An Ethical Justification for Expanding the Notion of Effectiveness in Vaccine Post-Market Monitoring: Insights from the HPV Vaccine in Canada

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Health regulators must carefully monitor the real-world safety and effectiveness of marketed vaccines through post-market monitoring in order to protect the public's health and promote those vaccines that best achieve public health goals. Yet, despite the fact that vaccines used in collective immunization programmes should be assessed in the context of a public health response, post-market effectiveness monitoring is often limited to assessing immunogenicity or limited programmatic features, rather than assessing effectiveness across populations. We argue that post-market monitoring ought to be expanded in two ways to reflect a 'public health notion of post-market effectiveness', which incorporates normative public health considerations: (i) effectiveness monitoring should yield higher quality data and grant special attention to underrepresented and vulnerable populations; and (ii) the scope of effectiveness should be expanded to include a consideration of the various social factors that maximize (and minimize) a vaccine's effectiveness at the population level, paying particular attention to how immunization programmes impact related health gradients. We use the case of the human papillomavirus vaccine in Canada to elucidate how expanding post-market effectiveness monitoring is necessary to close the gap between clinical practice and public health, and to ensure that vaccines are effective in a morally relevant sense.

Introduction

The introduction of a new vaccine, like the human papillomavirus (HPV) vaccine, requires health regulatory bodies to carefully monitor the vaccine's real-world safety and effectiveness through what is called 'post-market monitoring' (PMM) in order to protect the health of the public and promote those vaccines that best achieve public health goals. While vaccines are licensed on the basis of pre-market trials that assess vaccine *efficacy*, or the balance of benefits and harms of a vaccine under optimal, highly-controlled study conditions, PMM is required to determine vaccine *effectiveness*, or the balance of harms and benefits in the real-world context of use (Eichler *et al.*, 2011). For instance, the quadrivalent HPV vaccine Gardasil® was approved for use in immunization programmes in

Canada in 2006 in order to protect girls from select HPV strains and their sequelae, which include cervical cancer. Findings from phase III (pre-market) and phase IV (post-market) studies have shown that the HPV vaccine has the ability to significantly reduce the incidence of new, persistent infections with HPV-16/18 as well as the incidence of cervical intraepithelial neoplasia (CIN) 2 or more severe disease (CIN2+) associated with HPV-16/18 cervical infections (Hildesheim *et al.*, 2014). However, these indicators alone cannot tell us whether the vaccine is effective in achieving public health goals. To do so, health regulators must take into account information beyond that which is typically derived from phase IV biomedical studies and post-market, spontaneous adverse event reporting, such as distribution effects and uptake rates among vulnerable populations—information that is pertinent to fulfilling the goals of

public health. With the allocation of significant funding toward a school-based, HPV vaccine programme, the Canadian Government in effect identified HPV-related morbidity and mortality as a public health crisis warranting a public health intervention. Accordingly, the effectiveness of the HPV vaccine must be assessed in the context of a public health response.

Emerging scholarship in public health ethics has begun to investigate the ethical considerations pertinent to collective immunization programmes (Verweij and Dawson, 2004; Moodley *et al.*, 2013). However, there remains a paucity of in-depth ethical analysis of what it means for a vaccine to be called ‘safe’ and ‘effective’, for safety and effectiveness are background assumptions in existing analyses or are presented as a principle for collective immunization programmes. For instance, Verweij and Dawson’s principles for collective immunization programmes identify vaccine effectiveness as both a background assumption and as a principle that ‘each vaccine and the programme as a whole must be effective and safe’ (Verweij and Dawson, 2004: 3123). They go on to argue that safety and effectiveness standards for vaccines should be higher than they are for other pharmaceutical products owing to the fact that most vaccines are offered to healthy individuals, who are also often children (and thus vulnerable), as a way of preventing future harm (Verweij and Dawson, 2004).

In this article, we argue that vaccine effectiveness¹—as assessed in PMM activities—ought to be expanded to incorporate normative public health considerations and goals in addition to traditional regulatory, biomedical considerations. We argue that governments will be better able to discharge their overarching moral—and legal—obligations to protect the public from harms resulting from newly approved pharmaceuticals and biologics and promote pharmaceutically-based public health interventions that best achieve public health goals. We agree with Verweij and Dawson that collective immunization programmes ought to include considerations of vaccine storage, delivery, and administration safety. Our challenge in this article, though, is to show that it is ethically inappropriate to separate out vaccine effectiveness from programmatic effectiveness. It is our aim to further expand on the principles advanced by Verweij and Dawson, which entail that ‘immunisation should only be considered where relevant, detailed and full evidence exists about the efficacy and safety of the vaccines’, and that this responsibility includes ‘the process of monitoring and reviewing possible side-effects of the immunization programme’ (Verweij and Dawson, 2004: 3124). We will do this by articulating the

normative reasons why this expanded view of vaccine effectiveness is important for public health.

To do so, we take it as our starting ethical assumption that the moral and legal obligation to protect the public from harms resulting from newly approved pharmaceuticals and biologics obtains in all states, and find it is supported not only in statements by government regulatory bodies (ANZTPA, 2003; EMA, 2014; FDA, 2014; Government of Canada, 2014) but also within the public health ethics literature (Upshur, 2002; Verweij and Dawson 2004; Thompson *et al.*, 2006). We use the case of the HPV vaccine in Canada to ground our analysis of the notion of vaccine effectiveness, both because it is a recent vaccine and because it has been at the centre of much controversy (Lippman *et al.*, 2007; Erdman, 2008; Thompson, 2013). Using this case,² we have identified a number of ethical considerations that ought to be factored into an expanded *public health* notion of post-market effectiveness monitoring—something that ought to be considered a prerequisite for governments to discharge their principal duty of protecting the public from harm. Specifically, we argue that PMM ought to be expanded in two ways to reflect what we call a ‘public health notion of post-market effectiveness’: (i) post-market effectiveness monitoring should yield higher quality data and provide special attention to underrepresented and vulnerable populations; and (ii) the scope of effectiveness should be expanded to include a consideration of the social and political factors that maximize (and minimize) a vaccine’s effectiveness at the population level, paying particular attention to how an immunization programme impacts related health gradients. This will also require consideration of morally relevant populations’ (e.g., those who are most at risk from mortality from the disease the vaccine is intended to prevent) access to immunization, and whether their ability to mount an immune response is the same as those for whom there is already efficacy data. In addition, stewardship, transparency, conflicts of interest and stigma are normative considerations that need to be integrated into the establishment of vaccine effectiveness.

A Public Health Ethics Approach

The ethics of pre-market drug and vaccine research has been widely discussed within the research ethics literature (Faden *et al.*, 1994; Moore and Miller, 1999; Emanuel *et al.*, 2000; Zion *et al.*, 2000; Corrigan, 2002), but there is a dearth of ethical analysis of the post-market regulatory context (Callréus, 2013;

Thompson *et al.*, 2014). What has been written concerning the ethical conduct of post-market epidemiological research and surveillance is largely concerned with conceptualizing the boundary between public health practice and research, and articulating the implications of this distinction for the requirements of ethical oversight of monitoring activities (Dickens *et al.*, 1991; Fairchild and Bayer, 2004; Johnson and Taylor, 2007; Mello *et al.*, 2012; PHO, 2012; Callréus, 2013). For example, activities that fall under routine public health practice, such as quality improvement and programme evaluation, are typically regarded as distinct from public health research, with only the latter requiring formal research ethics review—a distinction that, for example, has implications for the nature and extent to which consent is required in public health monitoring. While this literature provides a solid foundation for further analysis of public health research ethics, we put aside the contested debate between public health research and practice in order to focus on articulating a justification for an expanded scope of PMM—in particular, a *public health* notion of vaccine effectiveness that incorporates normative considerations into the notion of what it means for a vaccine to be effective once it is approved.

Vaccine PMM is a matter of public health as it provides the information necessary to assess vaccine risk-benefit profiles across populations and justify the administration of vaccines as public health interventions. Accordingly, PMM should reflect the implicit and explicit normative values that are significant to public health. The health and well-being of communities and populations lie at the crux of public health, and undergird its emphasis on evaluating and addressing societal rather than individual-level factors associated with health and disease. Focusing on the multifaceted (e.g., physical, psychological, environmental, institutional, and social) conditions that affect population health and disease has normative implications for public health policy and practice since it motivates an explicit emphasis on prevention and social justice in public health (Starfield *et al.*, 2008; Thompson, 2013), which we now turn to outlining in greater detail.

Prevention and Justice

As vaccine PMM is aimed at facilitating anticipatory action and often involves assessing the safety and effectiveness of vaccines used in public health interventions, a public health ethics perspective, which focuses on ethical issues pertaining to the health of populations and preventive measures, ought to be instructive in

highlighting the limitations of the current state of vaccine PMM in Canada and internationally. While no single public health ethics approach exists, it is uncontested that public health ethics emphasizes the importance of population-wide prevention, requiring us to consider the extent to which governments are obligated to protect the public's health and welfare and to implement interventions that are in the public's health interests. Decisions concerning the post-market use of vaccines are usually made in an evidence-based paradigm, which uses evidence of causal associations between particular actions or products and risk to health in order to determine whether to intervene (Wilson, 2003). Accordingly, PMM is indispensable to addressing the questions of uncertainty and urgency that characterize the real-world harms and conditions associated with vaccine use (Callréus, 2013), as increasing the amount and quality of information available concerning the effects (and limitations) of immunization programmes enables regulators to more readily assess and implement anticipatory measures. Moreover, as risk-benefit profiles of collective immunization programmes must be analysed in the context of publicly acceptable levels of risk, higher safety and effectiveness thresholds are required to maintain trust given that there is a low public tolerance of risks associated with vaccination due to the small direct benefit to individuals and the fact they are most often administered to healthy individuals, and often to children (Verweij and Dawson, 2004).

Yet, the concept of prevention in public health has shifted from an emphasis on promoting population health and reducing health disparities to a focus on preventing specific risk factors and diseases at the individual level (Starfield *et al.*, 2008). In addition, the 'molecular revolution' has led to a focus on developing notions of effectiveness in the context of 'personalized medicine' (Wilson *et al.*, 2007), which tends to draw attention away from notions of effectiveness that have more to do with public health goals. Studying biomarkers has become more important than reducing mortality and morbidity in vulnerable populations. As a mechanism aimed at minimizing uncertainty, PMM should exemplify the anticipatory, preventive dimension of public health, but existing vaccine PMM often fails to assess morally salient aspects of vaccine effectiveness on a population level. Yet, the potential harms associated with diminished vaccine effectiveness include both individual-level harms, such as harms stemming directly from diminished or failed immunity, and harms arising from social or systemic factors, such as unidentified diminished vaccine effectiveness in

sub-populations which may be overlooked if risk–benefit profiles are assumed to be consistent across all sub-populations, behavioural changes that place individuals at greater risk of harm, or cultural, systemic or institutional barriers that prevent individuals from benefiting from a vaccine. Failure to account for the latter harms limits assessments of real-world risk–benefit profiles necessary for anticipatory action.

In addition to prevention at the population level, social justice, which features heavily in public health ethics (Beauchamp, 1976; Callahan and Jennings, 2002; Gostin and Powers, 2006; Powers and Faden, 2006), highlights the moral relevance of the social dimensions of health, and thus requires both an awareness of how public health interventions affect socially disadvantaged groups and an active effort to ameliorate their health and well-being when disadvantage is the result of injustice (Beauchamp, 1976; Powers and Faden, 2006). While public health ethics requires an assessment of PMM in light of its implications for socially vulnerable populations, existing monitoring often assesses only vulnerability that is biological in origin. Even immunization programme evaluations, which are usually conducted on a passive, *ad hoc* basis (i.e., outside of formal regulatory structures), tend to focus on adherence, behavioural changes and biological and individualized risk factors rather than on contextual, population-level or social factors (Weinberg and Szilagyi, 2010). This is problematic as morally-significant factors, such as access by and effectiveness in socially vulnerable populations, are left unexamined. Moreover, monitoring studies often fail to remediate the pre-market clinical trial exclusion or underrepresentation of socially vulnerable groups that renders these populations *prima facie* at greater risk of experiencing drug and vaccine-related harms. Biologically vulnerable groups include those who are at higher risk of morbidity or mortality due to biological factors such as genetic mutations, age, gender-related or physiological factors. Conversely, socially vulnerable groups face disproportionately higher health risks as a result of social, institutional and systemic disadvantages due to factors (e.g. race) that do not ethically justify unequal treatment.

As vulnerability is linked with identifying ‘high risk’ groups that warrant preventive health interventions, the exclusion of social vulnerability in defining health risks leads to a deceptive focus on individual, biological risks for disease, thus rendering up-stream causes and social determinants of health invisible (Starfield *et al.*, 2008; Thompson, 2013). Moreover, the biological and social dimensions of vulnerability have implications for how

vaccine-related harms and ineffectiveness are conceptualized. While vaccine-related harm and ineffectiveness are typically conceived of in biological terms as a worsening of one’s health or well-being as a result of vaccination (or, with respect to ineffectiveness, no change or suboptimal change in one’s immune status), social vulnerability draws attention to harms and ineffectiveness resulting from omissions, such as the inability to access a vaccine or the inability to mount an adequate immune response, when assessing the overall harms and benefits of a vaccine within the social context of its use. Accordingly, it is necessary to expand the notion of effectiveness to determine whether morally significant populations are receiving the purported benefits of a vaccine—information necessary to determine whether a vaccine is effective in a morally relevant sense—and ultimately to addressing the gap between clinical practice and public health.

Efficacy vs. Effectiveness

Once a vaccine is licensed for market use, PMM is conducted to assess whether the vaccine maintains an acceptable risk–benefit profile under conditions of real-world usage (Government of Canada, 2011). Currently, PMM primarily monitors vaccine safety, while vaccine and programme effectiveness, which are required to assess the purported benefits of a vaccine in a real-world context, are usually monitored on an *ad hoc* basis, that is, outside of formal regulatory structures (Standing Senate Committee on Social Affairs, Science and Technology, 2013). Vaccines are licenced for market use on the basis of pre-market trials, which assess vaccine efficacy, or how well a vaccine works in immunized individuals compared to unimmunized individuals under the optimal, highly-controlled conditions of a clinical trial.

Yet, the generalizability of efficacy trials is limited owing to a number of factors. First, the conclusions drawn from efficacy trials may not be generalizable in cases where idealized trial conditions differ from real-world conditions in a medically-relevant way (Berlin *et al.*, 2008). Second, it is erroneous to assume that the risk–benefit profile of a vaccine in one population is generalizable to all populations as relevant differences between populations may exist which could result in differential health benefits and risks. This is important because what might be considered ‘medically relevant’ may exclude social factors that influence biological variation (Gerhardus and Razum, 2010). Third, since pre-approval clinical trials are conducted over a limited time and involve a limited sample size, rare side-effects

often remain undetected prior to licensure and widespread, long-term use. Fourth, clinical trials often exclude or under-represent biologically and/or socially vulnerable populations such as children, the elderly, individuals with underlying health conditions, indigenous populations and other ethnic minorities. PMM within underrepresented populations is warranted as these groups are *prima facie* at greater risk of experiencing vaccine-related harms since there is limited or no safety and effectiveness data available for them. Finally, clinical trials often have no-treatment or placebo groups as comparators, thus leaving comparative effectiveness with other available treatments or public health measures an open question (Schneeweiss *et al.*, 2011). Thus, post-market trials are required to evaluate vaccine effectiveness, which describes the net balance of benefits and adverse events of a vaccine under conditions that more closely approximate real-world use.

In practice, however, effectiveness studies are limited, as they primarily consist of phase IV clinical trials designed to assess the immunogenicity of a vaccine in less-idealized trial conditions and in a broader, though still not necessarily representative, population. Effectiveness studies rarely examine the programmatic context of a vaccine's use across a population, but even when they do, they primarily examine vaccine uptake and behavioural changes, rather than examining a vaccine's effectiveness at reducing morally relevant outcomes like health inequities. In other words, effectiveness monitoring often fails to reflect the multifaceted determinants of effectiveness as highlighted by Weinberg and Szilagyi (2010: 1608):

‘... vaccine effectiveness is proportional to vaccine potency (i.e. vaccine efficacy) but is also affected by how well target groups in the population are immunized (which itself may reflect difficulties in maintaining proper storage conditions of a vaccine, such as the cold chain, access to health care, and vaccine cost), as well as by other nonvaccine-related factors that influence the real-world outcomes of hospitalizations, ambulatory visits, or costs.’

The complex nature of effectiveness has received increased attention in the context of translational research (Szilagyi, 2009; Weinberg and Szilagyi, 2010). Szilagyi argues that translational research, which typically focuses on translation from basic science to clinical research and from clinical research to clinical practice, should be expanded to ultimately assess outcomes at the community or population level. Doing so may even reinforce the notion that effectively translating clinical studies to widespread clinical practice can only go so far

in improving health at a population level, as factors other than traditional health care, such as social, financial, community, behavioral, educational and cultural factors, contribute to the health of populations (Szilagyi, 2009). Yet, social and systemic factors (e.g., differences in health care use or susceptibility in vaccinated and unvaccinated populations) are often dismissed as confounding factors or biases that make identifying vaccine-related effects, such as immunogenicity, more difficult in effectiveness studies than in efficacy trials (Weinberg and Szilagyi, 2010). However, such confounding factors, which are inherent to real-world use and which are intimately linked with health outcomes, are morally important, as differences in health care utilization and immune and general health status are often linked with social inequalities that are unjust (Powers and Faden, 2006).

A Public Health Notion of Effectiveness

Adopting a public health notion of effectiveness has two primary implications for post-market vaccine monitoring. First the quality of existing PMM activities must be improved in order to yield higher-quality data and reduce needless uncertainty to enable anticipatory action. Public health effectiveness requires that trials be designed using parameters and representative participants to facilitate an understanding of the risks and benefits of a vaccine at the population level, but also within the social context of use. The importance of assessing population-level effectiveness is all the more obvious when a vaccine is used in a collective immunization programme. Second, a public health notion of effectiveness demands that the scope of monitoring be expanded to include an assessment of the social and political context of vaccine use, which takes into account morally-significant dimensions of population health, such as social determinants of health that create health inequities, and to assess whether morally-significant populations are receiving the purported benefits of vaccination. In other words, evaluating a vaccine in its social context is an important addition to evaluating the vaccine's immunological effectiveness, since a vaccine that is immunologically effective, but is inaccessible to or less effective in morally-significant populations cannot be deemed truly effective in the context of public health, and may even inadvertently exacerbate health disparities and hinder more effective or accessible preventive measures.

Expanding both the quality and scope of PMM is required to: facilitate ethical regulatory oversight and proper stewardship of public health resources; assess

whether and how a vaccine should be marketed; determine whether a collective or targeted immunization programme is warranted; and determine if a vaccine is preferable to another public health intervention, such as population screening. We justify the notion of public health effectiveness and describe its practical implications for conducting PMM and expanding monitoring infrastructure by probing the case of the HPV immunization programme in Canada, which is comparable to programmes that have been implemented internationally over the past decade.

The Canadian School-Based HPV Vaccination Programme

HPV and Cervical Cancer

HPV is the most common sexually transmitted infection, with an estimated 70% of sexually-active individuals contracting HPV during their lifetime (PHAC, 2013a). HPV is the cause of almost all cervical cancer in women, and has been implicated in the development of genital warts, penile cancer in men and oral and anal cancers in men and women. In Canada, cervical cancer accounts for 1.1% of female cancer deaths or around 450 deaths per year (PHAC, 2013b). Globally, more than 270,000 women die from cervical cancer each year, with more than 85% of these deaths occurring in low- and middle-income countries (WHO, 2013). While HPV infection is relatively common, the healthy host immune system spontaneously clears approximately 70% of infections within 1 year and 90% of infections within 2 years. Moreover, there are over 130 HPV strains that vary in prevalence and oncogenic risk (PHAC, 2013b). Accordingly, it is inaccurate to conflate HPV infection with the development of cancer.

Notably, however, cervical cancer incidence and mortality are not equally distributed among the Canadian population (or internationally). Instead, a social gradient exists, as cervical cancer is associated with poverty and underserved populations (WHO, 2008; Crowcroft *et al.*, 2012), and is most common in low-income, Aboriginal and recently immigrated women (Donnelly *et al.*, 2009). The social gradient in cervical cancer incidence and mortality persists in Canada (Ng *et al.*, 2004; Booth *et al.*, 2010) and globally (Parikh *et al.*, 2003; Ueda *et al.*, 2006; McCarthy *et al.*, 2010; Jemal *et al.*, 2011; Singh *et al.*, 2011; Simard *et al.*, 2012), even despite the introduction of Pap testing, which has resulted in a significant decline in cervical cancer incidence and mortality across all income levels in Canada (Ng *et al.*, 2004). Low Pap screening rates, reduced access to

reproductive and primary health care (resulting in prolonged HPV infection), poor nutrition, immunocompromised states and low socio-economic status are all associated with the persistent health disparities observed in cervical cancer (Parikh *et al.*, 2003; McDonald and Kennedy, 2007; Lippman *et al.*, 2007; Donnelly *et al.*, 2009; Khadilkar and Chen, 2013).

The HPV Vaccine

In 2006, the first available HPV vaccine, Merck Frosst's Gardasil® (HPV4), was authorized for use in Canada, in girls and women aged 9–26 against four HPV strains. Of these, HPV strains 16 and 18 are responsible for 70% of cervical cancers, while strains 6 and 11 are implicated in the development of genital warts. Regular Pap screening is still required to detect lesions arising from the HPV strains not covered by the vaccine. In 2007, the National Advisory Committee on Immunization (NACI) issued a statement advising the immunization of females between the ages of 9 and 26. Moreover, the federal government allocated \$300 million dollars to fund the school-based vaccination programmes, and by 2008, all the provinces and territories in Canada had announced their intention to or had already introduced a voluntary, school-based HPV immunization programme targeting pre-adolescent or adolescent girls ranging from Grades 4 and 8, depending on the province or territory (NACI, 2012). Vaccine uptake rates vary greatly between provinces, ranging from as low as 50% to as high as 86% (Markowitz *et al.*, 2012). In 2011 the vaccine was approved for use in males, although males were not given access to the vaccine under the school-based public health programmes. Similarly structured, publicly-funded immunization programmes have been implemented internationally (e.g., in Australia, most European countries, Israel, Japan, several Central American countries, South Africa and the USA) (Markowitz *et al.*, 2012).

Insights from the HPV Case

Improving the Quality of Effectiveness Data

The first implication of adopting a public health notion of effectiveness in PMM concerns increasing the quality and scope of existing effectiveness monitoring. Determining comparative effectiveness of a vaccine and related treatment options is also necessary as clinical trials often calculate efficacy in relation to placebos or no-treatment, rather than other available screening or therapy options (Schneeweiss *et al.*, 2011). Moreover, in practice, the quality of data collected from these trials, as

well as the populations studied, is faced with limitations. For example, many pre-approval and post-market trials use surrogate end-points to calculate efficacy. Surrogate endpoints are known biomarkers that are correlated with, but may not guarantee a causal relationship with 'hard' end-points such as developing a disease or death. For example, given the long latency period (average 20 years) between initial HPV infection and cervical cancer development, there is currently no available data on the efficacy of the HPV vaccine in preventing the development of invasive cervical cancer. Instead, surrogate endpoints (CIN 2/3 or adenocarcinoma *in situ*) have been used to determine efficacy and effectiveness in clinical trials (NACI, 2012). Determining whether a vaccine is effective at reducing clinical endpoints requires long-term effectiveness studies. While surrogate endpoint may be indicative of efficacy, the case of HPV illustrates that greater caution is required when extrapolating results from surrogate endpoints. While Gardasil® is often cited as having an efficacy of 100%, the FUTURE I and FUTURE II clinical trials assumed the validity (i.e., that it actually measures what it purports to measure) of the CIN2+ surrogate endpoint and actually showed great variance in efficacy depending on the study participant pool (Gerhardus and Razum, 2010). It is necessary to recognize the limitations of surrogate endpoints and clinical trial study designs in order to assess the true, long-term effectiveness of a vaccine. Understanding long-term effectiveness is required to determine whether booster shots are required, evaluate whether Pap screening schedules should change and to reevaluate the programme's cost-effectiveness. Moreover, parents who decide not to vaccinate their daughters cite the lack of long-term effectiveness data as one of the most prominent concerns (Smith *et al.*, 2011). While the use of surrogate endpoints is relatively common and may be predictive of vaccine effectiveness, acquiring long-term effectiveness data is crucial to understanding whether women are and will remain protected against HPV. Significant harm from over-estimating effectiveness from surrogate endpoints can be done if women stop participating in screening programmes or if they fail to get the boosters they require to maintain immunity, especially for those who were not HPV naïve at the time of vaccination. Thus, the results of post-market effectiveness monitoring must be interpreted in light of the limitations inherent to the use of surrogate endpoints so as not to mislead health policy decisions, skew cost-effectiveness models, overlook heterogeneity between groups or lead to false security that evaluating effectiveness is not required (Gerhardus and Razum, 2010).

In addition to understanding the limitations of surrogate endpoints in effectiveness monitoring, high-quality PMM requires that relevant sub-populations are included in effectiveness studies. However, just as pre-market clinical trials often exclude or underrepresent biologically or socially vulnerable groups, post-market trials may sometimes do the same (e.g. with children). Yet, it is erroneous to assume that the risk-benefit profile of a vaccine in one sub-group of a population is generalizable to all sub-groups since medically—and socially—relevant differences may exist (Gerhardus and Razum, 2010). For example, differences in genotype and the health status of individuals or certain social vulnerabilities may render some sub-groups at higher risk of adverse events and diminished immunogenicity (i.e., less able to mount an effective immune response to a vaccine), thus leaving them more vulnerable to infection (Falsey and Walsh, 1997; Ulmer and Liu, 2002). With respect to the HPV vaccine, heterogeneity between age groups was largely overlooked when many countries issued recommendations for immunizing girls up to 17 years of age and assumed a constant effectiveness of 70%, despite the fact that the only direct effectiveness data available included girls over the age of 15 (Gerhardus and Razum, 2010). Indeed, at the time that the HPV vaccine programme was implemented and the vaccine was administered to thousands of girls aged 9-15, fewer than 1,200 girls younger than 16 years of age had been studied in clinical trials, the youngest of which were followed only 18 months (Lexchin *et al.*, 2010). Finally, as Verweij and Dawson note, collective immunization programmes themselves affect the spread of disease in ways that may differentially affect different sub-populations, and thus require 'an assessment of the possible shifts in the spread of disease and the moral consequences of these changes' (Verweij and Dawson, 2004: 3124). Thus, expanding the quality of effectiveness data collected is warranted to determine whether a vaccination programme results in a just distribution of benefits and burdens. More generally, the quality of effectiveness data could also be improved by ameliorating infrastructure as discussed in the final section of this article.

Expanding the Scope of Effectiveness

Starfield *et al.* (2008) assert that the practice of conflating risk factors with diseases has shifted the focus of public health interventions from promoting population health and reducing health disparities to a focus on preventing specific risk factors and diseases at the individual level. While this raises a fundamental question

concerning the objectives of public health practice, which is open for debate, we propose that as a public health measure, vaccine PMM should assess population-level factors and not only individual-level programme features such as adherence or uptake. In other words, effectiveness monitoring should be expanded to include evaluations of whether there are systemic social and political factors that affect a vaccine's effectiveness, and if so, how they can be amended to maximize effectiveness. Using public health effectiveness to include an assessment of systemic and institutional factors affecting the real-world benefits and limitations of a vaccine in effectiveness monitoring is necessary to ameliorate existing immunization programmes and assess whether policies other than collective immunization programmes are better suited to improving the health of populations, and especially socially vulnerable groups. Traditional PMM, which primarily consists of assessing vaccine safety, may not provide the requisite information to assess whether an intervention promotes population health or reduces health disparities (Szilagyi, 2009). This is problematic since systemic barriers such as inability to access a vaccine or socio-economic determinants of general health status may have significant implications for whether or not an individual receives the purported benefits of a vaccine. In overlooking these barriers, the very groups that may stand to gain the most from a public health intervention may incur greater harm if they are assumed to have access when in reality they do not. For example, HPV vaccine uptake rates are significantly lower in Hispanics and African-Americans in the USA (Gelman *et al.*, 2013), while in Ontario, Canada, girls from lower socio-economic status are less likely to complete all three HPV vaccine doses (Smith *et al.*, 2011) despite facing disproportionately higher HPV-related morbidity. Moreover, overlooking systemic factors shifts the burden of responsibility from regulators and health care providers, who would have less of an impetus to ensure the conditions for optimal vaccine use, to individuals, who are now charged with taking advantage of the effectiveness of vaccine itself.

The HPV vaccine is exemplary of a public health intervention that must be assessed in light of social vulnerabilities given the persistence of the social gradient in cervical cancer incidence and mortality. While not all health inequalities are necessarily unjust or morally significant, Thompson argues that by assessing the Canadian cervical cancer social gradient under Powers and Faden's theory of social justice, it becomes clear that 'the cervical cancer social gradient in Canada is the result of morally significant inequality [...] because it is the result of structural inequities that violate the

Canadian principle of collectivity [of health care access]' (Thompson, 2013: 12). Since the uneven distribution of cervical cancer in Canada arises largely due to systemic social inequities, social vulnerability is a relevant factor for shaping post-market surveillance strategies, and demands an assessment of whether such systemic inequities also hinder these populations from benefiting from the HPV vaccine. In particular, the women who potentially stand to gain the most from a safe and effective HPV vaccine are those who are at greatest risk of succumbing to cervical cancer due to systemic health disadvantages, including multiple barriers to accessing health care (e.g., rural residents, street youth, Aboriginals), and are thus also less likely to be vaccinated (Lexchin *et al.*, 2010). Vaccinating individuals who would undergo regular Pap screening will have a lesser impact on reducing cervical cancer incidence or redressing health disparities. The need to consider the systemic barriers that limit an individual's range of meaningful choices, and thus affect their ability to benefit from a public immunization programme, is also justified by the principle of respect for persons as interpreted through a public health lens. Public Health Ontario, a provincial public health organization in Canada, notes that public health ethics 'brings into focus forms of disadvantage such as the impact of social determinants that may affect autonomy' (PHO, 2012: 8–9), which suggests that allowing individuals to realize their autonomy requires the redressing of barriers that limit meaningful choice. It is only by assessing systemic and institutional barriers to health which result in health disparities that vaccine effectiveness can be determined in a morally-relevant sense. Moreover, without evaluating public health effectiveness of the immunization programme, the programme risks harming the very individuals it purports to help if the political will to address underlying social determinants of health is weakened by the assumption that the vaccine has resolved the health inequities associated with cervical cancer.

In the remainder of the article, we address several implications concerning the conduct of PMM that arise from employing a public health notion of vaccine effectiveness.

Further Ethical Considerations for Public Health Effectiveness

Transparency and Conflicts of Interest

Effectiveness data should be collected in a transparent manner so as to achieve the highest quality data by minimizing undue influence and manipulation of

data, and to foster public trust, which is essential to successful immunization programmes. As Verweij and Dawson assert, ‘trust is not just something to be promoted; it should be deserved as well’ (Verweij and Dawson, 2004: 3125). Earning and maintaining public trust takes on an even greater significance in the context of illnesses that disproportionately affect vulnerable or stigmatized populations, which may be wary of government intervention based on past negative experiences.

Transparency is especially pertinent given that the majority of active vaccine surveillance is conducted by vaccine manufacturers. For example, the majority of the studies evaluating the safety and efficacy of Gardasil® were conducted directly by or funded by the vaccine manufacturer, Merck Frosst (Lippman *et al.*, 2007). Manufacturer bias in the reporting of clinical trial data is widely recognized as a serious problem with respect to pharmaceutical drugs (Lexchin, 2012). Merck Frosst exerting pressure on the Ontario Government to frame the HPV vaccine as an anti-cancer vaccine rather than a vaccine against a sexually transmitted infection (STI) illustrates the reality of conflicting interests (Lippman *et al.*, 2007; Erdman, 2008; Polzer and Knabe, 2009). Even the independence of the Cochrane Collaboration, a well-known, scientific organization that purports to critically evaluate evidence in an independent manner, has come under scrutiny as 8 out of 12 primary authors of the oft-cited Cochrane reviews of the HPV vaccines have conflicts of interest with the vaccine manufacturers (Schaaber, 2013). Several authors failed to declare their conflicts, and two authors were involved in important HPV vaccine trials, including one which has been criticized for presenting data in a selective and misleading manner and failing to publish important data. Accordingly, it is necessary that PMM be conducted in a manner that minimizes the potential for bias and undue influence by manufacturers as biased results could have significant ramifications on the ability to properly evaluate safety and effectiveness and may result in harm and undermine public trust. Yet, the need to minimize potential conflicts of interest must be balanced with the reality of limited financial resources and research capacity.

Stewardship

Increasing the available evidence on effectiveness is also important to facilitating stewardship—a guiding principle in public health ethics—which demands that government officials act in a trustworthy and ethical manner when making decisions and distributing limited health resources (Thompson *et al.*, 2006). PMM of

vaccines is required to assess whether an immunization programme is an effective public health measure or whether resources should be allocated towards more effective interventions. However, stewardship also requires policymakers to consider whether the additional costs associated with PMM are justified.

Cost-effectiveness models are used in evaluating, justifying and comparing collective immunization programmes with alternate public health measures. In the absence of adequate data on vaccine safety, effectiveness and uptake, cost-effectiveness models must rely on estimates that can yield very different conclusions depending on the starting assumptions used, as seen with three models used to calculate the cost-effectiveness of the HPV vaccine in Canada (Seto *et al.*, 2012). Expanding PMM capacity and adopting a public health notion of effectiveness to include considerations of how systemic factors affect the distribution of burdens and benefits of an immunization programme can not only provide more detailed data for cost-effectiveness assessments, but may also help guide meaningful reform in how cost-effectiveness is conceptualized. Moreover, employing a public health notion of effectiveness is required to properly compare immunization programmes with other public health measures, which may prove to be equally or more cost-effective at reducing cancer morbidity and mortality, in order to determine how to best allocate public health resources. Doing so would also address current limitations in many pre- and post-market trials that have no-treatment or placebo as comparators.

Stewardship also highlights the tension between balancing the costs of expanded monitoring and the need to obtain high quality effectiveness data. Conducting thorough monitoring of the HPV immunization programme would be costly given the need for long-term monitoring, owing to the long latency period between HPV infection and the development of cervical cancer, and may draw resources away from other public health interventions. Yet, as expanding PMM is required for calculating cost-effectiveness, not to mention assessing long-term safety and effectiveness of an immunization programme which targets a large, healthy population of young girls, many of whom are at a low life-time risk of developing serious HPV-related illnesses, it is worth reforming drug regulatory infrastructure to increase the financial and research capacity for PMM. If PMM were recognized as being an integral part of the drug’s life-cycle, rather than a distinct process from approval and uptake, the costs of PMM could be factored into initial cost-effectiveness calculations that are used to justify the implementation of a programme. Scotland took a

similar approach with the HPV vaccine when it devised a strategy to concurrently fund both vaccination and monitoring (Wong *et al.*, 2011). Factoring the costs of PMM of vaccines into initial cost-effectiveness calculations is also necessary to determine whether it would be more cost-effective to implement a collective immunization campaign or to target vulnerable populations and use the remaining resources to improve overall health in the population. Additionally, industry ‘user fees’ could be increased to reflect the costs associated with PMM (Lemmens and Bouchard, 2007). Thus, an expanded notion of public health effectiveness can inform the ethical tensions that arise from the need to balance adequate monitoring with other public health goals when setting priorities for resource allocation, especially when cost-effectiveness must be balanced with the needs of vulnerable populations (Thompson, 2013).

Collective vs. Targeted Monitoring

When determining whether to adopt collective monitoring measures at the population level or whether to target relevant sub-populations, policymakers must balance factors such as costs and limited research with considerations such as stigma. For example, most HPV sentinel surveillance focuses on women, thus excluding groups such as men who have sex with men (MSM). However, limiting monitoring to women may have morally significant ramifications as it may mask the value of including groups such as MSM in the public vaccination programme. For example, several studies conducted outside of Canada have noted that incidences of HPV and associated anal disease continue to increase in MSM, especially in those who are HIV positive (NACI, 2012). In fact, rates of anal cancer in HIV positive MSM exceed those of the highest rates of cervical cancer in women. Furthermore, while a reduction in the prevalence of anogenital warts has been noted in heterosexual men following high vaccine uptake by girls, no reduction has been observed in MSM (NACI, 2012). Yet, given the stigma associated with a targeted campaign and the infeasibility of specifically targeting MSM at a young age prior to sexual debut, expanding sentinel monitoring to include all men may be the most appropriate method of assessing whether men who are at higher risk of developing serious HPV-related illness ought to have access to the HPV vaccine. Furthermore, expanding sentinel monitoring of HPV incidence to include men may help reduce the stigmatization of women. This is also valuable given that targeting the HPV vaccine towards girls has been criticized for characterizing the virus as women’s issue, thereby potentially

reinforcing negative gender and sexual stereotypes and asserting an individual imperative for women to stop the spread of the disease (Polzer and Knabe, 2009). Thus, while expanding effectiveness draws attention to vulnerable populations, the conduct of PMM must be attentive to the potential for stigma associated with targeted surveillance.

On the other hand, it is also important to be cognizant of structural barriers that may exclude vulnerable groups from monitoring systems that are otherwise designed to be collective. For example, in Canada, active pediatric vaccine safety monitoring is conducted by the hospital-based Immunization Monitoring Program ACTive (IMPACT), which monitors suspected adverse effects following immunization (AEFIs) in children admitted to hospital emergency rooms (Scheifele and Halperin, 2003). It is targeted in that it focuses on AEFIs that result in hospitalization in children and thus does not capture all AEFIs, but it is collective in that it purports to include all children. However, although IMPACT operates in 12 major pediatric centres accounting for 90% of tertiary care pediatric beds in Canada, these centres are located in large municipalities which may be inaccessible to certain vulnerable populations, such as in rural indigenous (e.g., in Canada, First Nations, Métis and Inuit) communities. Such considerations are relevant when assessing vaccine effectiveness.

Consultation with vulnerable populations prior to implementing monitoring is necessary to assess the effects of targeted surveillance prior to monitoring, and ongoing collaboration is required to manage how results are reported. It is necessary to consider whether conducting and reporting targeted monitoring results may reinforce existing stereotypes and prejudices around particular groups, and it is important that monitoring for an intervention such as the HPV vaccine not obscure the underlying conditions behind the social gradient in cervical cancer. As such, it is necessary to demarcate between risk markers, such as belonging to a vulnerable population, from risk factors, such as poor nutrition or poor access to health care.

Conclusion

The existing notion of effectiveness used in vaccine PMM is inadequate as it fails to sufficiently address the public health dimensions at the foundation of PMM. We have articulated a notion of public health effectiveness, which draws attention to prevention at the population level and to social justice, and have articulated its implications for improving the quality and expanding the

scope of effectiveness monitoring. While this analysis focuses on vaccine PMM, it is also relevant to the PMM of drugs. However, further analysis in the context of pharmaceutical drugs is necessary, since vaccines and drugs have potentially relevant differences (e.g., with the former typically being used in public programmes). Ultimately, PMM should be guided by the concept of public health effectiveness to address the gap between clinical practice, as determined by pre-market efficacy trials, and public health in order to ensure the best overall health outcomes across a population.

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Notes

1. This article addresses the notion of post-market vaccine effectiveness and leaves for future discussion the notion of post-market vaccine safety.
2. The argument developed herein and the case study of the Canadian HPV vaccine are most relevant to high- and middle-income countries. While the notion of public health effectiveness in post-market monitoring remains pertinent in low-income countries, significant variation in available public health resources and priorities will differentially affect the justification and implementation of immunization campaigns and accompanying post-market monitoring—an issue that lies beyond the scope of this article.

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