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Ethical considerations in post-market-approval monitoring and regulation of vaccines

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ABSTRACT

The objective of this paper is to identify and articulate ethical considerations to help guide decision-making around the regulation and monitoring of vaccines post-licensure. While these considerations are not intended to be an exhaustive account of the ethical concerns, they can facilitate the explicit examination of ethical issues in this context. We identify the protection of public from harm as the primary consideration, and identify others that help in the discharging of this governmental obligation. Others include: transparency, a publicly acceptable risk-benefit profile, public trust, minimization of stigma, and special obligations to vulnerable populations. Regulators and researchers can use these ethical considerations to help enhance their reasoning and to improve the accountability of their decision-making. These considerations can be used to inform rational deliberations about how to balance the obligation to protect the public from harm with other relevant considerations such as the need to be transparent, while taking into account the contextual features of the situation. Further research and debate on the relevance and refinement of these ethical considerations is desirable.

1. Introduction

It has been over a decade since scholars began to articulate principles to guide the ethical analysis of issues in public health. Public health ethics is now a robust field of study including theoretical and practical considerations. However, there is a paucity of ethical analysis about the issues associated with pharmaceutical and vaccine regulation, particularly in the post-licensure context [1,2]. Risk-benefit analysis and policy-making are not a value-free enterprises, and involve important moral trade-offs. Often these ethical trade-offs are not explicitly articulated, and remain invisible. In this paper, we focus on the post-market monitoring of vaccines and identify ethical considerations arising from their monitoring and regulation. Many of the ethical considerations raised here will be relevant to the post-market monitoring of drugs as well, but not necessarily to the pre-authorization phase of regulation and research because of the distinguishing conditions of uncertainty and, at times, urgency [1] that obtain in the real-world setting of vaccine use.

In the last decade there has been a growing acknowledgement internationally that government bodies responsible for ensuring the safety and effectiveness of pharmaceuticals and vaccines face serious challenges when protecting the public from harm once these products are used by people in the uncontrolled, real-world context [4–7]. In most jurisdictions, regulation has been moving towards an approach that takes into account the full lifecycle of a drug or vaccine. This shift to lifecycle regulation has brought with it a more comprehensive surveillance mandate and sometimes progressive licensing legislation as well as the need for more evidence-generating capacity about how drugs and vaccines behave outside of clinical trials. In some jurisdictions, such as Canada, the shift to a lifecycle approach has been slow though, and there have been calls for further changes to how regulators safeguard the public's health and public healthcare resources [8].

Within this post-market regulatory context, public health agencies seek to increase vaccination uptake rates in the wake of a growing trend for particular groups to be hesitant about vaccination. Parents who refuse or hesitate to vaccinate their children have often chosen to focus more on the perceived risks of adverse events from vaccination than on the risks of vaccine-preventable diseases [9,10]. This trend has meant that vaccine

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safety is foremost in the minds of many, and requires that regulators do their utmost to ensure that vaccines are safe and effective and to engender the public's trust in the regulatory system. In addition, Verweij and Dawson have argued that vaccines should be held to higher standards of effectiveness and safety than other pharmaceutical products because most "vaccinations are offered to healthy individuals as a measure to prevent possible future harm" [11], especially in places where herd immunity is in effect and the chances of contracting diseases are low.

Given the recent shifts towards lifecycle regulation, and the increasing reach of regulatory authorities to compel pharmaceutical companies to conduct post-market research [12–15] this is an opportune moment to ask what kinds of ethical concerns regulators should be factoring into decision-making when it comes to ensuring post-market vaccine safety and effectiveness. The set of considerations articulated herein is not meant to explicitly address the more narrow sub-set of concerns that pertain to the ethical conduct of research on and surveillance of post-market vaccines, such as privacy, informed consent, etc. that have been considered elsewhere [16–18]. Rather, the focus is on ethical considerations for regulatory decision-making. First we shall articulate the considerations, and then discuss their role within post-market monitoring and regulatory context.

2. Identification of ethical considerations

The considerations articulated herein are the result of bioethical analysis of the post-market regulatory context of vaccine regulation in developed countries. In some cases, they are reformulations of accepted ethical principles discussed within the bioethics literature [11,19–21], and others are based upon bioethical analysis of recent controversies around vaccines and their safety and efficacy, such as the human papilloma virus vaccine (HPVV) [22–24]. While there has been important work done on the ethics of collective immunization programs [11,19], vaccine safety and effectiveness is either taken for granted as a starting point for the analyses, or identified as an ethical principle but not examined in depth. This paper provides a more detailed ethical analysis of what needs to be taken into consideration ethically when regulators are conducting post-market vaccine monitoring and regulatory activities. For it is often the case that when collective immunization programs are initiated, especially in emergency circumstances, vaccines have limited real world data to support the claim that they are safe and effective, and thus vaccination programs can function as de facto real-world vaccine trials [23]. It is therefore necessary to articulate some ethical considerations, especially for cases where groups that are underrepresented in pre-market clinical trials are the target of collective immunizations programs, such as was the case with the HPVV in Canada [22].

3. Ethical considerations

(1) Protection of the public from harm,
(a) highest quality of evidence possible,
(b) anticipatory decision-making,
(c) duty to warn,
(d) proportionate monitoring.
(2) Transparency,
(3) Publicly acceptable risk benefit profile,
(4) Minimization of stigma
(5) Special obligations to vulnerable populations,
(6) Public trust.

3.1. Protection of the public from harm

The need to ensure that vaccines do not harm people because of lack of safety or effectiveness is of paramount concern and is the primary norm upon which monitoring activities are based. This moral obligation is typically enshrined in the mandates of government health and regulatory agencies. Regulators must also ensure that harm is not caused by withdrawals of vaccines from the market or by other restrictions that can cause channeling to other unsafe drugs, vaccines or therapies [1], or by leaving special sub-populations without alternatives for prevention or treatment. The subsequent four ethical considerations should be considered as related to protecting the public from harms that can arise from both safety and effectiveness issues. They will not all always be relevant, and some may even be in tension with this consideration and thus they will need to be weighed carefully by regulators.

3.1.1. Highest quality of evidence possible

Anticipating where problems may arise with vaccines requires the gathering of the best quality of evidence possible for use in decision-making. In most cases, active surveillance and research on all vaccinated populations is preferable to relying on passive reporting, although under many regulatory systems this is seldom feasible. Hard end-points should be used in studies where possible to compensate for the problems associated with using soft end-points in pre-market clinical trials, even though this may require long-term surveillance in some cases [25]. The most ethically-relevant aspect of this consideration, however, is the need to minimize conflicts of interest that can introduce bias in research design and reporting. Research that informs regulation ought to have integrity: whenever possible, monitoring and research should be free from industry influence [26,27]. Evidence about the comparative effectiveness of a vaccine is also necessary to evaluate whether it is effective compared to existing vaccines or other preventive actions or therapies [11]. This is needed in order to minimize the technological imperative to use the newest technologies that can sometimes result in discarding other equally or more effective methods of preventing disease [28]. The sharing of safety and effectiveness data across jurisdictions is also required and should be facilitated by increasing the capacity to do so both within countries and between them.

3.1.2. Anticipatory decision making

Regulators should take a proactive role in shaping safety and effectiveness surveillance and research, and engage in preemptive decision-making in order to prevent harm. Precautionary actions such as withdrawal of a vaccine from the market, or the use of black box warnings must be proportionate to the degree of scientific certainty, the severity of possible harm, the size and nature of the affected population, and the cost of the actions [29,30]. Decisions should also be subject to review in light of new information [20]. Anticipatory decision making can be fostered by the collection of the highest quality of evidence possible. It should be noted, however, that the premature or complete withdrawal of a vaccine from the market can also cause harm under certain circumstances, and thus a precautionary approach may not always be ethically appropriate.

3.1.3. Duty to warn

Regulators have the duty to warn people when safety and/or effectiveness issues are present with a vaccine. This can include important reminders about waning immunity requiring a booster in order that people remain protected from disease. For vaccines where long-term effectiveness is unknown this is particularly important, because other measures such as screening may become even more important for people in order to prevent morbidity and