of the disease.<sup>12</sup>

Zika is spread mostly by the bite of infected *Aedes* species mosquitoes, which primarily bite during the day, late afternoon, and early evening.<sup>13</sup> Rapid spread is nearly “guaranteed” in areas that have large mosquito populations.<sup>14</sup> Although mosquitoes are the primary mode of transporting Zika, it can also be transmitted via sexual intercourse.<sup>15</sup> Zika RNA has been detected in other body fluids like saliva, semen, and amniotic fluid.<sup>16</sup>

For most people, complications from infection with the Zika virus do not result in hospitalization or serious illness.<sup>17</sup> However, complications may be more serious in pregnant women and their newborn children.<sup>18</sup> Zika may be passed from a pregnant woman to her fetus.<sup>19</sup> The most common complications known are microcephaly in infants born to women who had Zika symptoms, pregnancy loss, ocular lesions, and temporary hearing loss.<sup>20</sup> Historically, Zika virus infections caused symptoms like fever, muscle aches, eye pain, prostration, and maculopapular rash.<sup>21</sup> These “. . . symptoms are usually mild and last for 2 to 7 days,” and may go unrecognizable or be misdiagnosed as dengue, chikungunya, or other viral infections that manifest with fever and rashes.<sup>22</sup> The Zika virus is also associated with Guillain-Barré syndrome.<sup>23</sup> Guillain-Barré syndrome is a disorder in which the body’s immune system attacks part of the peripheral nervous system and results in symptoms such as weakness, tingling sensations in the legs, and in some life-

11. Martin Enserink, *An Obscure Mosquito-Borne Disease goes Global*, 350 SCI. MAG. 1012, 1012 (Nov. 27, 2015), [https://www.cvmb.colostate.edu/mip/newsletter/images/Science-2015-Enserink-1012-3%20\(1\).pdf](https://www.cvmb.colostate.edu/mip/newsletter/images/Science-2015-Enserink-1012-3%20(1).pdf).

12. Michelle Roberts, *Zika Vaccine ‘Works Very Well’ in Mice*, BBC NEWS (June 28, 2016), <http://www.bbc.com/news/health-36645822>.

13. *Rapid Risk Assessment: Zika Virus Epidemic in the Americas: Potential Association with Microcephaly and Guillain-Barré Syndrome*, EUR. CTR. FOR DISEASE CONT. 9 (Dec. 10, 2015), <http://ecdc.europa.eu/en/publications/Publications/zika-virus-americas-association-with-microcephaly-rapid-risk-assessment.pdf> [hereinafter *Rapid Risk Assessment*].

14. Enserink, *supra* note 11, at 1012.

15. McNeill et al, *supra* note 10, at 360.

16. *Id.*

17. *Id.*

18. *Id.* (The 2 most common complications known to date are microcephaly in infants born to pregnant women who had ZIKV symptoms during pregnancy and Guillain-Barré syndrome in adults).

19. *About Zika: What We Know*, CTR. FOR DISEASE CONT., <http://www.cdc.gov/zika/about/index.html> (last updated Sep. 29, 2016).

20. McNeill et al., *supra* note 10, at 360.

21. Fauci & Morens, *supra* note 9, at 602.

22. *Rapid Risk Assessment*, *supra* note 13, at 2.

23. *Guillain-Barré Syndrome Fact Sheet*, NAT’L INST. NEUROLOGICAL DISORDERS & STROKE (July 2011), [http://www.ninds.nih.gov/disorders/gbs/detail\\_gbs.htm](http://www.ninds.nih.gov/disorders/gbs/detail_gbs.htm).

threatening cases, the disease may affect breathing, blood pressure, or heart rate.<sup>24</sup>

Zika infects populations at high rates. A 2009 study based on antibody surveys estimated that an “astonishing” 73% of the population had become infected with Zika virus during the big outbreak in Yap, an island group in the Western Pacific that is part of the Federated States of Micronesia.<sup>25</sup> “Over 60% of the United States population live in areas conducive to seasonal [Zika] transmission,” and even some that live in areas where yearlong Zika transmission is possible.<sup>26</sup> As of January 18, 2017, the Centers for Disease Control and Prevention (“CDC”) reported 217 locally acquired mosquito-borne cases of the Zika virus, and 4,682 travel-associated cases.<sup>27</sup>

### B. *The Scramble for a Vaccine*

Because of the devastating potential of Zika, public health authorities, academic researchers and vaccine manufacturers are in a race to develop a safe and effective vaccine that will protect against the disease.<sup>28</sup> While vaccines often take ten to fifteen years to develop, recent public health emergencies have demonstrated that political will and financial incentives may accelerate that time frame.<sup>29</sup> An H1N1 vaccine was developed within four months of the discovery of a new pandemic strain of the virus.<sup>30</sup> An Ebola vaccine developed through a complex research and development network involving the Public Health Agency of Canada, NewLink Genetics, Merck, and IDT Biologika, showed 100 percent effectiveness after the development process accelerated with the West Africa epidemic that

24. *Id.*

25. Enserink, *supra* note 11, at 1012.

26. McNeill et al., *supra* note 10, at 360.

27. *Case Counts in the United States*, CTR. FOR DISEASE CONT., <https://www.cdc.gov/zika/geo/united-states.html> (last updated Jan. 19, 2017).

28. Katie Thomas, *The Race for a Zika Vaccine*, N.Y. TIMES (Nov. 19, 2016), [http://www.nytimes.com/2016/11/20/business/testing-the-limits-of-biotech-in-the-race-for-a-zika-vaccine.html?\\_r=0](http://www.nytimes.com/2016/11/20/business/testing-the-limits-of-biotech-in-the-race-for-a-zika-vaccine.html?_r=0) (“Similar meetings were occurring elsewhere in the vaccine world — at small companies like Inovio Pharmaceuticals and NewLink, in the offices of big manufacturers like GlaxoSmithKline and Sanofi, and at the Walter Reed Army Institute of Research, which is a few miles from the N.I.H. campus . . .”); *Phase 2 Zika Vaccine Trial Begins in U.S., Central and South America*, NAT’L INST. OF HEALTH (Mar. 31, 2017), <https://www.nih.gov/news-events/news-releases/phase-2-zika-vaccine-trial-begins-us-central-south-america>.

29. *Vaccine Development, Testing, and Regulation*, HIST. VACCINES, <http://www.historyofvaccines.org/content/articles/vaccine-development-testing-and-regulation> (last updated Jan. 27, 2016); Thomas, *supra* note 28 (demonstrating the political and financial incentive of accelerating vaccine development in times of public health emergencies).

30. Zakariya Al-Muharrmi, *Understanding the Influenza A H1N1 2009 Pandemic*, 10 QU MED. J. 187, 187 (2010).

unfolded between 2014 and 2016.<sup>31</sup>

What has not changed, despite the unique threat Zika poses to pregnant women, is the exclusion of pregnant women during the potential vaccine's research and development process.<sup>32</sup> Even though Congress, in 1974, added specific requirements for undertaking research involving pregnant women (thus implicitly authorizing such research), vaccine and other medical therapy developers have rarely engaged in that kind of research.<sup>33</sup> The discussion below outlines approval recommendations to the FDA for vaccines intended for use during pregnancy and the alternative regulatory channels that actually authorize such use.

### III. THE REGULATORY PATHWAY(S) FOR VACCINES INTENDED FOR USE DURING PREGNANCY

#### A. *The FDA Approval Process*

The Food and Drug Administration's Center for Biologics Evaluation and Research ("CBER") is responsible for regulating vaccines in the United States. CBER's approval facilitates the use of vaccines in countries that lack regulatory capacity.<sup>34</sup> Although clinical vaccine development follows the same general pathway as for drugs and other biologics, the process in place for vaccines intended for use during pregnancy, is not used.<sup>35</sup>

#### 1. All Vaccines

As researchers understand and isolate the Zika virus, they seek to map, to the greatest extent possible, the biological mechanism or mechanisms that lead to disease.<sup>36</sup> While some candidate vaccines occur naturally, most

31. Ana Maria Henao-Restrepo et al., *Efficacy and Effectiveness of an rVSV-vectored Vaccine in Preventing Ebola Virus Disease: Final Results from the Guinea Ring Vaccination, Open-Label, Cluster-Randomised Trial*, 389 THE LANCET 505, 511 (2017).

32. Saad B. Omer & Richard H. Beigi, *Pregnancy in the Time of Zika: Addressing Barriers for Developing Vaccines and Other Measures for Pregnant Women*, 315 JAMA 1227, 1227 (2016).

33. Blehar et al., *supra* note 2, at e40.

34. *Vaccine Product Approval Process*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/biologicsbloodvaccines/developmentapprovalprocess/biologicslicenseapplicationsblaprocess/ucm133096.htm> (last updated Aug. 24, 2015); U.S. FOOD & DRUG ADMIN., CBER INTERIM STRATEGIC PLAN FY 2017-2019 9 (2017), <http://www.fda.gov/downloads/aboutfda/centersoffices/cber/ucm266867.pdf>.

35. *Vaccine Product Approval Process*, *supra* note 34; Omer & Beigi, *supra* note 32, at 1227.

36. EDUARDO A. GROISMAN, PRINCIPLES OF BACTERIAL PATHOGENESIS 134 (2001) ("Essential to the establishment of a complete understanding of the host-pathogen interactions that are necessary for the manifestation of disease is the identification and detailed characterization of virulence factors produced by pathogens at each stage of the infection

candidates are developed using empirical approaches, historically running the pathogen through a medium that substantially reduces its pathogenicity, or killing or dissecting the virus after cultivation and using it with adjuvants, or in multiple doses to prompt immune response.<sup>37</sup> More recent approaches like “reverse vaccinology” start from genomic sequences and, by computer simulation, predict those antigens that are most likely to be vaccine candidates.<sup>38</sup> Vaccine candidates are then tested in animals after developing models for immunogenicity and safety.<sup>39</sup>

After animal testing, a Zika vaccine sponsor would apply for Investigational New Drug (“IND”) status from the FDA which authorizes the sponsor to undertake clinical trials on humans for safety, efficacy, and, licensure. Phase I trials are designed to assess the safety, immunogenicity and dose-response of the vaccine in, typically, 20-100 healthy volunteers.<sup>40</sup> The IND application describes the vaccine, its method of manufacture and quality control tests for release, information about the vaccine’s safety and ability to prompt a protective immune response in animal testing, and the proposed clinical studies protocol.<sup>41</sup>

Phase II studies involve several hundred healthy volunteers and investigators focus on safety as well as immunogenicity.<sup>42</sup> Phase II studies focus on dose-ranges and vaccine components.<sup>43</sup> Phase III vaccine trials enroll up to thousands or tens of thousands of human subjects in order to detect sometimes rare adverse events.<sup>44</sup> In 1998, for example, a rotavirus vaccine was licensed for use in the United States after phase III trials on approximately 10,000 infants showed safety and efficacy.<sup>45</sup> However, when administered to a larger population, physicians and researchers observed an association between the vaccine and bowel obstruction.<sup>46</sup> If larger phase III studies confirm safety and efficacy, the vaccine is approved for marketing after additional review of study data.<sup>47</sup>

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process.”).

37. Rino Rappuoli, *Reverse Vaccinology, a Genome-Based Approach to Vaccine Development*, 19 *VACCINE* 2688, 2689 (2001) (illustrating conventional vaccine development in Figure 1).

38. *Id.* at 2690.

39. *Id.* (including animal models as an essential feature of reverse vaccinology).

40. See FDA IND Content & Format Rule, 21 C.F.R. § 312.23 (2017).

41. *Vaccine Product Approval Process*, *supra* note 34.

42. *Id.*

43. *Id.*

44. *Id.*

45. See L. Simonsen et al., *More on RotaShield and Intussusception: The Role of Age at the Time of Vaccination*, 192 *J. INFECTIOUS DISEASES* S36, S36 (2005).

46. *Id.*

47. NIH, *FAQ - Clinical Trial Phases*, U.S. NAT’L LIBRARY OF MED. (Jan. 1, 2001), <https://www.nlm.nih.gov/services/ctphases.html#top> (last updated Apr. 18, 2008).

## 2. Requirements for Vaccines Intended for Use During Pregnancy

Additional requirements apply to vaccines developed for use during pregnancy. Animal testing and clinical testing must be specified to address the potential reproductive risk of the product before pregnant women participate in clinical trials.<sup>48</sup> Phase I clinical trials must begin with non-pregnant women of childbearing age.<sup>49</sup> If results of the proposed vaccination are positive, studies of the vaccine may be advanced into early studies of pregnant women classified as low-risk (healthy mothers who experience few or no complications).<sup>50</sup> If adequate data from phase I clinical trials of pregnant women is observed, phase II may begin to identify a pilot evaluation of efficacy (i.e. a test to examine the feasibility of an approach that is intended to be used in a larger scale study).<sup>51</sup> Phase III trials for vaccine candidates intended for use during pregnancy use a randomized, blinded, well-controlled study, wherein the control arm receives placebo and the primary endpoint is prevention of clinical disease in a larger population of pregnant women.<sup>52</sup> After clinical development stages, the vaccination would advance to the licensing application where FDA reviewers would evaluate the information necessary for a risk/benefit analysis and issue a recommendation regarding approval of the vaccine.<sup>53</sup>

Evaluations of safety are crucial during each phase of clinic trials, and continue after the approval of the vaccine.<sup>54</sup> Until a vaccine is given to the general population, all potential adverse reactions are unknown.<sup>55</sup> Thus, many vaccines are subjected to post-marketing surveillance, known as “Phase IV” studies once on the market.<sup>56</sup> A key criterion during phase IV studies is to determine if there is a “reasonable possibility that the drug (or biologic) caused the event and whether the event (or a pattern of events) is unexpected.”<sup>57</sup> During general population use of the vaccine, it may be necessary to develop a pregnancy registry, in order to explore potential

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48. See Roberts & Gruber, *supra* note 4, at 968.

49. *Id.*

50. *Id.*

51. *Id.*

52. See Roberts & Gruber, *supra* note 4, at 968.

53. 42 U.S.C.A. § 262 (k) (2015); see also *Vaccine Product Approval Process*, *supra* note 41.

54. See Roberts & Gruber, *supra* note 4, at 967; see also Alberto E. Tozzi et al., *Assessment of Causality of Individual Adverse Events Following Immunization (AEFI): A WHO Tool for Global Use*, 31 *VACCINE* 5041, 5043 (2013), <http://www.sciencedirect.com/science/article/pii/S0264410X13011997>.

55. See *Vaccine Product Approval Process*, *supra* note 34.

56. *Id.*

57. See Roberts & Gruber, *supra* note 4, at 969.



changes and improve the quality and utility of the vaccination.<sup>58</sup>

### 3. Labeling

Vaccine approval also requires appropriate product labeling to inform health care providers about the vaccine's proper use, including its benefits and risks, to communicate with patients and parents, and to safely deliver the vaccine.<sup>59</sup> A product's package insert, also known as the "label," is a critical element of the evaluation of a vaccination.<sup>60</sup> Vaccine labels must include a section for usage during pregnancy.<sup>61</sup>

The FDA recently revised the regulations for the characterization of a drug or biologic as it affects pregnancy and issued the Pregnancy and Lactation Labeling Rule ("PLLR").<sup>62</sup> The PLLR changed the labeling rule for pharmaceuticals from categorizing risks into lettered categories (A, B, C, D, and X) to providing a narrative summary of the risks of using the drug or biologic during pregnancy.<sup>63</sup> Under the old system, Category A pharmaceuticals were those, like folic acid supplements, where adequate and well-controlled studies did not demonstrate a risk to the fetus in the first trimester of pregnancy.<sup>64</sup> Category B pharmaceuticals meant that there were no adequate and well-controlled studies in pregnant women and animal data were reassuring while Category C pharmaceuticals meant that there were no adequate and well-controlled studies in pregnant women and also no animal data.<sup>65</sup> Categories D and X conveyed fetal risk in investigational or marketing studies.<sup>66</sup>

The new rule not only requires that this information be adapted to be given in narrative form, but also that the labeling include clinical information to help healthcare providers make prescribing decisions and counsel women about the use of drugs during pregnancy.<sup>67</sup>

#### *B. Alternative Regulatory Channels for Vaccines Intended for Use During Pregnancy*

Despite FDA guidance on approval of vaccines through these channels,

58. *Id.*

59. *See Vaccine Product Approval Process, supra* note 34.

60. *See* 21 C.F.R. §§ 201.56–57 (2015).

61. *Id.*

62. 21 C.F.R. § 201.57 (2015).

63. Marion F. Gruber, *The US FDA Pregnancy Lactation and Labeling Rule – Implications for Maternal Immunization*, 33 *VACCINE* 6499, 6450 (2015).

64. *Id.*

65. *Id.*

66. *Id.*

67. Gruber, *supra* note 63, at 6500.

the system is unused. Instead, the approval for these vaccines is functionally given to national technical advisory groups like ACIP, a statutory body established to “develop recommendations on the use of vaccines in the civilian population of the United States.”<sup>68</sup> ACIP reports to the Director of the CDC.<sup>69</sup> Its statutory authority is based on the role of the CDC in preventing communicable diseases.<sup>70</sup> Similarly, professional organizations like the American Congress of Obstetricians and Gynecologists (“ACOG”) develop immunization recommendations for practitioners.<sup>71</sup> The FDA effectively allows these recommendations to substitute for regulatory review specific to pregnant women.<sup>72</sup>

In 2008, ACIP issued *Guiding Principles in Development of ACIP Recommendations for Vaccination during Pregnancy and Breastfeeding*.<sup>73</sup> Previously, the ACIP did not provide any guidance to its constituent workgroups to formulate policy for vaccination use during pregnancy.<sup>74</sup> These workgroups took differing approaches to maternal immunization issues, which resulted in a diverse number of recommendations that “var[ied] in clarity and underlying rationale.”<sup>75</sup> Since 2004, both ACIP and ACOG have recommended yearly vaccinations for all women who are pregnant or planning to become pregnant during the influenza season, regardless of the mother’s age.<sup>76</sup> Tdap is also recommended, even though neither is licensed for use during pregnancy.<sup>77</sup> It is through this system that a fairly small number of vaccinations have been generally accepted for use during pregnancy.

68. 42 U.S.C. § 217a; *see also* CTRS. FOR DISEASE CONTROL & PREVENTION, ABOUT ACIP, [www.cdc.gov/vaccines/acip/about.html](http://www.cdc.gov/vaccines/acip/about.html) (last updated Aug. 16, 2012).

69. *See* CTRS. FOR DISEASE CONTROL & PREVENTION, ACIP CHARTER, <https://www.cdc.gov/vaccines/acip/committee/charter.html> (last updated Apr. 20, 2016).

70. *Id.*

71. *Id.*

72. *See, e.g.*, U.S. FOOD & DRUG ADMIN., CLINICAL DEVELOPMENT & REQUIREMENTS FOR LICENSURE OF VACCINES INTENDED FOR USE DURING PREGNANCY TO PREVENT DISEASE IN THE INFANT (2015), [www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccineandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM471661.pdf](http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccineandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM471661.pdf).

73. *See* CTRS. FOR DISEASE CONTROL & PREVENTION, ACIP: GUIDANCE FOR VACCINE RECOMMENDATIONS FOR PREGNANT WOMEN, <http://www.cdc.gov/vaccines/acip/committee/guidance/rec-vac-preg.html>.

74. *Id.*

75. *Id.*

76. *See* Geeta K. Swamy & R. Phillips Heine, *Vaccinations for Pregnant Women*, 125 *OBSTETRICS & GYNECOLOGY* 1,4 (2015).

77. *See* CTRS. FOR DISEASE CONTROL & PREVENTION, MATERNAL VACCINES: PART OF A HEALTHY PREGNANCY, <http://www.cdc.gov/vaccines/pregnancy/pregnant-women/index.html> (recommending use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women).

Vaccinations during pregnancy are generally recommended because pregnant women are at high risk for the most adverse effects of many vaccine-preventable diseases.<sup>78</sup> Immunization during pregnancy provides maternal benefit and may have the added benefit of infant protection through passive immunity.<sup>79</sup> Children under the age of 2 months may not be able to receive a particular vaccine, which means they are dependent upon antibodies received from their mothers.<sup>80</sup>

Under this system, it is the phase IV surveillance studies that are particularly attentive to rare reactions, increases in known reactions, and signals for risks to pregnant women or their unborn children.<sup>81</sup> The Vaccine Adverse Event Reporting System (“VAERS”) is a safety surveillance project administered by the CDC and the FDA.<sup>82</sup> VAERS collects information about adverse events associated with the administration of vaccines.<sup>83</sup> VAERS provides a mechanism by which adverse events following immunization may be reported, analyzed, and made available to the public.<sup>84</sup> Providers must report adverse events for specific routine childhood immunizations, and are under professional obligations to report other health events.<sup>85</sup> Patients and other caregivers also submit reports through the system, which receives up to 30,000 reports per year.<sup>86</sup> Through VAERS, researchers detect new or rare events, increases in rates of known side effects, and enhance understanding of patient risk factors.<sup>87</sup> VAERS can facilitate studies analyzing the association, if any, between vaccination of pregnant women, and pregnancy outcomes.<sup>88</sup>

The Vaccine Safety Datalink (“VSD”) is another CDC immunization safety analysis project that partners with nine health care organizations.<sup>89</sup> Since 1990, the VSD has monitored the safety of vaccines and undertaken

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78. *Id.*

79. *Id.*

80. See U.S. DEP’T HEALTH & HUMAN SERVS., RECOMMENDED IMMUNIZATION SCHEDULE FOR PERSONS AGED 0 THROUGH 18 YEARS, [https://www.vaccines.gov/who\\_and\\_when/infants\\_to\\_teens/](https://www.vaccines.gov/who_and_when/infants_to_teens/) (last updated Feb. 1, 2016).

81. See U.S. NAT’L LIBRARY OF MED., *supra* note 47.

82. U.S. DEP’T HEALTH & HUMAN SERVS., ABOUT THE VAERS PROGRAM, <https://vaers.hhs.gov/about/index> (last visited Apr. 17, 2016).

83. *Id.*

84. *Id.*

85. *Id.*

86. *Id.*

87. *Id.*

88. See, e.g., GS Goldman, *Comparison of VAERS Fetal-Loss Reports during Three Consecutive Influenza Seasons*, 32(5) HUM. & EXPERIMENTAL TOXICOLOGY 464, 464 (2013).

89. CTRS. FOR DISEASE CONTROL & PREVENTION, VACCINE SAFETY DATALINK (VSD), <https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/> (last updated May 13, 2016).

analyses of associations between immunizations and vaccine side effects.<sup>90</sup> The VSD uses electronic health data from partner organizations including the type of vaccine administered, the date of immunization, and other vaccines administered on the same day.<sup>91</sup> The VSD gathers information on illnesses diagnosed at providers' offices, urgent care and emergency room visits, and hospital stays.<sup>92</sup> The VSD uses this information to develop vaccine safety studies as well as studies based on questions or concerns raised from the medical literature and reports to the VAERS.<sup>93</sup>

The project prioritizes studies evaluating the safety of vaccines given to women during pregnancy.<sup>94</sup> When new vaccines are recommended for use in the United States or if there are changes in vaccine recommendation (as there was for Tdap for pregnant women in 2013), the VSD monitors the safety of these vaccines and recommendations.<sup>95</sup> Because VSD has nine databases and retains information regarding up to 2 percent of the United States' population, VSD enables performance of active surveillance by using data mining processes.<sup>96</sup>

Results from VAERS and VDS are also linked with larger databases like the CDC's Clinical Immunization Safety Assessment Network ("CISA").<sup>97</sup> CISA is a resource for healthcare providers who may have safety questions with respect to certain patients.<sup>98</sup> CISA combines expertise in neurology, allergy, immunology, pediatrics, hematology, and obstetrics/gynecology to design research studies assessing influenza vaccine safety, vaccine safety in persons with autoimmune diseases, and vaccine safety in pregnant women.<sup>99</sup> Most relevantly for the changes proposed in this article, CISA studies are designed to address clinical vaccine safety questions in targeted or special populations that are often excluded from pre-licensure clinical trials, like pregnant women.<sup>100</sup>

#### IV. BRIDGING THE GAP BETWEEN REGULATORY PATHWAYS FOR

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90. *Id.*

91. *Id.*

92. *Id.*

93. *Id.*

94. *Id.*

95. *Id.*

96. *Id.*

97. CTRS. FOR DISEASE CONTROL & PREVENTION, CLINICAL IMMUNIZATION SAFETY ASSESSMENT (CISA) PROJECT, <https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/cisa/> (last updated Aug. 28, 2015).

98. *Id.*

99. *Id.*

100. *Id.*

## VACCINES INTENDED FOR USE DURING PREGNANCY

The regulatory alternative in place – exclusion of pregnant women from pre-licensure processes, with heavy investments in post-licensure surveillance and expert recommendations – has produced a short list of vaccines recommended for all women during pregnancy. Other vaccines are recommended for women before they become pregnant while others are recommended under certain circumstances like travel to locations with higher risk of food-borne illness. But recent public health emergencies – H1N1, Ebola, and Zika – as well as infections for which vaccination during pregnancy offers substantial promise show that the current system operates too slowly and with inadequate regard for the potential of vaccines intended for use during pregnancy to improve individual and public health.

For example, the current system distorts the development of an ethical framework for research that might benefit pregnant women and their unborn children. Under the law, the question is not whether to enroll pregnant women in clinical trials, but rather how to do so in an “ethically acceptable and scientifically rigorous manner.”<sup>101</sup> Because pregnant women are reflexively excluded, institutional review boards categorize research in pregnancies as high risk without undertaking more nuanced assessment of risks and benefits.<sup>102</sup>

Similar problems occur with respect to baseline rates of certain adverse events that effect women during pregnancy, an effective calculation of risk/benefit analysis with respect to research that might be done, and the language that should accompany product labeling to effectively convey that risk benefit analysis. While the changes to the PLLR described in Part III.A.3. are a step in the right direction, manufacturers should still seek guidance from the FDA on what product narrative will effectively inform providers and their patients about vaccine risks.

## V. CONCLUSION

Recent public health emergencies, especially Zika, have brought into sharp focus many of the weaknesses of the current system for immunizing pregnant women. This article has endeavored to trace the pathway for approval that would typically be used for other medical therapies and biologic products (including vaccines) and the pathway that is actually used, which depends upon the historical exclusion of pregnant women from medical research and long-term experience and expert recommendations instead of blinded, placebo-controlled trials. Given the threats that influenza, Ebola, and Zika pose to pregnant women and their unborn children, there is

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101. Omer & Beigi, *supra* note 32.

102. *Id.*

a compelling justification for making stronger financial and regulatory investments in rationalizing the process by which vaccines intended for use during pregnancy are developed and approved.