

# **Key Ethical Considerations to Guide the Adjudication of a Single-Dose HPV Vaccine Schedule**

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**Abstract**

There is a high burden of human papillomavirus- (HPV) associated cancers in low- and middle-income countries (LMICs). Reducing the recommended dosing schedule from two doses to one makes the vaccine schedule logistically simpler and lowers the cost. This, in turn, could make the distribution of the current vaccine supply more equitable and lead to the protection of more people. However, the clinical trials studying the efficacy of a single-dose schedule have not yet delivered final results, and people are still dying of preventable cancers. Against this background, the question is whether a single-dose HPV vaccine recommendation is appropriate now, and if so, what are the ethical considerations of such a recommendation? We interviewed 18 key informants with expertise ranging from HPV vaccinology to health ethics to policy implementation. We discussed the HPV single-dose policy and its ethical considerations. From these interviews, we developed an understanding of the serious issues surrounding HPV single dose, which informed the development of three key ethical recommendations policymakers should discuss when considering whether to implement the HPV single-dose schedule in their country. These three ethical recommendations are: (1) adopt a holistic view of evidence to justify policy decisions; (2) prioritize the reduction in global disparities in decision-making at all levels; and (3) be transparent in the reporting of how key stakeholder interests have shaped the collection and interpretation of the evidence, and ultimate decisions. The complex discussion regarding the HPV single-dose vaccine schedule highlights the need for in-depth engagement globally to improve our understanding of country-specific contexts, and how those contexts influence decisions regarding the HPV vaccine single-dose recommendation.

## Introduction

In 2014, the World Health Organization (WHO) issued a recommendation that National Immunization Programs (NIPs) should adopt a two-dose schedule of the human papillomavirus (HPV) vaccine, which they deemed to be non-inferior to the three-dose schedule that was the standard at the time.<sup>1</sup> Four years later, in May 2018, WHO issued a call for action towards global cervical cancer elimination.<sup>2</sup> This is estimated to increase total demand for HPV vaccines to 120M doses or more per year after 2025. Sizeable increases in supply will be required to serve this level of demand. Supply constraints are expected until at least 2023-24.<sup>3</sup> Moreover, some promising findings of the potential efficacy of a single dose of the HPV vaccine<sup>4-6</sup> have initiated a debate within the global vaccine community about the desirability of moving from the two-dose schedule to a single-dose schedule.

The consideration of a single-dose schedule occurs against the backdrop of staggering global disparities in HPV vaccine coverage<sup>7-9</sup> and cervical cancer incidence and prevalence between high-income countries (HICs) and low- and middle-income countries (LMICs).<sup>10</sup> Although appeals to “equity” are common in global health discussions, precisely how deliberations about ethics should be structured to help guide decisions about the single-dose HPV vaccine have not received adequate attention. Uptake of the vaccine has been heterogeneous. The annual global birth cohort of girls is currently 60 million, only 10 million of whom are currently being vaccinated. To achieve the elimination of cervical cancer, 40-50 million girls would need to be vaccinated annually. Furthermore, less than 5% of eligible girls in LMICs are vaccinated, even though LMICs account for ~90% of the cases of cervical cancer worldwide.<sup>11</sup> In this paper, we present the findings of our investigation into the ethics of the single-dose controversy. In the first

section, we report a summary of the findings of a set of interviews we conducted with 18 experts in HPV vaccines and ancillary fields. These interviews were intended to help us generate an initial set of insights about ethical issues expected to be prominent in the debate, and why. Section two presents our subsequent review and critical appraisal of the literature, and a set of recommendations distilled from these analyses. The recommendations are intended to help individuals and organizations intimately involved in the single-dose debate to frame the ethical implications of their deliberations and to encourage explicitness in the justification of decisions for or against the approval of the single-dose schedule.

### Interviews with experts in HPV vaccines and ancillary fields

From November 2019 through February 2020, we conducted 18 interviews with key informants

(Table 1) from 9 countries

(Figure 1). Half of the

interviewees were from

LMICs, with a host of

relevant expertise, ranging

from ethics to HPV

vaccinology to vaccine

policy. During the

interviews, we explored the

quality of the current evidence, opinions on recommending a single-dose schedule, and the

impact of a potentially differential HPV vaccine policy uptake. All interviews were conducted in

English, lasted between 40 and 60 minutes, and were conducted using a semi-structured

interview guide, which was based on the synthesis of multiple literature reviews. Audio

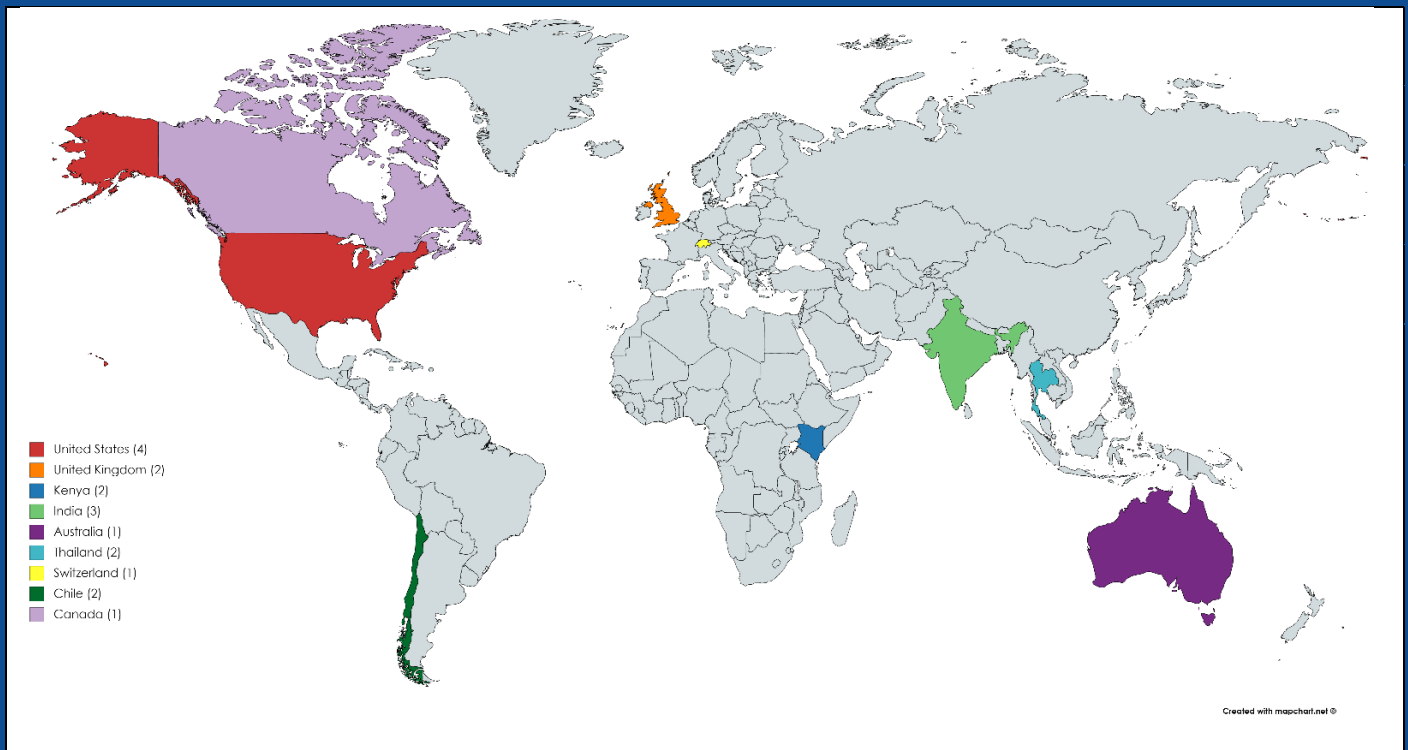
**Table 1. Types of Experts Interviewed**

<b>Interviewee Types</b>	<b>n</b>
Ethicists	2
Policy Makers	6
Government officials	4
HPV Researchers	6
Total	18

recordings of the interviews were transcribed using a HIPAA compliant transcription service.

Thematic analysis was used to analyze the transcripts. A high-level overview of the findings is described briefly below.

**Figure 1. Geographic Distribution of Experts**



### ***Findings***

We identified six dominant themes in our interviews: the state of the current data and available evidence; context and ethics; monitoring and surveillance; equity and differential policy uptake; communication; and cost. Many different points of view were reflected within each theme, demonstrating the complex nature of the debate around the ethics and policy of a single-dose HPV vaccine schedule. Most experts agreed that more evidence is needed regarding the efficacy and duration of protection of a single-dose HPV vaccine schedule. But, there was disagreement

about whether the current evidence provides a sufficient basis for recommending a single-dose schedule. Some expressed concern that acting on the current evidence is premature and could lead to an inferior vaccine schedule being recommended, which could lead to poor outcomes that could exacerbate distrust in the HPV vaccine, and in vaccination programs in general. Others stated that although it is possible that the efficacy of the single-dose schedule could be lower than the two-dose schedule, the difference may be modest and could be offset by wider coverage, especially if the early signals about the duration of protection offered by a single-dose prove to be true.<sup>5</sup>

Although the Strategic Advisory Group of Experts (SAGE) committee recommendations of October 2019 give countries considerable latitude with respect to the adoption of a single-dose, and/or delayed second dose policy,<sup>9</sup> several interviewees believed that the WHO will continue to recommend only one HPV vaccine policy for all countries. However, differential HPV vaccine policy uptake is common between HICs and LMICs, as WHO recommendations (1) are non-binding and (2) come with some latitude to accommodate countries' resources and disease burden. The world will likely witness the implementation of two-dose and one-dose schedules simultaneously. This highlights the importance of the country context and the perspectives of National Immunization Technical Advisory Groups (NITAGs) and other country-level health administrators, who will be charged with the decisions about which schedule is feasible and appropriate for their countries. Understanding the factors that constrain and shape their decisions, and how they influence the reasoning of country-level decision-makers with respect to how they view the relative merits of single-dose, two-dose and 1 + 1 policies, will be critical for ensuring fair processes and transparent standards for policy recommendations. For example, some

interviewees noted that middle-income countries that do not qualify for Gavi financing, especially the countries that have recently transitioned out of Gavi support, might weigh cost considerations more than high-income countries or countries that qualify for Gavi funding, — depending on their financial resources and specific goals for increased coverage.

### **Rationale for Single-Dose HPV Vaccine**

In the absence of a clear correlate of immunity to HPV infection, and with initial evidence of improved immune response after second priming and third boost doses, HPV vaccine development has followed a “classic” prime-boost dosing model, settling, initially, on a three-dose schedule. This approach was also deemed most likely to confer the longest duration of protective immunity, compared to shorter dose schedules.<sup>12</sup> Therefore, in 2009, the WHO recommended that countries adopt a three-dose schedule for their National Immunization Programs.<sup>13</sup>

Trials of the three-dose HPV vaccine schedule have demonstrated consistently high levels of efficacy and effectiveness.<sup>14</sup> However, due to incomplete dosing, or no doses in the case of those women assigned to placebo controls, post-hoc analyses from some of these trials have allowed comparisons of protective immunity in young women who received only 2 or 1 dose.<sup>4,6,15</sup> Evidence from prospective non-inferiority immunogenicity trials<sup>16</sup> led the European Medicines Agency (EMA) to approve a two-dose schedule in 2015,<sup>17</sup> and prompted the WHO to recommend the two-dose schedule for girls who receive the first dose prior to 15 years of age.<sup>1</sup> Because the analyses of the performance of a single dose of vaccine, compared to 3, 2 and 0 doses, have been surprisingly strong,<sup>5</sup> it has now turned the attention of the global vaccine

community to the desirability and advisability of a single-dose HPV vaccine schedule, which could greatly improve the low HPV vaccine uptake in LMICs.

The rationales for exploring the relative efficacy of a single-dose schedule compared to the current WHO-recommended two-dose schedule<sup>1</sup> have focused on 5 main considerations: (1) evidence regarding non-inferiority of immunogenicity and durability of protective immunity; (2) elucidation of immunological mechanisms of protective immunity; (3) potential for increased coverage; (4) potential for lower schedule and program cost and improved cost-effectiveness; and (5) improved market access and feasibility of incorporating HPV vaccination into NIPs for LMICs.

### *Non-Inferiority*

Despite a rich and extensive literature about all aspects of HPV vaccines, very few studies have been designed explicitly to compare three-dose vaccines with two or fewer doses. Numerous ongoing studies have reported encouraging efficacy data for a single-dose, but these have all been post-hoc analyses.<sup>4,5</sup> A randomized control trial (RCT) addressing the comparative efficacy of single-dose vs. two-dose HPV vaccine schedules is due to report findings in 2024-25.<sup>5,18</sup>

Published comparisons of two-dose schedules with one-dose schedules are drawn primarily from retrospective analyses of post-licensure studies from national immunization programs, nested observational studies of random allocations in clinical trials, immunogenicity studies, and case-control and other observational studies from national registries and commercial health systems data.<sup>19-22</sup>



Evidence from these sources is strongly suggestive that a single dose schedule is capable of conferring protective immunity, but limitations in the available data have made it extremely difficult to assess non-inferiority compared to three- and two-dose schedules, especially since antibody titers and neutralizing antibody production and durability are consistently higher in three- and two-dose schedules. The implications of these immunological differences for long-term clinical protection remain unclear. Additionally, because of the lack of prospectively designed and controlled comparative trials, the true implications of these findings for vaccine effectiveness against HPV infection and related cancers are difficult to assess. These uncertainties led the SAGE to recommend to the WHO in 2018 that there is currently insufficient evidence to support a determination of non-inferiority of a single-dose schedule.<sup>9</sup>

### ***Immunological Mechanisms***

Schiller and Lowy recently summarized the current immunology of HPV vaccination and concluded that “(t)here is mounting evidence that the vaccines have similar efficacy and effectiveness even when administered in a single dose.”<sup>23</sup> Their review highlights the unique morphology of the vaccine’s virus-like particles (VLPs), which self-assemble from 360 individual copies of the L1 major capsid protein of the virus. The biology of the VLPs is just one of the complexities of the vaccine manufacturing process. The L1 VLPs display a densely and highly ordered arrangement of epitopes that present a “pathogen-specific danger signal” [p. 4770],<sup>23</sup> common in a wide range of viruses and microbial surfaces. This unique structure makes the VLPs highly effective in causing the proliferation of B cells and antibody-producing long-lasting plasma cells (LLPCs) in particular, which appear to ensure a stable and durable source of

on-going antibody production. Schiller and Lowy address the concern that a single-dose vaccine appears to produce lower levels of antibody than multiple doses by speculating that “the observation that antibody levels that are more than 100-fold lower than the minimum level detected in the *in vitro* neutralizing assay are able to prevent *in vivo* infection is consistent with the idea that there are potent antibody-mediated mechanisms relevant to *in vivo* inhibition that are not detected *in vitro*” [p. 4771].<sup>23</sup> Although not determinative, the unique immunological dynamics of the HPV vaccine offer strong biological plausibility for durable protective immunity from a single dose HPV vaccine, an effect that may not be well reflected in the empirical evidence to date, which emphasizes the importance of antibody titers.

### ***Potential for Increased Coverage***

Approximately 90% of the 530,000 annual new cases of cervical cancer worldwide occur in LMICs, only about 5% of eligible women in LMICs have received HPV vaccination.<sup>12</sup> Since the HPV vaccine is difficult to manufacture<sup>24</sup> and relies on cold-chain delivery because of its relative heat-sensitivity,<sup>24,25</sup> it is costly to produce and distribute. Improved coverage from a single-dose versus a two-dose schedule is the most intuitive of the prospective benefits of a switch to single-dose schedule. However, more experience and data about distribution cost-savings will be required to quantify the potential increases in coverage that a single-dose policy is likely to produce.<sup>26</sup>

### ***Potential for lower costs and improved cost-effectiveness***

Compared to a two-dose HPV vaccine schedule, a single-dose should reduce logistical and administration costs per person vaccinated for NIPs. However, overall costs to NIPs in LMICs

could increase if a single-dose schedule facilitates a significant expansion of overall coverage beyond the current 5%. The cost-effectiveness of the single-dose policy will ultimately be determined by the vaccine's effectiveness at creating and sustaining individual and herd immunity, and by its impact on reducing the incidence of target cancers.<sup>27</sup>

In 2019, SAGE recommended that “countries that have already introduced HPV vaccine and face an imminent vaccine supply shortage can consider a 1+1 schedule.” This is also called an “extended interval” schedule, where the first dose is given to girls aged 9-10 years, and the second dose is given 3 to 5 years later. The implementation of a 1 + 1 schedule will require robust monitoring and surveillance in each implementing country to guide decisions about the need for a second dose. In theory, cost-savings from delayed purchase of the second dose at the outset could be applied to creating and/or strengthening the necessary surveillance capacity, which could support other vaccine and disease programs as well.

### **Key Ethical Issues**

The choice of HPV vaccine schedule raises ethical challenges for reasons of disparity in access, supply constraints, high cost, delivery complexity, and limitations of the existing scientific evidence. Decision makers, especially those at the country or regional levels, are faced with three key ethical questions:

1. **Zero versus one-dose:** Should a country that has not yet rolled out an HPV vaccination program, begin with a one-dose schedule?
2. **Two-doses versus one-dose:** Should countries that already have a two-dose HPV vaccination schedule in place move to a one-dose schedule?

3. **Fair interpretation of limited evidence:** What inferences can policy makers make from the existing scientific evidence? And, more specifically, how should “non-inferiority” be understood and operationalized?

Below, we lay out an ethical framework to help guide policy-makers, at all levels, facing these ethical challenges.

### **Ethical Framework**

The overarching ethical question facing the global vaccine community is how best to protect an entire generation of young women in LMICs from devastating and highly preventable cancers. Reduction in the per person cost of vaccination could facilitate expanded population coverage in those countries with the lowest coverage rates, which could provide a realistic pathway to reducing global disparities in HPV infection and cancer prevalence. Intra-country disparities are also common in HPV vaccine distribution. Although it is unclear to what extent these disparities are driven primarily by cost, as opposed to supply chain deficiencies and unfair distribution policies, cost reduction could offer new possibilities for improving the fairness of distribution within countries, in addition to expanded coverage. These are, fundamentally, and unavoidably, questions of global justice, both in absolute terms—i.e., whether entire generations of young women (and young men) are simply denied access to a life-saving intervention—and in relative terms—i.e., whether birth cohorts of young women (and young men) in HICs continue to reap a disproportionate share of the benefits of HPV vaccination compared to their counterparts in LMICs.

The complex scientific questions outlined above also present difficult ethical questions about the appropriate standards of evidence for justifying decisions to recommend a single-dose policy, or

not, or to endorse a 1 + 1 approach, or to support multiple dose schedules simultaneously. These policy decisions involve the navigation of complex and imperfect scientific evidence alongside key contextual considerations, such as affordability and different coverage and programmatic goals among NIPs.<sup>28</sup>

Conventional appeals to ethical principles and guiding values are likely to be inadequate to provide meaningful ethical guidance for all the relevant stakeholders, including manufacturers, researchers, regulators, normative bodies, national immunization programs, host country policymakers and health systems administrators, and vaccine funding and purchasing bodies. In the face of these challenges, we propose a set of key ethical considerations that can function as an “ethics roadmap” to help shape an approach to ethical reasoning that is ‘fit for purpose’ for the complex ethical challenges that must be navigated during the period of evaluation and possible transition to a single-dose regimen. We focus, in particular, on three key recommendations: (1) adopt a holistic view of evidence to justify policy decisions; (2) prioritize the reduction in global disparities in decision-making at all levels; and (3) be transparent in the reporting of how key stakeholder interests have shaped the collection and interpretation of the evidence, and ultimate decisions.

***Adopt a holistic view of evidence to justify policy decisions***

The evidence, described above, informing the debate about the relative effectiveness of a single-dose HPV vaccine schedule is impressive and compelling and will become more complete over time. The generation of the evidence that would be required to support a more definitive determination of non-inferiority compared to the two-dose schedule is constrained.<sup>29</sup> Economic

constraints include the prohibitive cost and time required to mount a very large comparative trial that could assess the impact on the relevant public health outcomes of reduced cancer incidence. Ethical constraints include the inability to follow women prospectively in controlled trials of untreated cancer precursors or to randomize large numbers of women to no vaccine when an effective vaccine is available.<sup>30</sup>

One ethical hazard associated with this evidence landscape is that decision-makers may, by convention, adopt an overly narrow analytic frame that relies predominantly on measures like the persistence of neutralizing antibodies over time, even though our understanding of the precise relationship between antibody titers and protective immunity for HPV vaccines is incomplete.<sup>23</sup> There is no debate about the relevance or importance of antibody titers as a signal of immune response and likely protective immunity. However, it is conceivable that decision-makers could find the single-dose schedule to be inferior to the two-dose schedule on the basis of this incomplete knowledge, and, in doing so, inadvertently establish a ‘double standard’ whereby LMICs may avoid the adoption of the vaccine, or the expansion of their coverage, to avoid having to justify the adoption of a ‘lower standard.’<sup>31</sup>

Although there are no simple solutions to evidence that is restricted to efficacy, we recommend that decision-makers adopt a holistic view of what evidence can be useful to support robust policy decisions. More explicitly factoring in considerations of cost and delivery logistics, for example, as relevant features of the ‘performance’ of the single-dose schedule could help to expand the working concept of “effectiveness” beyond the achievement of primary and secondary endpoints, to broader population goals of improved coverage and perhaps even

improved immunization infrastructure.<sup>28</sup> To do so might require setting more permissive bounds of non-inferiority for trial data and a more explicit “on balance” assessment of how the relevant features of the single-dose schedule might combine to produce a unique value profile, beyond efficacy alone.<sup>32</sup>

### ***Prioritize the reduction of global disparities***

One implication of adopting an excessively narrow interpretation of effectiveness, as described above, is that any decision that establishes a single-dose schedule as inferior to the two-dose schedule, in absolute terms, is unlikely to be overturned until the current Costa Rica RCT comparing single to two-dose regimens reports in 2024-2025.<sup>5,18</sup> In the meantime, uptake of a two-dose schedule (i.e., the ‘superior’ schedule) would likely remain inaccessible to low-income, and lower-middle-income countries due to cost considerations. Therefore, whatever reductions in uncertainty the Costa Rica trial might provide, will almost certainly be felt in a widening of global disparities. Thus, the opportunity for expanding immunization capacity and/or coverage that the single-dose schedule could provide for some countries would be delayed for another five years. This scenario would privilege individual-level gains *within* countries rather than relative gains *between* and *among* countries.

John Rawls’s theory of justice addresses the issue of fair distribution of social goods.<sup>33</sup> He contends that society is conceived of as a fair system of cooperation from one generation to the next between free and equal citizens possessed of the two moral powers, which are: (1) the capacity to form, revise, and rationally act upon a conception of the good; and (2) the capacity for a sense of justice. In the current controversy over whether the potential transition to a single-

dose HPV vaccine schedule is warranted scientifically, Rawls's framing makes explicit the importance of conceptualizing and generating evidence in a way that clarifies the nature and specific value of the social goods in question. Although relatively few LMICs have introduced the HPV vaccine into their national immunization programs, the coverage achieved in these countries has been high.<sup>34</sup> It would be unfair if the potential reductions in global disparities that this increased coverage represents were excluded from consideration simply by the conventions of RCT data collection and analysis.

### ***Transparency regarding the influence of stakeholder interests***

Many national introductions of the HPV vaccine in LMICs were funded by pharmaceutical companies' donations.<sup>7</sup> This changed in 2013 when LMICs were able to receive support for HPV vaccine programs through Gavi, the Vaccine Alliance.<sup>35</sup> The critical determinants of effectiveness, evidentiary standards and the potential social value of vaccines, or candidate vaccines, are routinely discussed by stakeholders within the complex global vaccine enterprise, including companies, public and private funders, regulators, Gavi, WHO, individual target country ministries, and national immunization programs. But although the discussions are well known to involve complex consultations and negotiations, the ways in which the interests of these stakeholders shape decisions—beyond the technical interpretation of the available data—are rarely made explicit or publicly accessible. This is important because these stakeholders' interests can carry significant weight, particularly in individual country decisions, and could distort the ethical intentions reflected in other aspects of the decision-making process, including the potential to undermine the priority of reducing global disparities.



*All decisions have implications*

The primary function of scientific evidence is to reduce our uncertainty about the nature of the phenomena we study and, by doing so, increase the confidence we can have in the decisions that evidence aims to inform. Although there is a common understanding that values play a critical role in decision-making, there is limited acknowledgement that values can play a critical role in the interpretation of evidence.<sup>36</sup> Upshur has argued that “inherent to the interpretation of evidence are very different animating values.”<sup>36</sup> He describes two forms of prudence—“active” and “precautionary”—that lean towards pragmatism and beneficence, and non-maleficence, respectively.

Given the current state of the evidence, described above, if a country decides to launch a new HPV vaccination program with a single-dose schedule, or switch from a two-dose to a single dose schedule, it seems likely that the ‘animating value’ motivating that decision would be a desire to maximize its ability to protect its young women (and young men) from preventable cancers. Such a decision would not constitute a disregard of the current evidence, but rather an interpretation favoring various elements of the evidence, e.g., the strong biological plausibility that a single dose can durably stimulate antibody production, and thereby sustain protective immunity, and that the single dose schedule represents a significant advantage in terms of feasibility and affordability. This type of ‘active prudence’ reflects the ethical burden that country-level decision-makers shoulder in terms of stewardship of resources and the accountabilities of a government to its people, in contexts that are experiencing dramatic increases in preventable cancers.

On the other hand, policy-developers, such as SAGE members as well as national and regional immunization technical advisory groups, are charged not only with interpreting the available evidence about safety and efficacy and likely effectiveness, but also with the broader mandate of protecting the scientific and evidentiary standards themselves. From this perspective, Upshur's notion of 'precautionary prudence' might be best understood as a defense against interpretations of available evidence that might lead to the dilution of, or manipulation of, evidentiary standards.

The challenge facing all decision-makers with respect to the adjudication of a single-dose HPV vaccine regimen is to ensure that these different forms of 'prudence' on the part of decision-makers do not result in millions of young women (and young men) being denied the opportunity for protection against preventable cancers because we lack sufficiently sensitive procedures for integrating value judgements with the best available evidence.

## Conclusion

This paper presents an overview of ethical considerations for policymakers engaged in deliberations and decision-making about the status of a single-dose HPV vaccine schedule. Specifically, we offer a 'roadmap' of three ethical considerations (Table 2) that we believe offer a constructive set of navigation aids to help keep ethical considerations tightly linked to the adjudication of

**Table 2. Key Ethical Parameters**

- |  |
|--|
| 1. Adopt a holistic view of evidence to justify policy decisions |
| 2. Prioritize the reduction of global disparities                |
| 3. Transparency regarding the influence of stakeholder interests |

emerging scientific evidence and contextual considerations.<sup>28</sup> These ethical parameters encourage a healthy tension between narrow interpretations of efficacy and effectiveness and broader considerations of the potential social value of a single-dose schedule, against the backdrop of crushing global disparities in HPV and cancer prevalence between HICs and LMICs.

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