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# Foreword – Will HPV Vaccines Prevent Cervical Cancers Among Poor Women of Color?: Global Health Policy at the Intersection of Human Rights and Intellectual Property Law

Kevin Outterson<sup>†</sup>

Cervical cancer is a disease of social inequality.<sup>1</sup> Women with access to effective screening and treatment rarely die from cervical cancer. The burden of cervical cancer mortality falls most heavily among the poorer women of the world.<sup>2</sup> Cervical cancer starkly illustrates global inequality across race, sex and class. Cervical cancer disproportionately kills poor women of color.

The HPV vaccine is a triumph of science. Current formulations may well prevent infection from the HPV subtypes responsible for approximately 70 percent of cervical cancers, and multi-valiant vaccines are under development to expand the scope of coverage.<sup>3</sup> Nobel Prizes are won for such path breaking science.

And yet, the HPV vaccine is the most expensive vaccine in human history, priced at approximately \$360 wholesale for the currently recommended regime of three doses.<sup>4</sup> Through an accident of patent litigation, we have two brand name manufacturers (Merck and GlaxoSmithKline), but no apparent competition on price.

More troubling, the vaccine is being initially sold to the very people who need it least: the well-insured daughters of the middle class in the US and

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<sup>1</sup> Joanna N. Erdman, *Human Rights in Health Equity: Cervical Cancer and HPV Vaccines*, 35 AM. J. L. & MED. 365, 366 (2009).

<sup>2</sup> See Emmanuela Gakidou et al., *Coverage of Cervical Cancer Screening in 57 Countries: Low Average Levels and Large Inequalities*, 5 PLOS MEDICINE 863, 863 (2008); R. Sankaranarayanan et al., *Effective Screening Programmes for Cervical Cancer in Low- and Middle-Income Developing Countries*, 79 BULLETIN OF THE WORLD HEALTH ORGANIZATION 954-62 (2001).

<sup>3</sup> S.M. Garland et al., *Quadrivalent Vaccine against Human Papillomavirus to Prevent Anogenital Diseases*, 356 NEW ENG. J. MED. 1928-43 (2007).

<sup>4</sup> J. Tanne, *CDC Recommends Expensive Vaccine for All Girls Aged 11-12*, 333 BRITISH MED. J. 114 (2006).

other wealthy OECD countries. Even within the US, the vaccine is going to those with social and financial capital to access vaccination programs, the very women most likely to also have access to effective screening and treatment.<sup>5</sup> In other words, the vaccine is prioritized to the women who need it least. The women most likely to die of cervical cancer in the US are poor women of color, and they may be the least vaccinated group. This inequality reflects the social realities on the ground in the U.S.

These inequalities are magnified when we look at cervical cancer globally. In the wealthiest 34 countries of the world, less than 19,000 women died of cervical cancer last year, compared to more than 240,000 in the rest of the world.<sup>6</sup> The primary commercial markets for the vaccine account for only seven percent of the mortality.<sup>7</sup> For the foreseeable future, the lion's share of HPV vaccine production will go to the countries that need it least, and within those countries to the women who need it least. All of this activity is protected by global intellectual property rules under the WTO TRIPS Agreement.

One surprising aspect of HPV is that most of the controversy focuses on claims about the sexual practices of adolescents<sup>8</sup> rather than these glaring global inequalities. A vaccine that prevents cancers that kill poor women of color is now available, but the primary recipients will be wealthy white women. This should be a human rights issue of the first rank.

The Symposium that follows begins these conversations. Key researchers, public health experts, global health activists, and representatives of Merck came to Boston to discuss these issues thoroughly. Dr. Jim Yong Kim of the Harvard Medical School gave the keynote lecture, focusing on the global inequalities in cervical cancer. He was introduced by Professor George Annas, a distinguished human rights scholar at the Boston University School of Public Health and School of Law. Dr. Mark Feinberg, a vice president in Merck's global vaccine unit, gave lunch keynote speech. Feinberg offered his perspectives, both in his speech and in many questions raised during the discussion periods. We are especially indebted to the Harvard Interfaculty Initiative on Medications and Society, which co-sponsored the Symposium with the American Society of Law, Medicine & Ethics; the Health Law Program at Boston University School of Law; and the AMERICAN JOURNAL OF LAW & MEDICINE. Jennifer Dixon did a superb job as Symposium Editor.

The Symposium begins where many of the key inventions occur: university research labs. Sara E. Crager, Ethan Guillen and Matt Price discuss the intellectual history of the HPV vaccines, deeply rooted in university and other publicly funded research.<sup>9</sup> Universities celebrate a unique social

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<sup>5</sup> Kevin Outterson & Aaron S. Kesselheim, *Market-Based Licensing For HPV Vaccines in Developing Countries*, 27 HEALTH AFFAIRS 130, 135 (2008); Erdman, *supra* note 1, at 387.

<sup>6</sup> F. Kamangar et al., *Patterns of Cancer Incidence, Mortality, and Prevalence Across Five Continents: Defining Priorities to Reduce Cancer Disparities in Different Geographic Regions of the World*, 24 J. CLINICAL ONCOLOGY 2137-50 (2006).

<sup>7</sup> Outterson & Kesselheim, *supra* note 5, at 134-35.

<sup>8</sup> R.A. Charo, *Politics, Parents, and Prophylaxis—Mandating HPV Vaccination in the United States*, 356 NEW ENG. J. MED. 1905-08 (2007).

<sup>9</sup> Sara E. Crager et al., *University Contributions to the HPV Vaccine and Implications for Access to Vaccines in Developing Countries: Addressing Materials and Know-how in University Technology Transfer Policy*, 35 AM. J. L. & MED. 253 (2009).

mission, not limited to strict corporate fiduciary duties to shareholders. Universities are also tasked with the creation of public goods, including knowledge for the benefit of humanity. In a nuanced article, they explore how university technology transfer offices could support access to university research for the developing world, without undermining the commercial and research enterprise. They draw upon their experience as leaders in a student-led organization, Universities Allied for Essential Medicines, as well as their work in medicine. Recognizing that large molecule vaccines are quite different from small molecule generics, Crager, Guillen and Price discuss the biology of HPV vaccine production in significant detail, avoiding overgeneralizations about these technical and difficult processes.

A second article follows this university-lab theme, but this time from lawyers. Beirne Roose-Snyder and Megan K. Doyle propose a Global Health Licensing Program to maximize equitable access to innovation from university labs.<sup>10</sup> They build upon the work of April Effort and Ashley Stevens of Boston University's technology transfer office,<sup>11</sup> articulating intellectual property licensing provisions that might find commercial acceptance while supporting global health. Their approach is pragmatic and flexible, looking for licensing language that meets the needs of all stakeholders, including global health. This article includes useful examples of language for the global licensing toolbox.

Another important institution in global vaccine markets is the Pan American Health Organization (PAHO). Jon Kim Andrus and his colleagues at PAHO and the Sabin Vaccine Institute discuss PAHO's important role in bridging the gap from the factory to the low-income patient.<sup>12</sup> Acting as a financial and management intermediary for vaccines in the Western Hemisphere, PAHO operates the Revolving Fund for Vaccine Procurement, which facilitates procurement on behalf of many PAHO member countries. Mexico<sup>13</sup> has negotiated a HPV vaccine price of \$34 for the three-dose course. The PAHO Revolving Fund price is likely to be lower than that price,<sup>14</sup> partially because PAHO insists on receiving the "best price" globally for Revolving Fund purchases, which would necessitate a price of \$34 or less. Merck is unhappy with the PAHO "best price" rule, arguing that in some cases the PAHO Revolving Fund shouldn't receive the absolute best global price, as its countries, on average, are not the poorest in the world. This position has merit, since price discrimination is generally welfare enhancing and this rule blocks price discrimination in favor of populations poorer than those served

<sup>10</sup> Beirne Roose-Snyder & Megan K. Doyle, *Global Health Licensing Program: A New Model For Humanitarian Licensing at the University Level*, 35 AM. J. L. & MED. 281 (2009).

<sup>11</sup> April E. Effort & Ashley J. Stevens, *Using Academic License Agreements to Promote Global Social Responsibility*, 43 LES NOUVELLES: J. LICENSING EXECUTIVES SOC'Y 85 (2008). Ashley Stevens discussed this paper at the Symposium.

<sup>12</sup> Jon Kim Andrus et al., *New Vaccines for Developing Countries: Will it be Feast of Famine?*, 35 AM. J. L. & MED. 311 (2009).

<sup>13</sup> Mexico is not a Revolving Fund recipient country.

<sup>14</sup> The cost effective price in Brazil has been estimated at approximately \$25. Jan M. Agosti & Sue J. Goldie, *Introducing HPV Vaccine in Developing Countries - Key Challenges and Issues*, 356 NEW ENG. J. MED. 1908, 1909-10 (2007). In poorer countries with per capital incomes around \$1000, the cost effective price is in the range of \$3 to \$6. HELEN SAXENIAN, PROGRAM FOR APPROPRIATE TECHNOLOGY HEALTH (PATH), HPV VACCINE ADOPTION IN DEVELOPING COUNTRIES: COST AND FINANCING ISSUES 8-11 (2007).

by the PAHO Revolving Fund.<sup>15</sup> Even if the PAHO price is less than \$34, the HPV vaccine is very expensive compared to the current childhood vaccine package (DPT-HiB-HB, BCG, MMR, and Polio), which is priced at \$24 in PAHO. This article provides important information on how HPV vaccines will require financing and management in order to roll out effectively across the Americas.

Our fourth article departs from the voluntary world of procurement and licensing contracts and suggests that the credible threat of compulsory licensing is an important component to achieving affordable HPV vaccines.<sup>16</sup> Peter Maybarduk and Sarah Rimmington, attorneys with Essential Action, discuss the practical barriers to compulsory licensing of HPV vaccines, including identifying relevant patents in the absence of a global Orange Book, attracting knowledgeable generic producers, overcoming barriers to export posed by Article 31(f) of TRIPS, achieving registration as a bio-similar, and paying adequate remunerations under Article 31(h). Their work here is practical and straightforward legal analysis on a controversial topic, leaving the politics of compulsory licenses for another day.

Abigail English, Carol A. Ford, and John S. Santelli's article, *Clinical Preventive Services for Adolescents: Position Paper of the Society for Adolescent Medicine*, moves away from intellectual property law to an explicit concern with human rights.<sup>17</sup> They focus on financial access to HPV vaccines and also with parental consent rules that may hinder population acceptance of the vaccine. They ground their concerns in international human rights law, particularly the United Nations Convention on the Rights of the Child.<sup>18</sup> In the U.S., relevant financing mechanisms to improve access include Medicaid, SCHIP, private insurance, and the Vaccines for Children and "Section 317" programs. Some of these programs terminate coverage at age 19, which is too young for some women eligible for the HPV and other adolescent vaccines.<sup>19</sup> The law must adapt to new health care modalities in order to protect human rights appropriately.

Joanna N. Erdman further explores the human rights context, and finds cervical cancer to be an especially compelling case, due to the social inequalities endemic in its mortality patterns.<sup>20</sup> For Erdman, something more compelling than mere health inequality is present here:

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<sup>15</sup> See Kevin Outterson, *Pharmaceutical Arbitrage: Balancing Access and Innovation in International Prescription Drug Markets*, 5 YALE J. HEALTH POL'Y L. & ETHICS 193, 203-05 (2005).

<sup>16</sup> Peter Maybarduk & Sarah Rimmington, *Compulsory Licenses: A Tool to Improve Global Access to the HPV Vaccine?*, 35 AM. J. L. & MED. 323 (2009).

<sup>17</sup> Abigail English et al., *Clinical Preventive Services for Adolescents: Position Paper of the Society for Adolescent Medicine*, 35 AM. J. L. & MED. 351 (2009).

<sup>18</sup> U.N. Convention on the Rights of the Child, G.A. Res. 44/25, U.N. Doc. A/RES/44/25 (Nov. 20, 1989), at Art. 24. The United States is not a party to this Convention.

<sup>19</sup> English, *supra* note 17.

<sup>20</sup> Erdman, *supra* note 1.

Central to health equity is thus not the association of health distribution with the social hierarchy, nor the fact of existing prevention measures, but the capacity of government to change the social hierarchy or to modify its effects on the distribution of health risks and outcomes. There are important reasons to empirically locate the cause of social health disparities in government action, among them, providing an explanation why social health disparities are unjust, the normative dimension of health equity.<sup>21</sup>

Erdman concludes that cervical cancer disparities violate the International Covenant on Economic, Social and Cultural Rights and the Convention on the Elimination of All Forms of Discrimination against Women.<sup>22</sup> She is careful to not claim a human right to the HPV vaccine, but calls for effective prevention and treatment of cervical cancer, especially for the poorest women most burdened. Prevention and treatment can come in many effective forms, including cervical screening and the HPV vaccine. But if weaknesses in infrastructure retard screening, Erdman argues, the moral and legal obligation increases for dissemination of the vaccine.

Leaving aside the manufacturing, financing and legal issues, Gregory D. Zimet asks how the vaccines should be delivered for maximum health impact. He explores both school-based and clinic-based programs, concluding that the former works better for HPV vaccination.<sup>23</sup> Domestic decisions can sometimes have unintended consequences for global public health, as in the case of the US FDA withdrawal of the rotavirus vaccine and thimerosal vaccine preservatives, which he claims inappropriately dampened demand in developing countries. He also highlights some of the work by PATH to streamline HPV delivery and study related cultural issues in developing countries.

PATH's important work is center-stage in Vivien Davis Tsu's article. She finds reasons enough to be "cautiously optimistic" that HPV vaccines will reach the women in greatest need, reducing health inequities rather than exacerbating them.<sup>24</sup> Tsu deploys cost-effectiveness analysis to identify the public health priorities for HPV. Vaccination of boys and older girls is set aside for the time being to focus on the group promising the greatest benefit: pre-adolescent girls before sexual debut.<sup>25</sup> While not discussed in her article explicitly, it seems clear that within that group the public health focus should be on those women least likely to have access to good screening and treatment for cervical cancer, namely, women in poverty in developing countries. Indeed, the balance of her article discusses cultural and other barriers to adoption in developing country and other resource-limited settings. Tsu also touches on financing, a persistent issue in this Symposium, noting that Merck and GlaxoSmithKline have publicly committed to tiered (differential) pricing,

<sup>21</sup> Erdman, *supra* note 1, at 380.

<sup>22</sup> *Id.* at 381.

<sup>23</sup> Gregory D. Zimet, *Potential Barriers to HPV Immunization: From Public Health to Personal Choice*, 35 AM. J. L. & MED. 389, 393-98 (2009).

<sup>24</sup> Vivien Davis Tsu, *Overcoming Barriers And Ensuring Access to HPV Vaccines in Low-Income Countries*, 35 AM. J. L. & MED. 401, 409 (2009).

<sup>25</sup> *Id.* at 404-05.

commensurate to the income level of the target countries.<sup>26</sup> A senior representative from Merck reiterated this commitment at the Symposium, vowing to sell Gardasil “at cost” for the poorest countries, presumably the GAVI-eligible countries. This pledge, if fulfilled, will go a long way to achieving the ultimate objectives of both Universities Allied for Essential Medicines and advocates for compulsory licensing, albeit through different means. Financing HPV vaccine acquisition remains a key hurdle for cervical cancer prevention, both in GAVI-eligible countries and in middle-income countries not eligible for international subsidies.

In our final article, Sean McElligott explores two other licensing options for HPV vaccines, the Generic Opportunity (GO) License,<sup>27</sup> and his own proposal to encourage voluntary contract production by developing world vaccine manufacturers.<sup>28</sup> He suggests that vaccine firms will flee the market if they are inadequately compensated under the GO License, but the GO License is entirely voluntary and does not affect patent-based firm revenues in the wealthy countries of the world, representing more than 90 percent of the HPV vaccine market in dollar terms.<sup>29</sup> Voluntary contract production is a good way to expand and diversify manufacturing capacity, but it does not necessarily lead to marginal cost pricing in developing countries. McElligott’s article discusses complex issues of pricing and intellectual property licensing with an appealing level of sophistication. These issues are multifaceted, and deserve thoughtful treatment, as he had given us.

In conclusion, I should note that while this Symposium focuses on HPV vaccines, many of these issues find resonance with any patented medicine or device that could have significant global health impact in across high-, medium- and low-income populations. Human rights, intellectual property, and global health intersect in this important field.

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<sup>26</sup> *Id.* at 408.

<sup>27</sup> Otterson & Kesselheim, *supra* note 5, at 135.

<sup>28</sup> Sean McElligott, *Addressing Supply Side Barriers To Introduction of New Vaccines To the Developing World*, 35 AM. J. L. & MED. 415 (2009).