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ZIKA, PREGNANCY, AND THE LAW

Sam F. Halabi*

I. INTRODUCTION

The public health emergency surrounding the spread of the Zika virus has resurrected and brought into sharp relief some of the most vexing questions surrounding the relationship between pregnancy and law: the appropriate circumstances, if any, in which fetal tissue research is permissible;¹ when and how the government may sponsor statements intended to influence reproductive decisions;² and how to balance the health and rights of both women and their unborn children when health threats target both.³ This latter question has come to the forefront in the

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1. Erika Check Hayden, *Zika Highlights Role of Fetal-Tissue Research*, 532 NATURE 16, 16 (2016), https://www.nature.com/polopoly_fs/1.19655!/menu/main/topColumns/topLeftColumn/pdf/nature.2016.19655.pdf [<https://perma.cc/J5RM-Q2DH>]; Doug Wassenaar, *Ethics Considerations in Zika Vaccine Research: An Approach*, WORLD HEALTH ORG. (June 7, 2016), http://www.who.int/immunization/research/meetings_workshops/2_Douglas_Wassenaar_zika_june_16.pdf [<https://perma.cc/7NH4-8LLJ>]; Julie Steenhuisen, *Researchers Find New Zika Clues to Birth Defect in Fetus Study*, REUTERS, Feb. 10, 2016, <http://www.reuters.com/article/us-health-zika-science-idUSKCN0VJ2M7> [<https://perma.cc/R47W-XM2Y>].

2. RUTH MACKLIN, ETHICS IN GLOBAL HEALTH: RESEARCH, POLICY, AND PRACTICE 50 (2012) (noting influence of governments in shaping reproductive decisions); *see generally Zika: How to Communicate Effectively*, CTRS. FOR DISEASE CONTROL & PREVENTION: ZIKA ACTION PLAN SUMMIT (Apr. 2016), <https://www.cdc.gov/zap/pdfs/presentations/zap-communicate-effectively.pdf> [<https://perma.cc/EAN5-USRS>]; Robert P.S. Jansen, *Evidence-Based Ethics and Regulation of Reproduction*, 12 HUM. REPROD. 2068 (1997), <https://doi.org/10.1093/humrep/12.9.2068> [<https://perma.cc/H5Y2-56MZ>] (detailing historical ethical difficulties between government sponsorship and reproductive choice).

3. AM. COLL. OF OBSTETRICIANS & GYNECOLOGISTS, COMM. OP. NO. 563, ETHICAL ISSUES IN PANDEMIC INFLUENZA PLANNING CONCERNING PREGNANT WOMEN 1-2 (2013, *reaff'd* 2016), <https://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Ethics/Ethical-Issues-in-Pandemic-Influenza-Planning-Concerning-Pregnant-Women> [<https://perma.cc/VT7H-8L38>].

Zika context. Because the virus inflicts its heaviest known toll in utero, research undertaken for treatments or vaccines will inevitably implicate application of that research to pregnant women.⁴

Yet the Zika public health emergency also arises at a time in which legal scholars have recently launched a reevaluation, reexamination, and reimagination of the relationship between pregnancy and law across a number of fields including criminal law, disability law, poverty law, and employment discrimination, among others. Broadly speaking, these scholars assert that legislatures, courts, and regulators have “essentialized” pregnancy—reducing it to factors specific to gestation—in ways that undermine pregnant women’s rights to work,⁵ disrespect or unequally burden their autonomy under statutory regimes informed and shaped by *Roe v. Wade*,⁶ and arbitrarily subject pregnant women to penal statutes in both the civil and criminal contexts.⁷ The debate under way is not limited to the academy: both Hillary Clinton and Donald Trump campaigned in part on

4. See generally Jon Cohen, *The Race for a Zika Vaccine is On*, 351 SCIENCE 543 (2016), <http://science.sciencemag.org/content/351/6273/543> [<https://perma.cc/3945-TBMJ>].

5. Deborah A. Widiss, *Gilbert Redux: The Interaction of the Pregnancy Discrimination Act and the Amended Americans with Disabilities Act*, 46 U.C. DAVIS L. REV. 961, 1002 (2013) (“Courts have also failed to develop the robust understanding of ‘equal opportunity’—that is, the right of ‘women, as well as men, to have families without losing their jobs’—endorsed in *Cal Fed* as a justification for providing pregnancy-specific benefits.”).

6. Michele Goodwin, *Prosecuting the Womb*, 76 GEO. WASH. L. REV. 1657, 1663 (2008) (“In fact, FDLs [fetal drug laws] do little to tell us about harms to fetuses as these laws exempt from prosecution a host of behaviors that negatively impact pregnancies and cause miscarriages, such as smoking, second-hand smoke, diabetes, obesity, depression, and hypertension. Indeed, a good number of FDLs have exemptions for legal abortions so that they may remain consistent with *Roe v. Wade*.”).

7. Doretta Massardo McGinnis, *Prosecution of Mothers of Drug-Exposed Babies: Constitutional and Criminal Theory*, 139 U. PENN. L. REV. 505, 511-13 (1990); see generally Barry M. Lester, Lynne Andreozzi, & Lindsey Appiah, *Substance Use During Pregnancy: Time for Policy to Catch Up with Research*, 1 HARM REDUCTION J. 5 (2004), <https://doi.org/10.1186/1477-7517-1-5> [<https://perma.cc/8JFK-QYE3>] (“We have Supreme Court rulings that define drug use as a mental problem, we have modern evidence that treatment is effective and that there is no reason to consider drug use as different than any other mental/medical problem; there are treatment programs shown to be effective with drug-using mothers; and there are treatments with the programs involving the courts. We have identified all other barriers, yet why has policy not changed? Is it because we are still angry and want to punish these mothers? That we will not forgive them for using drugs when they are pregnant?”).

expanding support for new mothers, implicitly acknowledging the social and medical importance of the “fourth trimester.”⁸

According to the essentialist argument, pregnancy is reduced, under the law, to “biological and physiological facets, obscuring the important ways in which society and culture shape the meaning of pregnancy and structure our experience of it.”⁹ Equality-promotion statutes like the Pregnancy Discrimination Act and the Family Medical Leave Act (FMLA) codify this essentialism.¹⁰ These statutes impose specific burdens that are measured and implemented, such as accommodations employers must provide for pregnant employees or appropriate windows for family medical leave, whatever the additional costs pregnancy might impose on a woman, her co-parents or caregivers (if any), and/or family.¹¹ As a result, new mothers are left to shoulder a burden related to reproduction heavier than that for men.¹² To the extent these scholars have explored the relationship between medical decisions made by pregnant women, they have done so largely around issues like reproductive choice, the constraints of the “code of perfect pregnancy,” and the disparate treatment the law accords specific decisions made by women during pregnancy.¹³ The *process* by which medical information is generated, filtered, and ultimately communicated to pregnant women has received far less scrutiny.¹⁴

8. Jill Cohen, *The Fourth Trimester*, 61 MIDWIFERY TODAY 26 (2002); Melinda Wenner Moyer, *If Trump Keeps His Promise on Paid Family Leave, Will Working Women Feel They Can Take It?*, SCI. AM. (Jan. 20, 2017), <https://www.scientificamerican.com/article/if-trump-keeps-his-promise-on-paid-family-leave-will-working-women-feel-they-can-take-it/> [https://perma.cc/Y3BR-SH5L]; Megan A. Sholar, *Donald Trump and Hillary Clinton Both Support Paid Family Leave. That's a Breakthrough.*, WASH. POST (Sept. 22, 2016), https://www.washingtonpost.com/news/monkey-cage/wp/2016/09/22/donald-trump-and-hillary-clinton-both-support-paid-family-leave-thats-a-breakthrough/?utm_term=.baff3914546c [https://perma.cc/S272-BH8G].

9. Saru M. Matambanadzo, *Reconstructing Pregnancy*, 69 SMU L. REV. 187, 190 (2016).

10. Deborah Dinner, *The Costs of Reproduction: History and the Legal Construction of Sex Equality*, 46 HARV. C.R.-C.L. L. REV. 415, 422 (2011) (“The PDA and the FMLA both prohibit sex-role stereotyping and impose cost-sharing mandates on employers.”).

11. *Id.*

12. *Id.*

13. See generally Lisa C. Ikemoto, *The Code of Perfect Pregnancy: At the Intersection of the Ideology of Motherhood, the Practice of Defaulting to Science, and the Interventionist Mindset of Law*, 53 OHIO ST. L.J. 1205 (1992).

14. It is worth noting here that this article is limited to legislative and regulatory efforts aimed at pregnancy as an intended condition. An entirely separate conversation is relevant

This Essay situates a crucial component of the public health response to Zika—the effort to develop a safe and effective vaccine—within this broader literature. It does so in an effort to highlight the need to revisit the relationship between law and pregnancy—not only in the areas legal scholars have prioritized so far, but also in the context of routine and emergency maternal health, which has heretofore been largely assumed to be governed by straightforward norms and practices based on medical evidence and physician ethics.¹⁵ In fact, whereas the current literature tends to assume or explicitly assert that the relationship between law and pregnancy is most troubled in the contexts of reproductive choice, the workplace, or criminal prosecution—i.e. predictable events and moments that may be assessed at any given time—it has paid far less attention to emergency contexts like H1N1, Ebola, or Zika, each of which uniquely affects or affected pregnant women.¹⁶ In so doing, the literature suggests that social constructions regulating pregnancy in the workplace or the prosecutor’s office also regulate the deliberations of public health officials, physicians, and the medical advice communicated from them.

Examining the approach adopted by health and medical regulatory authorities in the U.S. (and mimicked by competent national regulatory authorities elsewhere) toward pregnant women in public health emergencies, this Essay argues that medical research and therapeutic availability are structured so as to minimize accessibility to pregnant women, even where evidence suggests—as it did with Ebola and does with Zika—that

to legislative efforts to filter and shape medical information so as to deter abortion. See, e.g., Sandhya Somashekhar, *Ohio Governor Vetoes ‘Heartbeat Bill’ But Signs Another Abortion Restriction into Law*, WASH. POST., Dec. 13, 2016, https://www.washingtonpost.com/news/post-nation/wp/2016/12/13/ohio-governor-vetoes-heartbeat-bill-but-signs-into-law-another-abortion-restriction/?utm_term=.3939ee570b8a [<https://perma.cc/TPC5-HTQX>].

15. Margaret Olivia Little et al., *Ethics and Research with Pregnant Women: Lessons from HIV/AIDS*, in 3 CLINICAL RESEARCH INVOLVING PREGNANT WOMEN 227, 237-39 (2016).

16. Kate Greenwood, *The Mysteries of Pregnancy: The Role of Law in Solving the Problem of Unknown But Knowable Maternal-Fetal Medication Risk*, 79 U. CIN. L. REV. 267, 268 (2011) (identifying unique risks H1N1 posed to pregnant women); see generally Annick Antierens, *Ethical Challenges in the Development and Deployment of Medical Therapies and Vaccines in the Context of Public Health Emergencies*, in GLOBAL MANAGEMENT OF INFECTIOUS DISEASE AFTER EBOLA 207, 215 (Sam F. Halabi, Lawrence O. Gostin & Jeffrey S. Crowley eds., 2017) [hereinafter GLOBAL MANAGEMENT] (identifying unique risks Ebola posed to pregnant women and their fetuses).

accessibility for pregnant women needs to be prioritized. Under this approach, the U.S. Food and Drug Administration (FDA), which normally must approve medicines and vaccines intended for specific populations, effectively allocates maternal treatment and immunization regulation to the Centers for Disease Control and Prevention (CDC)' Advisory Committee on Immunization Practices, the World Health Organization's strategic advisory group of experts on immunization, and other national immunization technical advisory groups.¹⁷ Where those organizations recommend immunization of pregnant women, the FDA does not consider the use inconsistent with the product's authorized uses or "off-label," even if there are never double-blind, placebo controlled trials supporting safety and efficacy (regardless of whether there are healthy and willing volunteers)—and trials are rarely designed that seek pregnant participants.¹⁸

While this Essay has as its principal aim the expansion and catalysis of an important element of the debate now underway in the law, it also outlines the adverse consequences resulting from the existing regulatory framework for pregnancy-specific vaccines ("maternal vaccines") and foreshadows changes that will not only be necessary to address future public health emergencies that threaten pregnant women and their unborn children, but will also unlock the future of vaccine preventable deaths.¹⁹ As the world moves toward universal coverage of

17. Richard H. Beigi et al., *Research on Vaccines and Antimicrobials During Pregnancy: Challenges and Opportunities*, 31 *VACCINE* 4261, 4261—63 (2013), <http://www.sciencedirect.com/science/article/pii/S0264410X13006622> [https://perma.cc/S5G3-9ZLK].

18. Requirements for Pregnancy and Lactation Labeling, 73 Fed. Reg. 30,831, 30,840—41 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201) ("Therefore, human data concerning a drug's effect(s) on pregnant women and their offspring almost never come from controlled clinical trials. . . . Sources that may contribute to an evaluation of whether a drug increases the risk of developmental abnormalities include pregnancy exposure registries, cohort studies, case-control studies, case series, and case reports."); Jeffery N. Roberts & Marion F. Gruber, *Regulatory Considerations in the Clinical Development of Vaccines Indicated for Use During Pregnancy*, 33 *VACCINE* 966, 967 (2015), <http://www.sciencedirect.com/science/article/pii/S0264410X1401723X> [https://perma.cc/FSK3-SPZ7].

19. A "maternal" vaccine may designate an immunization administered before, during, or after pregnancy and the use is not consistent in the literature. *See generally* Stanley A. Gall, *A Maternal Immunization Program (MIP): Developing a Schedule and Platform for Routine Immunization During Pregnancy*, 29 *VACCINE* 9411, 9411—13 (2011), <http://www.sciencedirect.com/science/article/pii/S0264410X11017634> [https://perma.cc/G3SC-ZM45]. In this Essay, a "maternal" vaccine refers to one

childhood immunizations, the future of infant health will turn to immunizations delivered during pregnancy that impart protections unavailable after birth.²⁰ This Essay encourages a new national and international dialogue about maternal and infant health, and addresses the norms that now characterize biomedical innovation and corresponding regulatory approaches to pregnancy.

Part II of this Essay analyzes the recent trend among scholars to characterize the “essentialist” view of pregnancy legal regimes, ranging from criminal law to workplace discrimination, adoption, and the effects of essentialism on women generally and pregnant women specifically. It then demonstrates that this scholarship has tended to explicitly assert or implicitly suggest that there is nevertheless a zone, occurring within the provider-patient relationship, where the law is less distorted and medical evidence and physician good faith prevail, even if imperfectly so. Part III tests this assumption in the literature by analyzing the regulatory complexities surrounding the licensing of vaccines intended for pregnancy—including why pregnant women are excluded from clinical trials, the relationship between product labeling and vaccine hesitancy among pregnant women, and recent statutory and regulatory changes aimed at facilitating pregnant women’s access to essential medicines and vaccines. It concludes that the

administered or intended to be administered to a woman known to be pregnant between conception and the end of the pregnancy. See, e.g., *Maternal Vaccines: Part of a Healthy Pregnancy*, CTRS. FOR DISEASE CONTROL & PREVENTION (Aug. 5, 2016), <https://www.cdc.gov/vaccines/pregnancy/pregnant-women/> [<https://perma.cc/474L-HDL9>].

20. WORLD HEALTH ORG. ET AL., STATE OF THE WORLD’S VACCINES AND IMMUNIZATION 75 (3d ed. 2009), http://apps.who.int/iris/bitstream/10665/44169/1/9789241563864_eng.pdf [<https://perma.cc/Q7B7-ZM8G>] (“First came the vaccines: by the early 1970s, vaccines against about 20 diseases had become available, and in most countries were being used for high-risk population groups (travellers, the military, and so on), or for occasional mass campaigns, but not routinely in a systematic organized manner. Then, starting in the mid-1970s, came the [WHO Expanded Programme on Immunization]—set up to establish and coordinate, on a global scale, the systematic use of vaccines by national immunization programmes and thereby to protect as many children as possible in the world against six infectious diseases (diphtheria, tetanus, pertussis, measles, polio, and tuberculosis). In the mid-1980s, came the evidence that these immunization programmes could, in a matter of a few years, protect millions of children from disease and death. By the early 1990s, the drive for universal child immunization (UCI) launched by UNICEF, WHO, and other partners, had helped raise immunization coverage to a global average of about 80%.”); Seth Berkley, *Global Vaccine Access as a Critical Intervention to Fight Infectious Disease, Antibiotic Resistance, and Poverty*, in GLOBAL MANAGEMENT, *supra* note 16, at 179, 179-81 (noting progress toward universal childhood immunization).

essentialist approach identified in other legal fields is applicable to maternal immunizations in both the routine and emergency contexts; that, as a result, pregnant women's access to lifesaving vaccines is thwarted, and development of ethical approaches to pregnancy-related research is stymied; and that, as with other legal fields, pregnant women are ultimately disadvantaged relative to other populations.

II. PREGNANCY AND THE LAW: A REEVALUATION

As the 40th anniversary of the Pregnancy Discrimination Act and the 25th anniversary of the Family Medical Leave Act approach (as well as the 30th anniversary of the largest expansion of prenatal care to low-income pregnant women through Medicaid),²¹ legal scholars have undertaken a comprehensive review of multiple legal regimes aimed at promoting equality between pregnant women and other workers, criticizing aspects of the law that unfairly subject pregnant women to prosecution,²² and evaluating laws aimed at supporting pregnancy.²³ Contemporaneously, a growing body of medical and public health literature suggests the benefits of providing better financial and other forms of support to women after the birth of children, in addition to the long-known benefits of prenatal care.²⁴ The issue

21. Marilyn Rymer Ellwood & Genevieve Kenney, *Medicaid and Pregnant Women: Who is Being Enrolled and When*, HEALTH CARE FIN. REV., Winter 1995, at 7 (“During the late 1980s, Congress focused heavily on expanding Medicaid eligibility at the State level for low-income pregnant women.”).

22. Deborah L. Brake & Joanna L. Grossman, *Unprotected Sex: The Pregnancy Discrimination Act at 35*, 20 DUKE J. GENDER L. & POL’Y 67, 67-68 (2013); Saru Matambanadzo, *The Fourth Trimester*, 48 U. MICH. J.L. REFORM 117, 121 (2014), <http://repository.law.umich.edu/cgi/viewcontent.cgi?article=1121&context=mjlr> [<https://perma.cc/9DX4-SVUV>] (reviewing this scholarly undertaking).

23. Candace Marie Reder, *Framing Preglimony: Exploring the Implications of Pregnancy Support Models Through Family Law Values*, 20 DUKE J. GENDER L. & POL’Y 325, 327 (2013) (analyzing historical trends in American law supporting pregnancy and concluding that “the eventual implementation of a pregnancy support scheme seem[s] inevitable”).

24. See generally Greg R. Alexander et al., *Source of Bias in Prenatal Care Utilization Indices: Implications for Evaluating the Medicaid Expansion*, 81 AM. J. PUB. HEALTH 1013 (1991), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1405696/> [<https://perma.cc/N7UY-99HK>]; Pinka Chatterji & Sara Markowitz, *Family Leave After Childbirth and the Mental Health of New Mothers*, 15 J. MENTAL HEALTH POL’Y & ECON. 61 (2012), http://www.icmpe.org/test1/docs/15-061_text.pdf [<https://perma.cc/2VEK-N9UL>]; Ann D. Colle & Michael Grossman, *Determinants of Pediatric Care Utilization*, 13 J. HUM. RES. 115 (1978), <http://www.nber.org/papers/w0240.pdf> [<https://perma.cc/J9HB-F8QN>]; Mark

of better laws for pregnant women became a rare point of agreement between the two major presidential candidates in the 2016 U.S. elections.²⁵

At the core of this effort is the promotion of a more comprehensive view of pregnancy, of the costs it imposes, and how those costs are distributed over a society that, generally, aims to promote not only equality between men and women but healthy generations to succeed them.²⁶ The law, according to these scholars, takes an “essentialist” view of pregnancy, conceptualizing it “for much of gestation as an individual process that need not involve partners or other family members. Pregnancy is individual for the majority of [its] duration” because of a social choice to make it so.²⁷ This process is fundamentally biological and medical: it involves mainly gestation and perhaps gastrointestinal symptoms, fluctuation in blood pressure, chronic pain, nausea, changes in body size, and distribution of body mass.²⁸ That it involves a great deal more is, effectively, ignored, at least insofar as the law is concerned.²⁹

Daku, Amy Raub & Jody Heymann, *Maternal Leave Policies and Vaccination Coverage: A Global Analysis*, 74 SOC. SCI. & MED. 120 (2012), <http://www.sciencedirect.com/science/article/pii/S0277953611006563> [<https://perma.cc/HV59-BHQ4>]; Mary Kathryn Hamman, *Making Time for Well-Baby Care: The Role of Maternal Employment*, 15 MATERNAL & CHILD HEALTH J. 1029 (2011), <https://link.springer.com/article/10.1007/s10995-010-0657-9> [<https://perma.cc/8KG6-Q9ZF>]; R.S. McDuffie, Jr. et al., *Effect of Frequency of Prenatal Care Visits on Perinatal Outcome Among Low-Risk Women: A Randomized Controlled Trial*, 275 JAMA 847 (1996); Pat McGovern et al., *Postpartum Health of Employed Mothers 5 Weeks After Childbirth*, 4 ANNALS FAM. MED. 159 (2006), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1467019/pdf/0040159.pdf> [<https://perma.cc/Y557-5HFL>]; Claire Cain Miller, *The Economic Benefits of Paid Parental Leave*, N.Y. TIMES (Jan. 30, 2015), https://www.nytimes.com/2015/02/01/upshot/the-economic-benefits-of-paid-parental-leave.html?_r=0 [<https://perma.cc/6755-UDXL>].

25. *Paid Family and Medical Leave*, HILLARY FOR AM., <https://www.hillaryclinton.com/issues/paid-leave/> [<https://perma.cc/BTS8-9ZNP>] (“As president, Hillary will: Guarantee [sic] up to 12 weeks of paid family and medical leave to care for a new child or a seriously ill family member, and up to 12 weeks of medical leave to recover from a serious illness or injury of their own.”); Richard Pérez-Peña, *How the Trump and Clinton Child Care Plans Stack Up*, N.Y. TIMES (Sept. 14, 2016), <https://nyti.ms/2cPbody> [<https://perma.cc/8X9S-RE82>] (“[Trump] proposed requiring employers to give six weeks of maternity leave . . .”).

26. *Muller v. Oregon*, 208 U.S. 412, 421 (1908).

27. *See Matambanadzo, supra* note 9, at 252.

28. *Id.* at 256.

29. *See Matambanadzo, supra* note 22, at 129; *see also* Erma Jean Lawson & Shireen Rajaram, *A Transformed Pregnancy: The Psychosocial Consequences of Gestational Diabetes*, 16 SOC. HEALTH & ILLNESS 536, 537 (1994) (“Researchers have focused

This essentialism distorts laws aimed at promoting equality for pregnant women, subjects them to arbitrary legal disadvantages, and unfairly distributes the costs of reproduction over all of the social actors who benefit from healthy mothers and babies.³⁰ In the context of pregnancy discrimination, Saru Matambanadzo has argued that this essentialism explains why Congress has failed to pass legislation extending discrimination protection to reproductive choice, breastfeeding, fertility treatments, or even infant care.³¹ Even within the primary antidiscrimination statute meant to protect pregnant women—the Pregnancy Discrimination Act—“many courts currently reduce pregnancy discrimination to gestation-based discrimination, obscuring not only social and cultural aspects of pregnancy discrimination, but also a host of medical conditions that are explicitly related to pregnancy and childbirth”³² Deborah Dinner has persuasively argued that the “design of workplace structures” has incorporated this essentialism “in a manner that disproportionately burdens women” so as to conserve an obsolete model of family-wage earning under which men are breadwinners and women are caregivers.³³

While the Pregnancy Discrimination Act was intended to level the playing field between pregnant and non-pregnant workers,³⁴ the Family Medical Leave Act (though phrased in sex-

considerable attention on the psychological transitions of a ‘normal’ pregnancy. Sociological models have reported that the medicalisation of reproduction, the social subordination of women, and the social construction of motherhood influence the psychological disequilibrium of pregnancy”); *see generally* Claudia Barcellos Rezende, *The Experience of Pregnancy: Subjectivity and Social Relations*, 8 VIBRANT: BRAZ. J. ANTHROPOLOGY 529 (2011), http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1809-43412011000200026 [https://perma.cc/4ZJE-29DF].

30. The year 2018 is also the 30th anniversary of the effective date of the substantial Medicaid expansion for pregnant women under the federal Omnibus Budget Reconciliation Act. States rapidly adopted expansions for low-income pregnant women under the law. Deborah A. Calloway, *Accommodating Pregnancy in the Workplace*, 25 STETSON L. REV. 1, 19-21 (1995) (detailing adverse social outcomes from not supporting pregnant women); Ian T. Hill, *Improving State Medicaid Programs for Pregnant Women and Children*, HEALTHCARE FIN. REV., Dec. 1990, at 76.

31. *See* Matambanadzo, *supra* note 9, at 257.

32. *Id.* at 259; *see generally* Widiss, *supra* note 5.

33. *See* Dinner, *supra* note 10, at 487.

34. Pregnancy Discrimination Act of 1978, 42 U.S.C. § 2000e(k) (2006); Joanna L. Grossman, *Pregnancy, Work, and the Promise of Equal Citizenship*, 98 GEO. L.J. 567, 602-05 (2010); Joanna L. Grossman, *Hard Labor: New Pregnancy Discrimination Guidance*

neutral language), was aimed at protecting women generally and pregnant women specifically.³⁵ The FMLA allows women to take “serious health condition” leave for needed prenatal care or if the pregnancy causes inability to work, or as needed for childbirth, recovery, and to care for a newborn child.³⁶ Because of the FMLA’s notice requirements, limited benefits, and total 12-week protection from adverse employment consequences, it has had a modest impact in improving outcomes for women and children.³⁷ The essentialist critique explains, in part, this limited effect. Because the entire statutory leave is 12 weeks, women who must take leave for gestation-related conditions lose time that may be taken after birth.³⁸

This essentialism not only shapes and distorts law ostensibly aimed at protecting pregnant women from discrimination, but results in the drafting of criminal statutes that selectively favor some conduct during pregnancy but not other conduct that might be just as harmful to a pregnant woman or her fetus. Michele Goodwin, for example, argues that fetal drug laws, which subject women to prosecution for conduct that harms a fetus, substitute medical evidence as to fetal harm with notions of “birthing the right way” based on conceptions related to essentialist ideas.³⁹

from the EEOC, VERDICT (July 22, 2014), http://scholarlycommons.law.hofstra.edu/faculty_scholarship/355 [<https://perma.cc/9YSY-5YXE>].

35. 29 U.S.C. § 2601 (2012); Joanna L. Grossman & Gillian L. Thomas, *Making Pregnancy Work: Overcoming the Pregnancy Discrimination Act’s Capacity-Based Model*, 21 YALE J.L. & FEMINISM 15, 25 (2009).

36. 29 U.S.C. § 2612(a) (2012).

37. Rafael Gely & Timothy D. Chandler, *Maternity Leave Under the FMLA: An Analysis of the Litigation Experience*, 15 WASH. U. J.L. & POL’Y 143, 151 (2004) (“However, the data also suggests that the impact has been rather modest, particularly with regard to employees that need to take leave due to birth or adoption.”); Michael Selmi, *The Limited Vision of the Family and Medical Leave Act*, 44 VILL. L. REV. 395, 396 (1999) (arguing that “the FMLA was primarily a symbolic act, which afforded no significant assistance to working women, or men, and has perhaps retarded progress on the family leave front more than it has plausibly helped”); see generally Richard Bales & Sarah Nefzger, *Employer Notice Requirements Under the Family and Medical Leave Act*, 67 MO. L. REV. 883 (2002) (discussing notice provisions).

38. Lawrence M. Berger, Jennifer Hill & Jane Waldfogel, *Maternity Leave, Early Maternal Employment and Child Health and Development in the US*, ECON. J., Feb. 2005, at F31-32.

39. Michele Goodwin, *Fetal Protection Laws: Moral Panic and the New Constitutional Battlefield*, 102 CAL. L. REV. 781, 786 (2014) (“[L]egislative fetal protection efforts are on the rise, driving the creation, enactment, and enforcement of statutes authorizing criminal intervention in women’s pregnancies. These statutes dramatically exceed prior limits, extending beyond penalizing poor African American pregnant women

For pregnant women in prison, medical care and alternatives to prison routines are similarly structured around gestation-focused conceptions of how women experience pregnancy.⁴⁰

Yet, for the reach and strength of these arguments challenging the legal environment for pregnant women, the zone that surrounds the public health approach to pregnant women generally and the physician-patient relationship specifically has received far less scrutiny from legal scholars. So, for example, Professor Matambanadzo contrasts federal judges' knowledge (and the resulting narrowing interpretation of the Pregnancy Discrimination Act) with the "sophisticated medical and scientific knowledge that many doctors, maternal nurses, and midwives possess."⁴¹ Deborah Widiss identifies dozens of Pregnancy Discrimination Act cases in which women requested accommodations under doctors' orders and how courts failed to give the physician-patient relationship the deference it deserved.⁴² Even within the quite large literature on "maternal-fetal" conflict, which as Michelle Oberman points out, may be rearticulated as a "maternal-physician" conflict, the arguments largely revolve around points where evidence and advice diverge—like cesarean births—as opposed to routine maternal care or recommendations made in the course of public health emergencies.⁴³

for illicit drug use, particularly crystallized cocaine (crack). Contemporary fetal protectionism includes sanctioning women for refusing cesarean sections, forcibly confining them to bed rest, and instigating prosecutions for otherwise legal conduct."); Goodwin, *supra* note 6, at 1661-62.

40. Deborah Ahrens, *Incarcerated Childbirth and Broader "Birth Control": Autonomy, Regulation, and the State*, 80 MO. L. REV. 1, 4 (2015) ("In the past decade, there have been a number of academic articles and interest-group reports that document the problems that women who are pregnant and birthing face while incarcerated, and those articles and reports have focused in particular on the practice of shackling women who are pregnant during transportation, court appearances, and, most sympathetically, labor."); Pricilla A. Ocen, *Punishing Pregnancy: Race, Incarceration, and the Shackling of Pregnant Prisoners*, 100 CAL. L. REV. 1239, 1310 (2012); Kelly Parker, *Pregnant Women Inmates: Evaluating Their Rights and Identifying Opportunities for Improvements in Their Treatment*, 19 J.L. & HEALTH 259, 261-64 (2004).

41. See Matambanadzo, *supra* note 9, at 190.

42. See Widiss, *supra* note 5, at 1018-25.

43. Michelle Oberman, *Mothers and Doctors' Orders: Unmasking the Doctor's Fiduciary Role in Maternal-Fetal Conflicts*, 94 NW. U. L. REV. 451, 473-74 (2000). For literature regarding the maternal-fetal conflict after *Roe v. Wade* more generally see Janet Gallagher, *Prenatal Invasions and Interventions: What's Wrong with Fetal Rights*, 10 HARV. WOMEN'S L.J. 9, 51-53 (1987); see generally Susan Markens et al., *Feeding the Fetus: On*

Recent public health emergencies provide substantial reasons to question these assertions and oversights. The approaching anniversaries of these laws have been accompanied by major public health emergencies that uniquely affected pregnant women and their unborn children. Pregnant women infected with H1N1 were more likely to be hospitalized and die from the virus.⁴⁴ All reported pregnancies in Ebola-infected women ended in “spontaneous miscarriage, stillbirth or neonatal death.”⁴⁵ The Zika virus, of course, uniquely attacks fetal tissue, resulting in a wide range of serious birth defects that cause death and permanent disability.⁴⁶ These health emergencies brought new urgency and focus to the relationship between pregnant women and vaccines—and, as argued herein, exposed how essentialist critiques applied to the workplace or in the criminal context have as much or more force in the advice given to women about both routine and emergency vaccinations.

III. THE SHADOW REGULATORY REGIME FOR EMERGENCY AND ROUTINE MATERNAL VACCINES

Interrogating the Notion of Maternal-Fetal Conflict, 23 FEMINIST STUD. 351 (1997); Lawrence J. Nelson, *Legal Dimensions of Maternal-Fetal Conflict*, 35 CLINICAL OBSTETRICS & GYNECOLOGY 738 (1992); Matthew C. Reid & Grant Gillett, *The Case of Medea—A View of Fetal-Maternal Conflict*, 23 J. MED. ETHICS 19 (1997).

44. Sonja A. Rasmussen, Denise J. Jamieson & Joseph S. Bresee, *Pandemic Influenza and Pregnant Women*, 14 EMERGING INFECTIOUS DISEASES 95, 95 (2008) (“Pregnant women are at high risk for severe complications of influenza during interpandemic periods and previous pandemics. In addition, some studies suggest an increased risk for adverse outcomes among infants born to mothers infected with influenza during pregnancy.”); Sonja A. Rasmussen, Denise J. Jamieson & Timothy M. Uyeki, *Effects of Influenza on Pregnant Women and Infants*, 207 AM. J. OBSTETRICS & GYNECOLOGY S3, S3 (2012), [http://www.ajog.org/article/S0002-9378\(12\)00722-3/pdf](http://www.ajog.org/article/S0002-9378(12)00722-3/pdf) [<https://perma.cc/9GY8-H6NJ>].

45. Benjamin O. Black et al., *Ebola Viral Disease and Pregnancy*, OBSTETRIC MED., Sept. 2015, at 108, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4582839/pdf/10.1177_1753495X15597354.pdf [<https://perma.cc/5YJ8-EXS6>].

46. *Microcephaly and Other Birth Defects*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/zika/healtheffects/birth_defects.html [<https://perma.cc/G7NX-B6L4>] (“Congenital Zika syndrome is described by the following five features: [s]evere microcephaly where the skull has partially collapsed[;] [d]eased brain tissue with a specific pattern of brain damage[;] [d]amage to the back of the eye[;] [j]oints with limited range of motion, such as clubfoot[;] [and] too much muscle tone restricting body movement soon after birth[.]”); see generally Fernanda R. Cugola et al., *The Brazilian Zika Virus Strain Causes Birth Defects in Experimental Models*, 534 NATURE 267 (2016).

There has arguably never been as strong a case for the development of a pregnancy-specific (“maternal”) vaccine as there is for Zika.⁴⁷ Discovered in Uganda in 1947, the *Aedes* mosquito-borne virus has long been associated with relatively mild symptoms like “fever, muscle aches, eye pain, prostration, and maculopapular rash.”⁴⁸ In 2015, however, a cluster of microcephaly cases—a condition that results in a smaller than normal head size and sometimes severe disability—was discovered in Brazil and quickly associated with the *Aedes* and the Zika virus it carried.⁴⁹ Not only had the virus evolved to attack fetal tissue, but it also demonstrated a potential to infect populations at high rates.⁵⁰ A 2009 study based on antibody surveys estimated that an “astonishing” 73% of the population had become infected with Zika virus during an outbreak in Yap, an island group in the Western Pacific.⁵¹ Over 60% of the United States’ population lives in areas conducive to seasonal Zika transmission, and there are even some that live in areas where yearlong Zika transmission is possible.⁵² During 2016, the CDC

47. *Zika Epidemic Highlights Need for Priority Vaccine Research and Guidelines for Pregnant Women*, EMORY NEWS CTR. (Feb. 24, 2016), http://news.emory.edu/stories/2016/02/zika_highlights_need/ [<https://perma.cc/ZN W6-74R9>].

48. Anthony S. Fauci & David M. Morens, *Zika Virus in the Americas—Yet Another Arbovirus Threat*, 374 NEW ENG. J. MED. 601, 601-02 (2016); see also Andrew Green, *Uganda Discovered the Zika Virus. And the Solution For It*, FOREIGN POL’Y (Feb. 10, 2016), <http://foreignpolicy.com/2016/02/10/uganda-discovered-the-zika-virus-and-the-solution-for-it/> [<https://perma.cc/NSR7-7FK7>].

49. Wanderson Kleber de Oliveira et al., *Increase in Reported Prevalence of Microcephaly in Infants Born to Women Living in Areas with Confirmed Zika Virus Transmission During the First Trimester of Pregnancy—Brazil, 2015*, 65 MORBIDITY & MORTALITY WKLY. REP. 242, 242-44 (2016), <https://www.cdc.gov/mmwr/volumes/65/wr/mm6509e2.htm> [<https://perma.cc/N2TM-UVT2>]; *One Year into the Zika Outbreak: How an Obscure Disease Became a Global Health Emergency*, WORLD HEALTH ORG., <http://www.who.int/emergencies/zika-virus/articles/one-year-outbreak/en/index3.html> [<https://perma.cc/YZQ5-NUVR>].

50. Rafael A. Larooca et al., *Vaccine Protection Against Zika Virus from Brazil*, 536 NATURE 474, 474, 477 (2016), <http://www.nature.com/nature/journal/vaap/ncurrent/full/nature18952.html> [<https://perma.cc/US4A-FD7F>].

51. See Mark R. Duffy et al., *Zika Virus Outbreak on Yap Island, Federated States of Micronesia*, 360 NEW ENG. J. MED. 2536, 2536, 2539 (2009), www.nejm.org/doi/pdf/10.1056/NEJMoa0805715 [<https://perma.cc/7FPT-9BQ4>]; see also Mary Kay Kindhauser et al., *Zika: The Origin and Spread of a Mosquito-Borne Virus*, WORLD HEALTH ORG. (Feb. 9, 2016), http://www.who.int/bulletin/online_first/16-171082/en/ [<https://perma.cc/RZ8H-9ZA3>].

52. Isaac I. Bogoch et al., *Anticipating the International Spread of Zika Virus from Brazil*, 387 LANCET 335, 335-36 (2016), <http://www.thelancet.com/journals/lancet/article>

reported 224 locally-acquired mosquito-borne cases of the Zika virus, and 4,830 travel-associated cases; as of August 8, 2017, 2,112 pregnant women showed evidence of Zika infection in the U.S. alone.⁵³

Yet, not only have medical researchers made clear they will not enroll pregnant women in trials for Zika vaccine candidates, but there is, in fact, *not a single vaccine specifically licensed for use by pregnant women in the United States*, for either routine or emergency purposes.⁵⁴ Despite the availability of a detailed channel for review and licensing by the FDA, physicians advise pregnant women as to recommended vaccinations (both routine and emergency) through an alternative regulatory regime that emphasizes the role of national technical advisory groups, but not double-blind, placebo-controlled clinical trials. The existence of this alternative regulatory pathway is explained by the same essentialism that influences other legal regimes: the narrow focus on gestation as the touchstone characteristic of pregnancy.

While FDA review plays an important role in vaccine confidence—because vaccines are administered to otherwise healthy adults and children, a high standard of safety is expected—the upshot of circumventing the FDA for maternal vaccines is less access both at the experimental stage and, through hesitancy, at the patient stage.⁵⁵ Perceptions of safety risk, even mild ones, may exert a disproportionate effect on the willingness

/PIIS0140-6736(16)00080-5/abstract [https://perma.cc/8Y3L-KC9F]; see generally Andrew J. Monaghan et al., *On the Seasonal Occurrence and Abundance of the Zika Virus Vector Mosquito Aedes Aegypti in the Contiguous United States*, PLOS CURRENTS: OUTBREAKS (Mar. 16, 2016), <http://currents.plos.org/outbreaks/article/on-the-seasonal-occurrence-and-abundance-of-the-zika-virus-vector-mosquito-aedes-aegypti-in-the-contiguous-united-states/> [https://perma.cc/L8TB-FBCC].

53. 2016 Case Counts in the US, CTRS. FOR DISEASE CONTROL & PREVENTION (May 10, 2017), <https://www.cdc.gov/zika/reporting/2016-case-counts.html> [https://perma.cc/7M3N-BVQX]; *Pregnant Women with Any Laboratory Evidence of Possible Zika Virus Infection in the United States and Territories*, CTRS. FOR DISEASE CONTROL & PREVENTION (Aug. 8, 2017), <https://www.cdc.gov/zika/reporting/pregwomen-uscases.html> [https://perma.cc/KC8L-3L88].

54. Geeta K. Swamy & R. Phillips Heine, *Vaccinations for Pregnant Women*, 125 OBSTETRICS & GYNECOLOGY 212, 221 (2015).

55. Saad B. Omer & Sam F. Halabi, *Evidence, Strategies, and Challenges for Assuring Vaccine Availability, Efficacy, and Safety*, in GLOBAL MANAGEMENT, *supra* note 16, at 223, 228.

of pregnant women to accept vaccinations.⁵⁶ The critical role of trust explains the robust regulatory review to which vaccines are subjected before licensure as well as the systems in place to search for rare adverse events that would not be necessary in the context of approval or acceptance for other kinds of pharmaceuticals.

A. The FDA Approval Process

The FDA's Center for Biologics Evaluation and Research (CBER) is responsible for regulating vaccines in the United States, and its approval facilitates the use of vaccines in countries that lack regulatory capacity.⁵⁷ While vaccine clinical development follows the same general pathway as drugs and other biologics, the process in place for maternal vaccines has never been used.⁵⁸

As researchers identify and isolate the relevant pathogen, they seek to understand, to the greatest extent possible, the biological mechanism or mechanisms that lead to disease.⁵⁹ Most vaccine candidates are developed using empirical approaches—historically serial propagation of a pathogen through media that diminishes pathogenicity or which is killed or dissected after

56. WORLD HEALTH ORG., REPORT OF THE SAGE WORKING GROUP ON VACCINE HESITANCY 26 (2014), http://www.who.int/immunization/sage/meetings/2014/october/1_Report_WORKING_GROUP_vaccine_hesitancy_final.pdf [<https://perma.cc/HG66-78EN>]; Allison T. Chamberlain et al., *Factors Associated with Intention to Receive Influenza and Tetanus, Diphtheria, and Acellular Pertussis (Tdap) Vaccines During Pregnancy: A Focus on Vaccine Hesitancy and Perceptions of Disease Severity and Vaccine Safety*, PLOS CURRENTS: OUTBREAKS (Feb. 25, 2015), <http://currents.plos.org/outbreaks/article/factors-associated-with-intention-to-receive-influenza-and-tetanus-diphtheria-and-acellular-pertussis-tdap-vaccines-during-pregnancy-a-focus-on-vaccine-hesitancy-and-perceptions-of/> [<https://perma.cc/5LJR-VATG>].

57. See *Vaccine Product Approval Process*, FOOD & DRUG ADMIN., <http://www.fda.gov/biologicsbloodvaccines/developmentapprovalprocess/biologicslicenseapplicationsblaprocess/ucm133096.htm> (last accessed Aug. 26, 2017) [<https://perma.cc/92WU-PTEM>]; Michael J. Brennan, *The US Food and Drug Administration Provides a Pathway for Licensing Vaccines for Global Diseases*, PLOS MED. (Jul. 21, 2009), <http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000095> [<https://perma.cc/S3XD-6A59>].

58. 42 U.S.C. § 262(i), (k) (2012); see also FOOD & DRUG ADMIN., CLINICAL DEVELOPMENT AND REQUIREMENTS FOR LICENSURE OF VACCINES INTENDED FOR USE DURING PREGNANCY TO PREVENT DISEASE IN THE INFANT 3 (2015) [hereinafter CLINICAL DEVELOPMENT].

59. PRINCIPLES OF BACTERIAL PATHOGENESIS, at xv (Eduardo A. Groisman ed., 2001).

cultivation and used in relatively large doses.⁶⁰ More recent techniques like “reverse vaccinology” start from “genomic sequences” and, by computer simulation, predict “those antigens that are most likely to be vaccine candidates.”⁶¹ Vaccine candidates are then tested in animals after developing models for immunogenicity and safety.

After satisfactory animal testing, the FDA authorizes the sponsor to undertake clinical trials on humans. Phase I of these trials “is designed to assess the safety, immunogenicity, and dose response of the vaccine in, typically, 20 to 100 healthy volunteers.”⁶² In Phase II, the sample size is increased to several hundred healthy volunteers and investigators focus on safety as well as immunogenicity.⁶³ Phase III vaccine trials enroll up to thousands of human subjects in order to detect sometimes rare adverse events.⁶⁴ If Phase III trials “confirm safety and efficacy . . . the vaccine is approved for marketing after internal review of study data.”⁶⁵

In addition to pre-licensure vaccine clinical trials, the FDA requires a biologics license application, inspection of the manufacturing facility, presentation of findings to the FDA’s Vaccines and Related Biological Products Advisory Committee, and usability testing of product labeling.⁶⁶ The ‘Vaccines and Related Biological Products Advisory Committee “reviews and evaluates data” to determine “safety, effectiveness, and

60. Nicola P. Klein et al., *Waning Protection After Fifth Dose of Acellular Pertussis Vaccine in Children*, 367 NEW ENG. J. MED. 1012, 1013 (2012), <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1200850> [<https://perma.cc/FA8C-W3B7>]; Bo Ma et al., *Characteristics and Viral Propagation Properties of a New Human Diploid Cell Line, Walvax-2, and Its Suitability as a Candidate Cell Substrate for Vaccine Production*, 11 HUM. VACCINES & IMMUNOTHERAPEUTICS 998, 1004-05 (2015).

61. Rino Rappuoli, *Reverse Vaccinology, a Genome-Based Approach to Vaccine Development*, 19 VACCINE 2688, 2689 (2001).

62. Omer & Halabi, *supra* note 55, at 225; *see also* 21 C.F.R. § 312.23(a)(6)(i) (2016).

63. *Phase II Trial: About Phases of Clinical Trials*, U.S. NAT’L INSTS. HEALTH, <https://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0022683/> [<https://perma.cc/WN6-HWD2>].

64. L. Simonsen et al., *More on RotaShield and Intussusception: The Role of Age at the Time of Vaccination*, 192 J. INFECTIOUS DISEASES S36, S37 (2005), <https://academic.oup.com/jid/article-lookup/doi/10.1086/431512> [<https://perma.cc/VA-2Z-8DRC>].

65. *See* Omer and Halabi, *supra* note 55, at 226.

66. *Vaccine Testing and the Approval Process*, CTRS. FOR DISEASE CONTROL & PREVENTION, <http://www.cdc.gov/vaccines/basics/test-approve.html> [<https://perma.cc/ZE3B-GA65>].

appropriate use of vaccines.”⁶⁷ Members and the Chair are selected by the Commissioner or designee from among “authorities knowledgeable in the fields of immunology, molecular biology, rDNA, virology[,] bacteriology, epidemiology or biostatistics, vaccine policy, vaccine safety science, federal immunization activities, vaccine development including translational and clinical evaluation programs, allergy, preventive medicine, infectious diseases, pediatrics, microbiology, and biochemistry.”⁶⁸ The committee reviews vaccinations as one of the final steps before approval by the FDA.⁶⁹

B. Requirements for Vaccines Intended for Use During Pregnancy

Under guidelines issued by the FDA, 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 enrolling any pregnant women into clinical trials.⁷⁰ Phase I clinical trials for maternal immunizations begin with non-pregnant women of childbearing age.⁷¹ If results of the proposed vaccination are positive, studies of the vaccination may be advanced into early studies of pregnant women classified as low-risk.⁷² If adequate data from Phase I clinical trials of pregnant women is observed, Phase II may begin to identify a “pilot evaluation of efficacy.”⁷³ As with Phase III trials generally, trials for vaccine candidates intended for use during pregnancy are required to use a prospective, randomized, blinded, well-controlled study, wherein the control arm receives a placebo (or unrelated vaccine) and the primary endpoint is prevention of

67. *Vaccines and Related Biological Products Advisory Committee*, FOOD & DRUG ADMIN., <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/default.htm> [https://perma.cc/J44K-E98Q].

68. *Id.*

69. *Vaccine Product Approval Process*, *supra* note 57.

70. Roberts & Gruber, *supra* note 18, at 968.

71. *Id.*

72. *Id.*

73. *Id.*

clinical disease in a wider population of pregnant women (not limited to low-risk pregnancies).⁷⁴ After clinical development stages, the vaccination would advance to the licensing application, where FDA reviewers would assess the information necessary to make a risk/benefit decision and a recommendation for the approval of the vaccine.⁷⁵

Safety evaluations are incredibly important during each phase of the clinical trials, but continue after the approval of the vaccine.⁷⁶ It is essential to develop a systematic approach to classifying adverse events to be able to assess causality when an adverse event is observed in the clinical trial.⁷⁷ Until a vaccine is given to the general population, all potential adverse reactions cannot be anticipated.⁷⁸ Thus, many vaccines undergo Phase IV studies once on the market, and strict safety reporting standards are in place during and after clinical trials.⁷⁹ A key criterion during Phase IV studies is to determine if there is a “*reasonable possibility* that the drug (or biologic) caused [an adverse] event and whether the event (or pattern of events) is *unexpected*.”⁸⁰ During general population use of the vaccination, it may be necessary to develop a pregnancy registry in order to explore potential changes and improve the quality and utility of the vaccination.⁸¹

C. Labeling

Approval of vaccines “also requires . . . adequate product labeling to allow health care providers to understand the vaccine’s

74. *Id.*

75. 42 U.S.C. § 262(k) (2012); *Vaccine Product Approval Process*, *supra* note 57.

76. *See Vaccine Product Approval Process*, *supra* note 57.

77. Roberts & Gruber, *supra* note 18, at 969; Alberto E. Tozzi et al., *Assessment of Causality of Individual Adverse Events Following Immunization (AEFI): A WHO Tool For Global Use*, 31 VACCINE 5041, 5041-5042 (2013), <http://www.sciencedirect.com/science/article/pii/S0264410X13011997> [<https://perma.cc/P7JT-MZL9>].

78. *See Vaccine Product Approval Process*, *supra* note 57.

79. *Id.*; *see also* Geert Leroux-Roels et al., *Vaccine Development*, 1 PERSPECTIVES IN VACCINOLOGY 115, 123 (2011) (“Phase IV surveillance studies, because of the large sample size involved, are designed to detect very rare adverse events (AEs) that are difficult to pick up in Phase III studies.”).

80. Roberts & Gruber, *supra* note 18.

81. *Id.* at 969; *see generally* Eileen Wilson et al., *Varicella Vaccine Exposure During Pregnancy: Data from 10 Years of the Pregnancy Registry*, 197 J. INFECTIOUS DISEASES S178 (2008).

proper use, including its potential benefits and risks, to communicate with patients and parents, and to safely deliver the vaccine to the public.”⁸² A product’s package insert, also known as the label, is a critical element of the evaluation of a vaccination.⁸³ Vaccine labels must include a section for usage during pregnancy.⁸⁴

Until recently, information on a product insert was categorized using a letter system under which each letter represented the relative availability of clinical information.⁸⁵ Category A pharmaceuticals were those, like folic acid supplements, where “adequate and well-controlled studies failed to demonstrate a risk to the fetus in the first trimester of pregnancy.”⁸⁶ Category B pharmaceuticals meant that there were no adequate and well-controlled studies over human pregnancy, but animal data was reassuring, while Category C pharmaceuticals meant that there were no adequate and well-controlled human studies and also no positive animal data.⁸⁷ Categories D and X conveyed “fetal risk [in] investigational or marketing . . . studies”⁸⁸

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”).⁸⁹ The PLLR changed the labeling rule for biologics (e.g. vaccines) and 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 biological product during pregnancy.”⁹⁰ The new rule not only requires that this

82. See *Vaccine Product Approval Process*, *supra* note 57; see also INST. OF MED., THE CHILDREN’S VACCINE INITIATIVE: ACHIEVING THE VISION 164-69 (Violaine S. Mitchell et al. eds., 1993).

83. See generally 21 C.F.R. §§ 201.56-.57 (2016).

84. Requirements for Pregnancy and Lactation Labeling, 79 Fed. Reg. 72,064, 72,064 (Dec. 4, 2014) (to be codified at 21 C.F.R. pt. 201).

85. Marion F. Gruber, *The US FDA Pregnancy Lactation and Labeling Rule—Implications for Maternal Immunization*, 33 VACCINE 6499, 6500 (2015).

86. U.S. Dep’t of Health & Human Servs., *FDA Pregnancy Categories*, CHEMM, <https://chemm.nlm.nih.gov/pregnancycategories.htm> [<https://perma.cc/3MWN-T37U>].

87. *Id.*

88. *Id.*

89. See generally Requirements for Pregnancy and Lactation Labeling, 79 Fed. Reg. 72,064 (Dec. 4, 2014) (to be codified at 21 C.F.R. pt. 201).

90. Gruber, *supra* note 85, at 6499-500.

information be adapted to be given in narrative form, but also that the labeling “include . . . clinical information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy”⁹¹

Even under the new system, the relative risk to pregnant women considering use is opaque. Consider the product insert language for a seasonal influenza vaccine still marketed under Category B:

There are . . . no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this vaccine should be used during pregnancy only if clearly needed.⁹²

Or the language for vaccines approved under the new rule:

Available data on Prevnar 13 administered to pregnant women are [sic] insufficient to inform vaccine-associated risks in pregnancy.⁹³

As analyzed below, the continuing difficulty in obtaining relevant information about vaccines during pregnancy—and the resulting effect on product labeling—is not the result of a more comprehensive or objective approach to pregnancy. Rather, it is a continuation of culturally informed conceptions inseparable from those influencing regimes dedicated to antidiscrimination, prosecution, or family support.

D. The Alternative Regulatory Framework for Maternal Vaccines

Despite FDA guidance on approval of maternal vaccines through normal channels, the system is unused. Instead, the approval for maternal vaccines is effectively allocated to national technical advisory groups like the Advisory Committee on Immunization Practices (ACIP), a statutory body established to

91. *Id.*

92. SEQIRUS INC., FLUVIRIN PRODUCT INSERT (2017), <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM123694.pdf> [<https://perma.cc/78V3-SH5H>].

93. PFIZER INC., PREVNAR PRODUCT INSERT (2017), <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM201669.pdf> [<https://perma.cc/T34B-H6P2>]; see also *Guidelines for Vaccinating Pregnant Women*, CTRS. FOR DISEASE CONTROL & PREVENTION (2016), <https://www.cdc.gov/vaccines/pregnancy/hcp/guidelines.html> [<https://perma.cc/M24N-8ULB>].

“develop recommendations on the use of vaccines in the civilian population of the United States.”⁹⁴ The 15 member steering committee is appointed by the Secretary of Health and Human Services after “an application and nomination process,” with 14 of the 15 members being medical experts and one serving as a consumer representative.⁹⁵ The committee reports to the Director of the CDC.⁹⁶

ACIP provides assistance to the CDC “regarding the most appropriate selection of vaccines and related agents for effective control of vaccine-preventable diseases.”⁹⁷ It also addresses issues of specific populations such as pregnant and breastfeeding women.⁹⁸

The committee votes on whether to include a new vaccine in the routine immunization schedule, vaccine use in high risk groups, and use of vaccines outside the routine schedules For each recommended vaccine, the committee develops written guidance, subject to the approval of the CDC Director, for administration of FDA-licensed vaccines to children and adults in the US civilian population, including age for vaccine administration, dose and frequency of administration, and precautions and contraindications of vaccine use and information on adverse events.⁹⁹

ACIP uses work groups to investigate data, which the groups then present to the committee.¹⁰⁰ These work groups “focus on one vaccine or group of vaccines,” and formulate proposed policy options by “review[ing] data on morbidity and mortality

94. *About ACIP*, CTNS. FOR DISEASE CONTROL & PREVENTION (Apr. 15, 2016), <https://www.cdc.gov/vaccines/acip/about.html> [<https://perma.cc/F46Q-NKXL>]; *see also* 42 U.S.C. § 217(a) (2012).

95. *See About ACIP*, *supra* note 94.

96. *ACIP: Guidance for Vaccine Recommendations for Pregnant and Breastfeeding Women*, CTNS. FOR DISEASE CONTROL & PREVENTION [hereinafter *Vaccine Recommendations*], <https://www.cdc.gov/vaccines/acip/committee/guidance/rec-vac-preg.html> [<https://perma.cc/6BSY-W4ES>].

97. *Id.*

98. *Id.*

99. Jean Clare Smith, *The Structure, Role, and Procedures of the U.S. Advisory Committee on Immunization Practices (ACIP)*, 28S VACCINE A68, A71 (2010), <http://www.sciencedirect.com/science/article/pii/S0264410X10002057> [<https://perma.cc/4T69-G3WW>].

100. *Id.* at A72.

associated with the disease in the general US population and in specific risk groups.”¹⁰¹

While its statutory authority falls within broadly worded provisions aimed at the role of the CDC in preventing communicable diseases, ACIP’s authority to recommend unlicensed vaccines comes from its charter—a document that is required to be filed under the Federal Advisory Committee Act, but is otherwise of uncertain legal status.¹⁰² Under ACIP’s charter, “[g]uidance for use of unlicensed vaccines may be developed if circumstances warrant. For each vaccine, the committee advises on population groups and/or circumstances in which a vaccine or related agent is recommended.”¹⁰³ Similarly, professional organizations like the American Congress of Obstetricians and Gynecologists, which serve as liaison organizations to ACIP, develop immunization recommendations for practitioners that are guided by, but not necessarily coextensive with, labeling recommendations.¹⁰⁴ The FDA, in turn, allows these recommendations to substitute for regulatory review, declaring that “programmatic recommendations (such as those from WHO, ACIP, and other national immunization technical advisory groups (NITAGs)) for use during pregnancy are not inconsistent with FDA labeling.”¹⁰⁵

In March 2008, ACIP approved its *Guiding Principles in Development of ACIP Recommendations for Vaccination During Pregnancy and Breastfeeding*.¹⁰⁶ Previously, ACIP did not provide any direction to technical advisory groups about creating policy for vaccination use during pregnancy,¹⁰⁷ so those groups adopted recommendations that “var[ied] in clarity and underlying

101. *Id.*

102. CTRS. FOR DISEASE CONTROL & PREVENTION, CHARTER OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES 1 (2016), <https://www.cdc.gov/vaccines/acip/committee/acip-charter-2016.pdf> [<https://perma.cc/K9FM-YTLP>].

103. *Id.* at 2.

104. *See, e.g.*, ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP), SUMMARY REPORT 6, 10, 23-24 (2012), <https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-oct12.pdf> [<https://perma.cc/WF7D-YNDD>]; Jean Clare Smith et al., *History and Evolution of the Advisory Committee on Immunization Practices—United States, 1964-2014*, 63 MORBIDITY & MORTALITY WKLY. REP. 955, 956 (2014).

105. CLINICAL DEVELOPMENT, *supra* note 58, at 10.

106. *Vaccine Recommendations*, *supra* note 96.

107. *Id.*

rationale.”¹⁰⁸ Generally, “[o]bstetrician-gynecologists (ob-gyns) provide more general medical care to women than either family practice or internal medicine providers, and” therefore have better “opportunities to incorporate vaccination into standard clinical care.”¹⁰⁹

It is through this system that a fairly small number of vaccinations have been generally accepted for use during pregnancy.¹¹⁰ ACIP, for example, recommends that all pregnant women receive Tdap and seasonal influenza vaccinations, even though they are not licensed for use during pregnancy.¹¹¹ Some other vaccinations may be recommended based on travel or specific patient profiles, but, as with influenza and Tdap, none have been specifically tested in pregnant women.¹¹²

Safety data for maternal immunization is largely gathered through post-vaccination adverse event monitoring systems, including pregnancy registries and Phase IV post-immunization studies. For example, the Vaccine Adverse Event Reporting System (“VAERS”) collects and analyzes information from reports of negative side effects that occur during the administration of U.S. licensed vaccines.¹¹³ This program, co-sponsored by the FDA and the CDC, receives around 15,000 reports per year.¹¹⁴ Because of this program, “researchers detect new or rare events, identify increases in rates of known side effects, and enhance understanding of patient risk factors.”¹¹⁵ The Vaccine Safety Datalink (“VSD”), run cooperatively by nine healthcare organizations and the CDC, “monitor[s] safety of vaccines and conduct[s] studies about rare and serious adverse events following immunization . . . based on questions or

108. *Id.*

109. Swamy & Heine, *supra* note 54, at 212-13.

110. *See id.* at 214.

111. *Maternal Vaccines: Part of a Healthy Pregnancy*, *supra* note 19; Swamy & Heine, *supra* note 54, at 221 (“To date, vaccines in the United States are not specifically licensed or targeted for use during pregnancy.”).

112. *See* Swamy & Heine, *supra* note 54, at 214, 221.

113. *Vaccine Adverse Event Reporting System*, U.S. DEP’T OF HEALTH & HUM. SERVS., <https://vaers.hhs.gov/index> [<https://perma.cc/D7ML-J9RX>].

114. U.S. FOOD & DRUG ADMIN., REVIEW OF VAERS ANTHRAX VACCINE REPORTS RECEIVED THROUGH 8/15/05, AND ADVERSE EVENT REPORTS SUBMITTED TO DOCKET NO. 1980N-0208, at 1-2 (2005), <http://www.fda.gov/ohrms/dockets/dockets/80n0208/80n-0208-bkg0006-19-Ref-17-VAERS-Vol225.pdf> [<https://perma.cc/87ZZ-F66Q>].

115. *See* Halabi & Omer, *supra* note 55, at 229.

concerns raised from the medical literature and reports to the [VAERS].”¹¹⁶ The results from each data collection program are “linked with larger databases like the CDC’s Clinical Immunization Safety Assessment Network (CISA), which provides a clinical case evaluation service for US healthcare providers who have vaccine safety questions.”¹¹⁷

IV. SHADOW REGULATION OF MATERNAL VACCINES AND THE FUTURE OF MATERNAL AND INFANT HEALTH

As with analogues in Pregnancy Discrimination Act jurisprudence and the reach of the Family Medical Leave Act, the shadow regulatory system for approving vaccines for use during pregnancy does not reflect the consensus in the medical literature regarding pregnant women’s participation in clinical trials, protections for mothers and fetuses codified in federal law, or the potential value of maternal vaccines for the future of human health. It reflects a narrow view of pregnancy that focuses on gestation instead of looking comprehensively at the social and medical changes that accompany pregnancy.

Although there is substantial evidence to support the use of vaccines to prevent diseases in mothers and infants, there has historically been little interest in developing vaccines for use during pregnancy.¹¹⁸ Maternal immunization strategies have been proven to protect infants against neonatal tetanus, and to protect mothers and infants against influenza and pertussis.¹¹⁹ There have not been any safety concerns identified with regard to vaccinating women during pregnancy, but regulatory barriers such as evaluating efficacy and safety pose a limitation.¹²⁰

116. *Vaccine Safety Datalink (VSD)*, CTRS. FOR DISEASE CONTROL & PREVENTION, <https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/> [<https://perma.cc/QZN3-6U24>].

117. Halabi & Omer, *supra* note 55, at 230.

118. See K. Zaman et al., *Effectiveness of Maternal Influenza Immunization in Mothers and Infants*, 359 NEW ENG. J. MED. 1555, 1555-1563 (2008), <http://www.nejm.org/doi/full/10.1056/NEJMoa0708630#t=article> [<https://perma.cc/BV8R-ZZB8>]; see generally Swamy & Heine, *supra* note 54.

119. Flor M. Munoz, *Respiratory Syncytial Virus in Infants: Is Maternal Vaccination a Realistic Strategy?*, 28 CURRENT OPINION INFECTIOUS DISEASES 221, 223 (2015).

120. See Roberts & Gruber, *supra* note 18, at 966.

Federal law authorizes the inclusion of pregnant women in medical research and conditions authorization on several criteria related to the risk and benefit for both mother and fetus.¹²¹ Despite the care taken within federal regulations to facilitate participation of pregnant women and implement a meaningful risk/benefit framework, researchers “reflexively exclude” pregnant women from clinical research aimed at discovering safe and effective vaccines.¹²² While researchers must justify the *inclusion* of pregnant women in a research protocol and specify what special protections will be implemented, there is no requirement to justify their *exclusion*.¹²³ Since the U.S. National Institutes of Health (NIH) began to require inclusion of women, ethnic minorities, and children in research, pregnant women are the only population for which justification for exclusion does not need to be given.¹²⁴

The reasons for excluding pregnant women are consistent with the essentialist critique leveled against legal regimes aiming to protect pregnant women from employment discrimination, to support them comprehensively during and after pregnancy, and to selectively promote or punish certain behaviors during pregnancy. In their path breaking work on barriers to inclusion of pregnant women in medical research, a joint NIH/FDA team led by Mary Blehar concluded that:

[R]easons [for excluding pregnant women] include . . . fear of harm to the fetus and threat of legal liability, concern about the complicated physiology of pregnant women, uncertainty whether pregnant women would be willing to participate, regulations which classify pregnant women as a ‘vulnerable’ population in need of special protections in research, and vague, ambiguous, and restrictive wording of

121. 45 C.F.R. §§ 46.201-.211 (2016); Vanessa Merton, *Impact of Current Federal Regulations on the Inclusion of Female Subjects in Clinical Studies*, in 2 WOMEN AND HEALTH RESEARCH: ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES 65, 67-68 (Anna C. Mastroianni, Ruth Faden & Daniel Federman eds., 1994); COMM. ON THE ETHICAL AND LEGAL ISSUES RELATING TO THE INCLUSION OF WOMEN IN CLINICAL STUDIES, INST. OF MED., 1 WOMEN AND HEALTH RESEARCH: ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES 142 (Anna C. Mastroianni, Ruth Faden, & Daniel Federman eds., 1994).

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

123. *Id.* at e42.

124. *Id.*

regulations, which IRBs in turn interpret conservatively for pregnant subjects.¹²⁵

In their study of industry trials specifically, Kristine Shields and Anne Lyerly found that only 1% of studies were designed specifically for pregnant women, and 95% of studies of conditions that can affect pregnant women excluded pregnant women from participation.¹²⁶ Those studies were Phase IV studies undertaken as retrospective analyses.¹²⁷ As they note: “A common explanation for the exclusion of pregnant women from research is the desire to ‘do no harm,’ yet clinical care during pregnancy often requires the use of medications untested in pregnancy.”¹²⁸ This is true in the context of Zika as well, where even promising vaccine candidates, if proven safe and effective, are likely to be administered to women or adolescent girls who are not pregnant.¹²⁹

These exclusions have multiple ramifications for both maternal and infant health.¹³⁰ Because pregnant women are excluded from vaccine research, the information that accompanies even recommended vaccines—like seasonal

125. *Id.* at e40.

126. Kristine E. Shields & Anne Drapkin Lyerly, *Exclusion of Pregnant Women From Industry-Sponsored Clinical Trials*, 122 *OBSTETRICS & GYNECOLOGY* 1077, 1077 (2013).

127. Viraj Suvana, *Phase IV of Drug Development*, 1 *PERSP. CLINICAL RES.* 57, 59 (2010) (“Some of these studies may be retrospective case-control evaluations. These are done to evaluate rare suspected side effects.”).

128. Shields & Lyerly, *supra* note 126, at 1080.

129. WORLD HEALTH ORG., WHO/UNICEF ZIKA VIRUS (ZIKV) VACCINE TARGET PRODUCT PROFILE (TPP): VACCINE TO PROTECT AGAINST CONGENITAL ZIKA SYNDROME FOR USE DURING AN EMERGENCY 1, 6 (2017), http://www.who.int/immunization/research/development/WHO_UNICEF_Zikavac_TPP_Feb2017.pdf [<https://perma.cc/U93U-S3K6>] (“It is not expected that initial products would contain an indication for use in pregnant women.”); Hilary D. Marston et al., *Considerations for Developing a Zika Virus Vaccine*, 375 *NEW ENG. J. MED.* 1209, 1209-12 (2016) (“Second, vaccine safety and immunogenicity are generally established in nonpregnant adults before vaccination of pregnant women is considered—a standard practice that delays vaccine use in the latter population until some assurances of safety are provided. Hence, it is likely that vaccinating women of childbearing age (and men in order to prevent sexual transmission) would be the optimal initial public health strategy. In the longer term, it may be advisable to vaccinate pediatric populations, well before their first sexual contact. Here, the experience with rubella is instructive: protection of pregnant women was achieved through broad vaccination of young children. Adoption of this strategy would depend on the durability of protection offered by a Zika vaccine.”).

130. 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, 1227-1228 (2016).

influenza and Tdap—confuses many physicians and depresses uptake by pregnant women who justifiably question the safety and efficacy profile of the immunizations. The reflexive exclusion of pregnant women, without justification, deters the development of a meaningful risk/benefit framework to apply to research even where vaccines may do much to address infections, like RSV and Group B Strep infection that pose serious risks to infants.

A. The Development of an Ethical Framework and Risk-Benefit Analysis

Medical researchers and institutional review boards (“IRBs”—also known as “independent ethics committees”—assure that appropriate steps are taken to protect the rights and welfare of humans participating as research subjects) have largely dodged risk, benefit, and ethics decisions involving research on pregnant women.¹³¹ Federal law, under “Subpart B” regulations, requires that risks and benefits be assessed when undertaking research with pregnant women volunteers, including the nature and quality of informed consent communications, the definition of “important biomedical knowledge,” and the research alternatives, if any, to specific medical interventions.¹³² Because pregnant women are reflexively excluded, often without explanation, there are confused and competing interpretations of what these principles might mean.¹³³

131. *Institutional Review Boards Frequently Asked Questions—Information Sheet*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126420.htm> [<https://perma.cc/4TK8-J8ZY>].

132. See 45 C.F.R. §§ 46.203-.204 (2016).

133. See, e.g., *IRB Assessment of Risk & Benefit for Research Involving Pregnant Women and Fetuses (Subpart B)*, U.C.-IRVINE (Mar. 2013), <http://www.research.uci.edu/compliance/human-research-protections/docs/pregnant-women-fetus-neonates-laminated-sheet.pdf> [<https://perma.cc/DBC2-SBCR>] (“The risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means. Only Mother’s consent is required. NOTE: For DoD supported research, there are exceptions (e.g., the phrase ‘biomedical knowledge’ in subpart B shall be replaced with ‘generalizable knowledge’ throughout the subpart). Refer to DoDI 3216.02, version November 8, 2011.” (emphasis omitted)); Janice K. Bush, *The Industry Perspective on the Inclusion of Women in Clinical Trials*, 69 ACAD. MED. 708, 712-14 (1994) (detailing conflicting principles with respect to pregnancy and clinical trials).

“Minimal risk” is a concept that informs the ethical review of research and is poorly defined in the Subpart B context.¹³⁴ IRBs often categorize research in pregnancies as “high risk” without any meaningful development of a decision framework.¹³⁵ The lack of a broadly accepted ethical framework and definition of risk for guiding clinical research during pregnancy has a limiting effect on both academic and industry-led clinical trials regarding the Zika virus.¹³⁶ The lack of an ethical framework has a chilling effect on clinical research in pregnancy and could lead to a similar effect for research of the Zika vaccine because the virus has implications for pregnant women and women of reproductive age.¹³⁷

Definitions of “risk” and “direct benefit” for both mothers and fetuses are crucial for this fundamental scientific endeavor.¹³⁸ For example, researchers cannot identify appropriate animal models during development research without a framework under which their interventions will be assessed later.¹³⁹

Public health emergencies magnify the need for these definitions because they require a real-time assessment of risks.¹⁴⁰ For example, in 2009, during the H1N1 influenza pandemic, the risks of disease greatly outweighed the expected risks from the vaccination of pregnant women, which led to much needed insight on necessary improvements in research.¹⁴¹ These challenges included the need for further articulation of baseline rates, which would define relevant, expected clinical and laboratory standards in pregnancy, and the need for accurate assignment of pregnancy complications.¹⁴² The baseline rate of outcomes is extremely important when a disease emerges that is associated with adverse birth outcomes, and development of these baseline rates could generate large multi-location data sets that

134. See Omer & Beigi, *supra* note 130, at 1227.

135. *Id.*

136. *Id.*

137. *Id.*

138. See generally Seema Shah et al., *How Do Institutional Review Boards Apply the Federal Risk and Benefit Standards for Pediatric Research?*, 291 JAMA 476 (2004), <http://jama.jamanetwork.com/article.aspx?articleid=198070&resultclick=1> [<https://perma.cc/PWS8-ZQLF>].

139. See Beigi et al., *supra* note 17, at 4262.

140. See Omer & Beigi, *supra* note 130, at 1228.

141. See Beigi et al., *supra* note 17, at 4262.

142. *Id.*

would optimize the evaluation of clinically important outcomes, such as microcephaly.¹⁴³ The Ebola public health emergency illustrates the dilemma posed by the absence of meaningful frameworks for ethical review, risk, and benefit. Pregnant women were excluded from Ebola vaccine trials even though all reported pregnancies in Ebola infected women ended in spontaneous miscarriage, stillbirth or neonatal death.¹⁴⁴

B. Toward a More Comprehensive Understanding of Pregnancy and Its Outcomes

1. Immunity and Early Pregnancy

Most of the current knowledge about vaccine response comes from studies conducted in the latter part of pregnancy.¹⁴⁵ Pregnancy is a “physiologically dynamic state” and the immune profile of a pregnant women is responsive to changing levels of sex hormones throughout different stages of pregnancy.¹⁴⁶ Yet there is “limited data available from the first and early second trimester[s]” or from randomized clinical studies, even for vaccines now recommended by ACIP.¹⁴⁷ For example, while it is known that pertussis immunization during pregnancy confers protection on newborns, the “effectiveness and optimal concentration of maternal antipertussis antibodies in newborns” is not.¹⁴⁸ High levels of antibodies in the first weeks after birth likely confer protection and might prevent pertussis or modify disease severity, but a great deal remains unknown.¹⁴⁹ Similarly, there are knowledge gaps with respect to the impact of the timing

143. See Omer & Beigi, *supra* note 130, at 1228.

144. LEONTINE ALKEMA ET AL., TRENDS IN MATERNAL MORTALITY: 1990 TO 2015, at 26 (2015), http://apps.who.int/iris/bitstream/10665/112682/2/9789241507226_eng.pdf [<https://perma.cc/75QL-PWCE>]; Black et al., *supra* note 45, at 108; Agence Fr.-Presse, *A New Ebola Vaccine May Be 'Up to 100 Percent Effective'*, PUB. RADIO INT'L (Dec. 24, 2016, 11:15 AM), <https://www.pri.org/stories/2016-12-24/new-ebola-vaccine-may-be-100-percent-effective> [<https://perma.cc/C35X-3CKA>].

145. See Omer & Beigi, *supra* note 130, at 1227.

146. *Id.*

147. *Id.*; see also CLINICAL DEVELOPMENT, *supra* note 58, at 3.

148. Mark Sawyer et al., *Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine (Tdap) in Pregnant Women*, 62 MORBIDITY & MORTALITY WKLY. REP. 131, 131 (2013), <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6207a4.htm> [<https://perma.cc/BJ3S-PKZQ>].

149. *Id.*

of Tdap during pregnancy on infant pertussis, the safety of multiple doses of the vaccine in pregnant women, and its overall effectiveness.¹⁵⁰ With respect to influenza, the medical community lacks understanding of how different strains of the influenza virus affect mothers and newborns differently.¹⁵¹

The Zika emergency highlights the need for better understanding: the harmful effects of Zika virus infection likely occur in the early parts of pregnancy, so a Zika vaccine may work best if administered prior to pregnancy or early in pregnancy.¹⁵² Zika's link to fetal development highlights the need for pregnant women and those of reproductive age to be a priority while moving forward in the developmental stages of this vaccine.¹⁵³

2. Understanding Background Events and Outcomes

Because pregnancy is conceptualized as it is at the IRB level—a physiological process that should result in the birth of a healthy baby—there is in fact inadequate understanding of population level phenomena related to adverse outcomes that would be necessary to adequately study maternal vaccines. A major barrier in the approval of pregnancy-specific vaccinations is the inability to arrive at a “definite etiology for reproductive effects such as congenital malformations and spontaneous abortions.”¹⁵⁴ Only one-third of malformed children can be provided with a diagnosis, and 15% percent of all pregnancies result in spontaneous abortions.¹⁵⁵ Another challenge is that these

150. Bahaa Abu Raya et al., *The Effect of Timing of Maternal Tetanus, Diphtheria, and Acellular Pertussis (Tdap) Immunization During Pregnancy on Newborn Pertussis Antibody Levels—A Prospective Study*, 32 VACCINE 5787, 5790-92 (2014); see also CLINICAL DEVELOPMENT, *supra* note 58, at 9-10; Sawyer et al, *supra* note 148, at 131-32.

151. Sarah J. Short et al., *Maternal Influenza Infection During Pregnancy Impacts Postnatal Brain Development in the Rhesus Monkey*, 67 BIOLOGICAL PSYCHOL 965, 971 (2010).

152. See Omer & Beigi, *supra* note 130, at 1227.

153. Ian Sample, *Zika Virus Vaccine for Animals Brings Hope for Human Protection*, GUARDIAN (June 28, 2016, 11:00 AM), <https://www.theguardian.com/world/2016/jun/28/zika-virus-vaccine-for-animals-brings-hope-for-human-protection> [<https://perma.cc/ARE7-93QZ>].

154. Robert L. Brent, *Immunization of Pregnant Women: Reproductive, Medical and Societal Risks*, 21 VACCINE 3413, 3415 (2003), <http://www.sciencedirect.com/science/article/pii/S0264410X03003967> [<https://perma.cc/U3Z8-QNZA>].

155. *Id.*

reproductive issues are “clouded by an emotional stigma” that can lead to partisan positions and produce distracting non-objective opinions that misinform the public.¹⁵⁶

Indeed, there is not even consensus around standard definitions for assessing outcomes even if background rates of malformation and spontaneous abortion might be more effectively ascertained.¹⁵⁷

For example, a review commissioned by the World Health Organization highlighted the lack of standard definitions of outcomes, and standards for measurement of these outcomes, relevant to evaluation of vaccines in pregnancy. This lack of standardization poses a challenge for conduct of clinical trials, generalizability of safety data, and merging of large safety data sets. This last point is critical because large multilocation data sets could optimize the evaluation of rare but clinically important outcomes, such as microcephaly.¹⁵⁸

Standard definitions are needed for measuring outcomes when evaluating vaccine safety studies in pregnant women.¹⁵⁹

C. The Physician-Patient Relationship and the Effect on Maternal and Infant Care

1. Doctor-Patient Communication

While the most immediate effect of these knowledge gaps is the lack of data on safety and efficacy for drugs and vaccines that may support maternal and infant health, another area affected is the communication between physicians and patients. There is good evidence showing that pregnant women refuse immunizations based on information in package inserts which ranges from statements about there being no information to “safety and effectiveness of [X vaccine] have not been established

156. *Id.* at 3414-15.

157. *See generally id.*; T. Roice Fulton et al., *A Systematic Review of Adverse Events Following Immunization During Pregnancy and the Newborn Period*, 33 *VACCINE* 6453 (2015).

158. Omer & Beigi, *supra* note 130, at 1228.

159. *See generally* Fulton et al., *supra* note 157.

in pregnant women”¹⁶⁰ The inability of physicians and public health authorities to connect statements regarding maternal health with product information deters important interventions that may help both pregnant women and their unborn children.¹⁶¹

Healthcare providers are well-positioned to explain the benefits of immunizations against vaccine-preventable diseases to pregnant women; they have proven their capacity to do so through their heavy involvement in administering the H1N1 vaccine to pregnant women during the 2009 pandemic.¹⁶² However, research suggests that, broadly speaking, barriers remain high between providers and vaccinations because of the fear of adverse pregnancy outcomes and lack of awareness of national recommendations and product safety information.¹⁶³

A 2008 study “analyzed patient and physician knowledge regarding the influenza vaccine in pregnancy and examined the impact of several interventions to increase immunization rates.”¹⁶⁴ Approximately 86% of physicians “stated that they always recommended vaccinations to their patients” during prenatal care.¹⁶⁵ When the approximately 14% of physicians who did not recommend vaccinations were asked via questionnaire about vaccinations during pregnancy, “25% of physicians said that there [was] not enough data concerning influenza-related complications during pregnancy and concerning vaccine efficacy.”¹⁶⁶ They were also worried about vaccination side effects and the legal risks of vaccinating pregnant women.¹⁶⁷ However, the most frequent answer was that physicians understood their patients did not want to be vaccinated (42.8%).¹⁶⁸

160. Shannon Mulvihill, *TDaP Vaccine During Pregnancy? A Difficult Decision for Any Mom.*, FOCUS FOR HEALTH, <https://www.focusforhealth.org/tdap-vaccine-during-pregnancy-a-difficult-decision-for-any-mom/> [<https://perma.cc/YU64-SZ55>].

161. See generally Birte Bodeker et al., *Skewed Risk Perceptions in Pregnant Women: The Case of Influenza Vaccination*, 15 BMC PUB. HEALTH no. 1308 (2015); Britta Panda et al., *Influenza Vaccination During Pregnancy and Factors for Lacking Compliance with Current CDC Guidelines*, 24 J. MATERNAL-FETAL & NEONATAL MED. 402 (2011).

162. Swamy & Heine, *supra* note 54, at 213.

163. *Id.* at 222.

164. See Panda et al., *supra* note 161, at 403.

165. *Id.*

166. *Id.*

167. *Id.*

168. *Id.* at 405.

In the context of influenza, the combination of physician ambivalence and patient refusal can be fatal. While pregnant women comprise approximately 1% of the United States population, they totaled 5% of the deaths caused by H1N1 in the United States in 2009.¹⁶⁹ Moreover, influenza vaccines administered during pregnancy may impart important benefits to newborns as well. A study conducted in Bangladesh suggests that an influenza shot during pregnancy lowers the risk of influenza both for the woman and for the baby in the first six months of life,¹⁷⁰ while a more recent study from South Africa found vaccination in pregnant HIV-uninfected and HIV-infected African women was immunogenic and provided protection against confirmed influenza.¹⁷¹ “The vaccination was also effective in HIV-unexposed infants up until 24 weeks after birth.”¹⁷²

2. Product Labeling

A key component of facilitating the communication between physician and patient with respect to immunizations is what the physician may say about a vaccine when a pregnant woman asks about its safety and efficacy profile.¹⁷³ Because current clinical data used for vaccine labeling comes “either from post hoc analyses of inadvertent exposures during pre-licensure trials designed to exclude pregnant subjects, or from uncontrolled, observational postlicensure studies,”¹⁷⁴ physicians may say little more than what the product insert says along with language adapted from ACIP or ACOG recommendations.¹⁷⁵

The new PLLR adopted by the FDA and effective as of June 2015 is intended to facilitate meaningful communications

169. Alicia M. Siston et al., *Pandemic 2009 Influenza A (H1N1) Virus Illness Among Pregnant Women in the United States*, 303 JAMA 1517, 1522-23 (2010).

170. See generally K. Zaman et al., *Effectiveness of Maternal Influenza Immunizations in Mothers and Infants*, 359 NEW ENG. J. MED. 1555 (2008), <http://www.nejm.org/doi/pdf/10.1056/NEJMoa0708630> [<http://perma.cc/3L8J-A43Z>].

171. Shabir A. Madhi et al., *Influenza Vaccination of Pregnant Women and Protection of Their Infants*, 371 NEW ENG. J. MED. 918, 930 (2014), <http://www.nejm.org/doi/full/10.1056/NEJMoa1401480#t=article> [<https://perma.cc/S7AN-XYSP>].

172. *Id.*

173. See generally Bödeker et al., *supra* note 161.

174. See Roberts & Gruber, *supra* note 18, at 967.

175. *Id.* at 966-67.

between physicians and pregnant and lactating women in a manner that the old letter-risk system made difficult.¹⁷⁶ But, as pregnant women are excluded from clinical trials, there is little manufacturers may do with respect to adapting their current approaches to product labeling.¹⁷⁷

Pediatrician Saad Omer and obstetrician Richard Beigi recommend that the FDA issue a “mock label” related to pregnancy as a guide to help the industry and public health leaders effectively phase into the new PLLR system and provide obstetrical care providers clear information.¹⁷⁸ This mock label should provide guidance for inclusion and format of pregnancy-related information in sections of the drug labeling that are specifically relevant to pregnant women.¹⁷⁹ Having clarity regarding vaccine labeling related to pregnancy “will help ensure that clinicians have a higher level of confidence in pregnancy-related vaccines and could provide a road map for conducting research that can inform labeling and hence clinical decisions.”¹⁸⁰

D. Maternal Vaccines: the Future of Healthy Mothers and Children

This Essay has emphasized that pregnant women are, by virtue of the structure of medical research norms, effectively disadvantaged as a group relative to other populations just as they are in disability jurisprudence, employment, and under other legal regimes. This disadvantage adversely affects *them as pregnant women* (as opposed to, for example, their unborn children). For example, while the reasons are not well-understood (due to practices detailed above), pregnant women are at much higher risk for severe illness and death when infected by certain strains of influenza. The available medical evidence suggests that immunization protects them while conferring less relative benefit upon a newborn. So the constraints on research, labeling, and physician attitudes are primarily a disadvantage for women.

176. *Id.*; see generally Requirements for Pregnancy and Lactation Labeling, 79 Fed. Reg. 72,064 (Dec. 4, 2014) (to be codified at 21 C.F.R. pt. 201).

177. See Roberts & Gruber, *supra* note 18, at 967.

178. Omer & Beigi, *supra* note 130, at 1227.

179. *Id.* at 1227-28.

180. *Id.* at 1228.

The system also stymies the development of vaccines that represent the future of infant and early childhood health. It is nearly impossible to overstate the contribution that childhood immunizations have made to the lives of children over the last century:

Diseases that used to be common in [the U.S.] and around the world, including polio, measles, diphtheria, pertussis (whooping cough), rubella (German measles), mumps, tetanus, rotavirus and *Haemophilus influenzae* type b (Hib) can now be prevented by vaccination. Thanks to a vaccine, one of the most terrible diseases in history—smallpox—no longer exists outside the laboratory. Over the years vaccines have prevented countless cases of disease and saved millions of lives.¹⁸¹

Programs aimed at expanding access to vaccines—especially childhood immunizations—have enjoyed enormous global financial support from governments, charities, and international organizations like UNICEF and the World Health Organization. “Worldwide, more than 30 vaccine doses are delivered every second through routine immunization programs. This number has increased dramatically as more vaccines are developed . . . and the global community acknowledges that vaccines, as a fundamental medical intervention, positively affect more lives than any other.”¹⁸² In 2013, 6.3 million children under five died, compared with 12.7 million in 1990. Between 1990 and 2013, under-five mortality declined by 49%, from an estimated rate of 90 deaths per 1000 live births to 46. “The global rate of decline has also accelerated in recent years—from 1.2% per annum during 1990-1995 to 4.0% during 2005-2013.”¹⁸³ In other words, the world is nearing universal coverage of children for known early-childhood immunizations.

Improving the current system for development and licensure of maternal immunizations is critical not only for public health emergencies like Zika but also for the next generation of

181. *Why Are Childhood Vaccines So Important?*, CTRS. FOR DISEASE CONTROL & PREVENTION (Aug. 18, 2017), <http://www.cdc.gov/vaccines/vac-gen/howvpd.htm> [https://perma.cc/56QQ-YZKA].

182. Berkley, *supra* note 20, at 179.

183. *Millennium Development Goals (MDGs)*, WORLD HEALTH ORG. (May 2015), <http://www.who.int/mediacentre/factsheets/fs290/en/> [https://perma.cc/2R5Y-5C5G].

preventative health measures that are likely to make major gains in children's health. The first twenty-eight days of life (the newborn period), are a child's most vulnerable.¹⁸⁴ In fact, newborns account for nearly half of all child deaths before five years of age—about 2.9 million deaths each year.¹⁸⁵ Although additional childhood and adolescent vaccines are being developed, immunizations for pregnant women represent a next step, supported by a great deal of preliminary evidence, in the effort to ensure that mothers remain healthy during pregnancy and children are born with as great a chance as possible to lead healthy lives. Vaccination of women during pregnancy is considered the most plausible strategy to provide direct antibody protection against respiratory syncytial virus (RSV), an infection that kills tens of thousands of infants worldwide annually.¹⁸⁶ The main limitations on the production of a Group B streptococcus vaccine—a leading cause of severe invasive disease in young infants—are not technical or scientific, but regulatory and legal because they involve a vaccine delivered during pregnancy.¹⁸⁷ Many other promising maternal vaccines that may improve infant health remain stalled at the conceptual stage.¹⁸⁸

184. *Advancing Maternal Immunization*, PATH, <http://sites.path.org/cvia/advancing-maternal-immunization/> [<https://perma.cc/XVZ2-TCKX>].

185. *Id.*

186. Helen Y. Chu & Janet A. Englund, *Maternal Immunization*, 59 CLINICAL INFECTIOUS DISEASES 560, 565 (2014), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4168293/> [<https://perma.cc/JF2G-N457>]; Harish Nair et al., *Global Burden of Acute Lower Respiratory Infections Due to Respiratory Syncytial Virus in Young Children: A Systematic Review and Meta-Analysis*, 375 LANCET 1545, 1545 (2010), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2864404/> [<https://perma.cc/E7FH-7NFR>].

187. Clare L. Cutland et al., *Increased Risk for Group B Streptococcus Sepsis in Young Infants Exposed to HIV, Soweto, South Africa, 2004-2008*, 21 EMERGING INFECTIOUS DISEASES 638, 638 (2015) (“We estimate that use of trivalent GBS vaccine (serotypes Ia, Ib, and III) could prevent 2,105 invasive GBS cases and 278 deaths annually among infants in South Africa; therefore, vaccination of all pregnant women in this country should be explored.”), https://wwwnc.cdc.gov/eid/article/21/4/14-1562_article [<https://perma.cc/X265-3DWW>]; Paul T. Heath & Robert G. Feldman, *Vaccination Against Group B Streptococcus*, 4 EXPERT REV. VACCINES 207, 207 (2005), <https://www.ncbi.nlm.nih.gov/pubmed/15889994> [<https://perma.cc/9JGV-X9ZQ>] (“The main limitations on the production of a Group B streptococcus vaccine are not technical or scientific, but regulatory and legal.”).

188. See CLINICAL DEVELOPMENT, *supra* note 58, at 3 (“Scientific advances and increasing recognition of unmet potential have led to a recent surge in activity and interest in maternal immunization.”); Richard Beigi et al., *Maternal Immunization: Opportunities for Scientific Advancement*, 59 CLINICAL INFECTIOUS DISEASES S408, S412 (2014), <https://www.ncbi.nlm.nih.gov/pubmed/25425719> [<https://perma.cc/W8AP-GVVF>].

V. CONCLUSION

Legal scholars are undertaking a crucial and comprehensive review of laws aimed at protecting pregnant women from discrimination, arguing for improvement of laws in place to support the multiple factors that affect healthy pregnancies, and urging a more comprehensive view of pregnancy to inform law-making generally. This Essay has suggested that there is as great or greater a need to apply these critiques to the process that leads to lifesaving vaccines for pregnant women, improves meaningful communication between pregnant women and their healthcare providers, and opens the window to the next advances in individual and public health that will secure healthy lives for children. Vaccine-preventable diseases associated with adverse maternal, fetal, or infant health may be prevented by immunization during pregnancy. As immunizations like MMR, Tdap, and polio reach the world's poorest children and coverage rates in developed countries move higher, the next generation of immunizations will be those for which administration during pregnancy imparts health benefits to both mothers and children that are not realizable either before or after pregnancy.