Vaccine 38 (2020) 6975–6978

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Commentary

Integrating public health programs and research after the malaria vaccine implementation program (MVIP): Recommendations for next steps

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ARTICLE INFO

Article history:
Received 6 April 2020
Received in revised form 21 April 2020
Accepted 28 August 2020
Available online 25 September 2020

Keywords:
Research ethics
Malaria vaccines
CIOMS guidelines
Cluster-randomized trials
WHO

ABSTRACT

Background: In February 2020, international controversy arose about the ethical acceptability of the WHO Malaria Vaccine Implementation Program (MVIP). Whereas some have argued that this program must be seen as research that is not in line with international ethical standards, notably regarding informed consent and local ethical review, some WHO representatives consider the MVIP as a public health implementation program that need not adhere to these standards.
Methods: We performed a case analysis in light of the 2016 CIOMS International Ethical Guidelines for Health-related Research involving Humans.
Findings: We argue that the MVIP has a substantial research component, and that it is prudent to therefore apply ethical norms for research involving humans, such as the CIOMS guidelines. Accordingly, we agree that the ethical requirements of informed consent and independent ethical review have not been met. In addition, we are concerned that the study might not meet CIOMS's social value requirement.
Recommendations: We urge WHO to release more details about the process that led to the MVIP program and make the MVIP protocol publicly available. The full protocol should be assessed by the relevant ethics committees, new and already enrolled parents should be informed about the uncertainties under investigation and given a real opportunity to consent or refuse (continued) participation, communities should

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https://doi.org/10.1016/j.vaccine.2020.08.077
0264-410X/Published by Elsevier Ltd.

be engaged, and aspects of MVIP that require alteration in light of ethical review should be altered, if possible. Furthermore, in order to improve good ethical practices, it is necessary to engage in international debate regarding the integration of research and public health programs. Procedurally, vaccine implementation programs that combine both prevention and research should involve the wider international ethics community and ensure participation of the target populations in setting the proper conditions for launching such programs.

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1. Background

In February 2020 international controversy arose about the ethical acceptability of the WHO-coordinated Malaria Vaccine Implementation Program (MVIP) [1,2]. The MVIP is a pilot implementation program of the RTS,S/AS01 malaria vaccine (sold as Mosquirix™ by GlaxoSmithKline). It is provided through the routine immunization services of the Ghana, Kenya and Malawi and aims "to vaccinate about 360 000 children per year" in over two years [3]. The MVIP is registered as a "cluster randomized pilot program" on clinicaltrials.gov [NCT03806465], with the goal of collecting "information on a larger scale on the safety of the malaria vaccine with focus on cerebral malaria and meningitis". Recently, several commentators have argued that the MVIP commits "a serious breach of international ethical standards" [1,2,4,5]. WHO representatives "strongly disagree" with this charge, arguing that "the systematic evaluation of a newly approved product is considered good practice – not medical or scientific experimentation" [6].

Among others, Charles Weijer has argued [1,2,5] that the MVIP violates both The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials [7] and the International Ethical Guidelines for Health-related Research Involving Humans of the Council for International Organizations of Medical Sciences (CIOMS) [8]. According to WHO representatives, the MVIP does not seek written informed consent from parents because the vaccine has received a "positive scientific opinion from the European Medicines Agency [EMA]" and is therefore "not ... experimental" [6]. Instead, "parents receive information about the vaccine from the ministry of health and can decide to present for, or to opt-out of, any or all vaccinations" that are provided through the national routine immunization services [6]. Given the opportunity to opt-out, parents give "implied consent" to vaccination [1]. But implied consent is no consent, says Weijer [1], and parents should provide explicit and fully informed consent [1]. Jonathan Kimmelman agrees. As he observes, "the fact that the activity has been registered in clinicaltrials.gov ... amounts to an open declaration that this is research," to which participants must consent "unless certain conditions are met" [1].

Weijer also argues that the MVIP is in breach of the CIOMS guidelines because local ethics review was not conducted [5]. The MVIP received approval from the WHO Ethics Review Committee (WHO ERC) and, according to WHO representatives, "the national ethics review boards" [6]. But Weijer argues that local ethics review was done "by the Ministries of Health of Ghana, Kenya, and Malawi and not the research ethics committees" [5]. Indeed, local research ethics committees (RECs) do not seem to have reviewed the MVIP itself, but only the observational studies tagged onto it [3].

We concur with these criticisms of the MVIP. However, a more detailed ethical analysis of the MVIP is warranted to avoid possible negative repercussions for the MVIP itself, and for malaria vaccine development and vaccine and clinical research more generally. We therefore analyze the MVIP in light of the CIOMS guidelines [8] and provide recommendations both for how the MVIP can ethically be continued and how vaccine implementation programs similar to the MVIP should be approached in the future. Since the protocol of the MVIP is currently not publicly available, our analysis primarily draws on the limited public information about the MVIP [2] and our broad expertise in international research ethics.

1.1. MVIP's substantial research component

WHO has been unclear about whether the MVIP is a public health implementation program or a research project. As mentioned, some WHO representatives assert that the RTS,S/AS01 vaccine is "not...experimental" and hence the MVIP is "not medical or scientific experimentation," but "the systematic evaluation of programmatic implementation of a newly approved product" [6]. However, a prior WHO position paper recognizes a "number of uncertainties" about the vaccine and "recommends further evaluation ... in a series of pilot implementations, addressing several gaps in knowledge, before considering wider country level introduction" [9].

It is important to highlight the uncertainties mentioned in the WHO position paper [9]. A phase III clinical trial involving over 6000 children showed that 4 doses of the RTS,S/AS01 vaccine prevented approximately 4 in 10 (39%) cases of malaria, and about 3 in 10 (29%) cases of severe malaria, in children aged 5–17 months. Additionally, the vaccine reduced overall hospital admissions and admissions due to malaria, as well as the need for blood transfusions to treat life-threatening malaria anaemia [10]. However, the trial also showed higher risks of meningitis among children who received the vaccine, and post-hoc analyses revealed an increased risk of cerebral malaria and doubled female mortality [11]. Moreover, because an additional appointment has to be added to the routine vaccination schedule, there were also concerns that the RTS,S/AS01 vaccine might be less effective in practice than in clinical trials [12]. Furthermore, EMA—while giving a "positive scientific opinion"—issued a detailed risk management plan and stated that cerebral malaria should be considered "an important potential risk," and that "mortality by gender" should be added "as missing information" [13]. Apparently EMA concluded the doubled female mortality was likely a chance finding, though this should be "monitored during vaccine introduction" [6,11].

More fundamentally, whether or not an *intervention* is regarded as "experimental" [6] is irrelevant to the question of whether a particular *activity* constitutes research. If the activity is designed to "...develop or contribute to generalizable knowledge" [14] and to reduce uncertainty about the given intervention, it counts as research. In the case of the MVIP, the use of cluster randomization to assess the endpoint of safety and registration on clinicaltrials.gov clearly establishes that the MVIP was designed, at least in part, to generate new knowledge. The MVIP program therefore must *also* be seen as research.

WHO representatives have argued that the MVIP was implemented in a cluster-randomized fashion as a "fair way to allocate limited vaccine doses" [6]. Indeed, certain cluster-randomized designs have sometimes been used in this way [15]. But as Weijer observes, fair distribution remains an unusual reason for using ran-

domization and GlaxoSmithKline had donated sufficient vaccine to the MVIP [5]. This suggests that the MVIP was planned with a deliberate and substantial research component, and hence that relevant ethical guidelines for research, such as the CIOMS guidelines [8], appropriately apply to the program. Of note, the CIOMS guidelines were produced in close collaboration with WHO and WHO states that its ERC is "guided in its work by the CIOMS guidelines" [16].

1.2. Ethical concerns about MVIP in light of the CIOMS International Ethical Guidelines

1.2.1. Informed consent and the minimal risk criterion for waiving consent

The default presumption in research ethics is that informed consent from study participants must be sought unless a REC grants a waiver or alteration of consent [8]. One condition for granting such a waiver or alteration is that the study must not pose more than minimal risk to participants [8, Guideline 10]. However, the concerns about the safety and real-world effectiveness of the RTS,S/AS01 vaccine suggest that the vaccine's benefits might not outweigh the risks and, given the possibility of a doubled mortality risk, the foreseeable risks of study participation were greater than minimal. This also likely explains why the MVIP included a Data and Safety Monitoring Board (DSMB), which would be an unusual measure for a minimal risk study, or indeed for an implementation program. Thus, a waiver of consent is not compatible with the CIOMS guidelines, which require minimal risk as a condition.

Moreover, the CIOMS guidelines specifically explain with regard to cluster-randomized trials that "if the interventions are directly carried out on patients, they would normally also be considered research subjects and their consent to receive the intervention would be required." [8, Guideline 21]. To illustrate this requirement, the guidelines describe a vaccination campaign applied at the school level. In that campaign, "parents will not be able to consent to their children's school being randomized to a vaccination programme or to being allocated to the cluster, but they could consent or refuse to consent to their child's vaccination at school" [8]. When applied to the MVIP, this implies that parents should have been asked for their explicit informed consent before their children were vaccinated with the RTS,S/AS01 vaccine [5].

1.2.2. Independent ethical review

Another default presumption in research ethics is that research protocols must be independently reviewed and approved before participants can enroll [8, Guideline 23]. In addition, "in externally sponsored research, ethical review must take place in both the host and the sponsoring institution". The MVIP is divided in implementation and observational parts [3], it appears that the WHO ERC and local RECs did not review the full MVIP protocol that describes the cluster randomization and administration of the vaccine clusters, but only the protocol part that details data collection process. Thus, the ethical review process of the MVIP presents a potential second violation of the CIOMS guidelines.

1.2.3. Social value of the research

Concerns about the severity of the safety concerns surrounding the malaria vaccine also raise questions about the decision to use a pragmatic research design embedded in the implementation of the RTS,S/AS01 vaccine. As highlighted by the CIOMS guidelines, "the ethical justification for undertaking health-related research involving humans is its scientific and social value" [8, Guideline 1]**.** This is "generally grounded in three factors: the quality of the information to be produced, its relevance to significant health problems, and its contribution to the creation or evaluation of interventions, policies, or practices that promote individual or public health [8]."

As discussed, there are still significant uncertainties about the RTS,S/AS01 vaccine, and high-quality research to reduce these uncertainties certainly has social value given that malaria poses a major burden of disease globally. However, others have pointed out that the MVIP is designed in ways that make it, for example, possible to "overlook if the RTS,S vaccine truly increases female mortality" [17]. Similarly, WHO intends to decide on extending the vaccine to other African countries after 24 months using the prevention of "severe malaria" in the MVIP as a surrogate marker of overall mortality. Yet if a decision is taken without having the actual all causes mortality results, one of the key objectives of the MVIP—namely, assessing all-cause mortality—will be "de facto" dismissed [10,12].

More generally, the CIOMS guidelines state that conventional randomized controlled trials are often considered the gold standard for testing the relative merits of investigational interventions [8, Guideline 5]. While other study designs can also yield valid results, "researchers and sponsors must carefully consider whether the research question can be answered with an alternative design, and whether the risk–benefit profile of alternative designs is more favorable when compared to a conventional randomized controlled trial [8]." Cluster-randomized designs generally raise concerns about potential bias [7] and inefficiency and, in the context of vaccine trials, the difficulty of inferring the protective effects of vaccines on the individual level from measures at the cluster or population level [3,18]. Although the social value of the MVIP is difficult to judge without having access to the full protocol, these considerations raise the possibility that some of the underlying design choices might not meet the social value requirement of the CIOMS guidelines.

1.3. Recommendations for next steps

First, with regard to the MVIP, it is essential to continue the program and collect data on the safety and efficacy of the RTS,S/AS01 vaccine in the hundreds of thousands of children vaccinated to date, as it is not clear whether and when alternative studies will be conducted. However, we urge WHO to release more details about the process that led to the MVIP and make the protocol publicly available. Given its substantial research component, we recommend treating the MVIP as research. This means that the full protocol should be assessed by the relevant RECs. In addition, a process of informed consent should be introduced for parents to guarantee that they are fully informed and given a real opportunity to decide if they want their children to receive the vaccine. Parents of children who have already been vaccinated should be contacted and similarly informed in advance of their next visit, including about the risks and potential benefits of completing the vaccination regimen versus stopping it prematurely. Furthermore, communities should be engaged and aspects of the MVIP that are found to require alteration in light of the ethical reviews should be altered, if possible.

Second, when research and implementation are combined because important uncertainties about the safety and efficacy of products remain, it seems prudent to apply ethical norms for research involving humans, such as the CIOMS guidelines [8], rather than the generally less demanding norms that currently govern routine care programs. This is especially important in the context of implementation programs that pilot vaccines, given well-known concerns about vaccine hesitancy [19]. An illustrative past example is a pilot implementation program in India, which was ethically controversial and led to the derailment of national roll-out plans for the HPV vaccine [20]. Because of the outstanding moral uncertainty about integrating public health programs and research, it can be justifiable to deviate from recognized ethical

norms for research, provided this is supported by sound reasons and clearly communicated to relevant stakeholders.

Procedurally, pilot implementation programs that integrate public health interventions and research should involve local and the wider international human rights and ethics community in addition to RECs. Moreover, target populations should be engaged about setting the proper conditions for launching such programs [8, Guideline 7], drawing on relevant additional guidance [21,22]. Such engagement should be conducted in a transparent and inclusive manner before rolling out important, but complex and potentially controversial programs like the MVIP. If the current debate had taken place prior to launching the MVIP, it would have helped to develop reasonable approaches to respect the dignity and integrity of the participants and potentially enhance its social value. It could also have helped to safeguard public trust in vaccines, public health interventions and research.

2. Disclosures**a

The views expressed in this paper are those of the authors and do not necessarily reflect the opinion or policies of CIOMS, the National Institutes of Health or the U.S. Department of Health and Human Services or any other institute they might be affiliated with.

Funding: This work was supported in part by the Clinical Center Department of Bioethics, which is in the Intramural Program of the National Institutes of Health.

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RG, RM, DG, SH, DS and JD conceived of the idea for this manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript. RG took the lead in writing the manuscript. RM, AR and JD aided in preparing the drafts for circulation among all authors. The other authors contributed equally and are therefore listed alphabetically.

All authors have approved the final article should be true and included in the disclosure.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: RG is a member of the independent Bioethics Advisory Committee to Sanofi. The other authors declare no competing interests.

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