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WHO’s malaria vaccine study represents a “serious breach of international ethical standards”

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Petition demanding WHO respond to ethical problems with its malaria vaccine study

A new petition is calling on the World Health Organization to respond to ethical problems with its malaria vaccine study.

Petition link: https://www.change.org/p/oms-exigez-le-respect-des-lois-%C3%A9thiques-de...

Short URL: https://tinyurl.com/WHO-petition

The bilingual French-English petition was launched by Dr. Jérôme Munyangi on April 6 and has garnered over 8,000 signatures thus far.

Competing interests: I authored the article that the WHO has criticized. See https://www.bmj.com/about-bmj/editorial-staff/peter-doshi for a general statement of competing interests.

09 April 2020

Peter Doshi
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The BMJ
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Re: WHO’s malaria vaccine study represents a “serious breach of international ethical standards”

Dear Editor:
Excepting a response from WHO [1], the several contributing comments to Doshi's [2] criticism of the malaria vaccine (RTS,S/AS01) implementation assessment (MVIP) each [3-7] support Doshi's argument of a failure to meet ethical standards within the operational framework of that programme. Those contributors argue, principally, that the recipients of vaccine not being offered informed consent to participate in what they forcefully argue to be an experiment constituted a “serious breach” of ethics. This accusation is levelled not just at WHO, but a very large community of their research partners (representing many government, academic, and civil society organisations) that engaged with the MVIP. That included at least several highly regarded ethical oversight committees, in addition to the several regulatory agencies involved. According to Doshi and supporters [2-7], all of those players in the MVIP, collectively, seriously breached ethical standards in the conduct of that programme.

At the heart of this issue lies the process by which the vaccine was administered to participants of the MVIP and the subsequent collection of medical intelligence to be gathered and learned from it. Doshi and correspondents argue that the cluster-randomised distribution of the vaccine, taken together with deeply concerning safety signals from the earlier phase 3 clinical trial of the vaccine, represented a compelling need for informed consent by the vaccinated. Those responsible for the MVIP [1] point to a process whereby individuals were informed of the risks and benefits of vaccination and offered the opportunity to decline receiving it, calling that process “implied consent”. That terminology is arguably misleading – there is nothing implicit in parents presenting their children for vaccination; it is autonomous, dignified consent. Moreover, MVIP representatives [1] make the key point of the vaccine having been approved for practice by the regulatory agencies of the participating African nations. In other words, those authorities, by legal statute being responsible for the safety of their constituents, deemed the vaccine suitable for such offer to those constituents.

What Doshi and others take issue with is those parents not being taken through a formal process of informed consent via a protocol under responsible ethical oversight. That process offers a document describing vetted and thorough risks and benefits (along with key elements of voluntary consent) for witnessed signature affirming an informed willingness to participate. That appropriately lawyerly approach to the conduct of research involving human subjects protects us from intentional or unintentional abuse by exposure to unreasonable (extreme or unnecessary) risk of harm by medical experimentation. This is precisely the same responsibility borne by national regulatory agencies regarding the myriad devices and products applied to us in the practice of medicine. Where the responsibility of one ends and the other begins, depends as much on the intent to experiment as the product itself being experimental or registered for practice.

What constitutes relatively high risk experimentation and an obligation for direct ethical oversight is necessarily tied to that classification of a medical product. In experimenting with a product approved for practice, the high risk may not be considered to derive from indicated use of the product. By regulatory process, statute, and authority, that use does not carry intrinsically unacceptable risk. When one applies an approved product in a manner deviating from indicated use as a means of learning something about the product or the illness it relieves, we indeed incur the necessity of ethical oversight; especially if such deviation even slightly makes the medical product or state of illness a higher risk proposition. The MVIP did not do this, with or without an intent to experiment.

Doshi and correspondents point to an intent to experiment as the basis of required ethical oversight. Applied broadly and literally, as van der Graff does [7], phase 4 post-marketing surveillance undertaken by medical developers (often on the demand of responsible regulators) constitutes an experiment for which formal informed consent must be an ethical requirement. However, we routinely accept phase 4 studies of approved products without the informed consent of those on the receiving end of that practice. Those studies explicitly address uncertainty regarding the safety and efficacy of newly licensed products having relatively limited exposures in human populations. The MVIP did precisely that, but by implementing a cluster randomised distribution of vaccine. Doshi and correspondents [2-7] view that specifically as having crossed the line separating experiment from practice.

The “serious breach”, it seems, boils down to the inarguably deliberate intent to maximise the medical intelligence to be gained from MVIP rather than having placed vaccine recipients at unreasonable or unmeasured risk of harm. The experiment versus practice argument in this instance may be reasonably made, but no one should perceive what may be implicit in the “serious” verbiage used by Doshi [2], i.e., that vaccine recipients were placed at greater risk because the MVIP offered it to them in cluster-randomised fashion. The manner of distributing vaccine alone could not have done that. According to DuBois et al. [7] “serious ethical violations in medicine” include, “sexual abuse, criminal prescribing of opioids, and unnecessary surgeries, directly harm patients and undermine trust in the profession of medicine.” These exemplars attach physical meaning to what may be construed as “serious”. Even if flawed ethics occurred in the conduct of MVIP by perhaps overstepping the experiment vs. practice line, that should not be construed or misrepresented as a serious breach of ethical conduct. That terminology should be reserved for instances of real harm done lest we invite equity in harmless deviation from nuanced ethical standards with real harm in criminal deviation from the same.

The broad acceptance of phase 4 studies without informed consent hinges on the trust placed in the professionalism and expertise of the regulators approving products for practice as safe and effective, and the same in the practicing physician offering it to patients. Perhaps the most disturbing element of the criticisms of the MVIP is the conspicuous and nearly complete evacuation of trust in the regulatory authorities approving the vaccine and the healthcare professionals executing its initial implementation. The frank exaggeration of the gravity of perceived deviation from ethical standards in the MVIP, taken with the dismissal of trust in those responsible for it, unfairly and unreasonably impugns the professionalism of the WHO and its many partners in that enterprise.

If the current COVID-19 crisis teaches us nothing else, let it at least demonstrate the vital need of trust in the WHO – in all of its efficacy and imperfection – as a disinterested arbiter of what is good for humanity in health. That advice could perhaps be taken by WHO and its critics alike. Humanity requires an unconflicted and transparent WHO, without regard to whether conflict of interest is real or perceived. Either damages that institution in its intended, necessary, and enormously beneficial role for all of us. This ideal should not insulate the WHO from earned, measured, and reasoned criticism by the communities it genuinely strives to honourably serve.

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Competing interests: The author has a long history of collaboration and consultation with the WHO Global Malaria Programme that does not include engagement of any sort with specific regard to the Malaria Vaccine Implementation Programme discussed here.

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Integrating public health programs and research and the CIOMS guidelines

Integrating public health programs and research and the CIOMS guidelines

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Recently several commentators have argued that the WHO Malaria Vaccine Implementation Program (MVIP) involves “a serious breach of international ethical standards” [1,3,4]. WHO representatives have responded that they consider the MVIP a routine public health implementation program and “strongly disagree” with the claim that the MVIP “is at odds with international ethical standards” [5].

Charles Weijer has argued [1,3,4] that the MVIP violates both The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials [6] and the International Ethical Guidelines for Health-related Research Involving Humans of the Council for International Organizations of Medical Sciences (CIOMS) [7]. The CIOMS guidelines were produced in close collaboration with WHO and WHO states that its Research Ethics Review Committee (ERC) is “guided in its work by the CIOMS guidelines” [8]. In what follows, we respond from the perspective of the CIOMS guidelines [8,9].

Whether or not MVIP as an intervention is regarded as “good practice” and non-experimental [5] is irrelevant to the question of whether a particular activity within that program constitutes research. If the activity is “designed to … develop or contribute to generalizable knowledge” [10] and to reduce uncertainty about the given intervention, it counts as research. The use of cluster randomization to assess the endpoint of safety and registration of the program on clinicaltrials.gov clearly establishes that the MVIP was designed, at least in part, to generate valuable information rather than solely to advance the goals of public health [1]. The MVIP program therefore must also be seen as research.

The protocol is not publicly available, but based on the currently available information we agree with the concerns about the informed consent and ethical review process [1,4]. In addition, we emphasize that to justify a waiver of

informed consent, the intervention must be regarded as minimal risk (guideline 10). Yet the outstanding concerns about higher risks of meningitis, risks of cerebral malaria and doubled female mortality [11-14] suggest the risks of receiving the vaccine were greater than minimal at the start of the MVIP. Another concern is whether the MVIP meets the social value requirement (guideline 1). High-quality research to reduce lingering uncertainties certainly has social value since malaria poses a major burden of disease globally. However, compared to a conventional randomized controlled trial a cluster randomized trial involves more people and creates weaker evidence, which is not preferable in a situation of serious doubts about safety [15]. In addition, the MVIP is designed in ways that make it, for example, possible to “overlook if the RTS,S[/A01] vaccine truly increases female mortality” [16].

When research and public health interventions 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 [7], 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 [17]. An illustrative past example is a pilot vaccination implementation/post licensure demonstration project in India, which was ethically controversial and led to the derailment of national roll-out plans for the HPV vaccine [18].”

We recommend treating the MVIP as research. 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 be engaged, and aspects of MVIP that require alteration in light of ethical review should be altered, if possible.

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Competing interests: 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. RG is a member of the independent Bioethics Advisory Committee to Sanofi.

25 March 2020

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The WHO Malaria Vaccine Implementation Program: the lack of informed consent is not the only ethical challenge

Dear Editor

In WHO's response to Peter Doshi's feature article, the WHO authors emphasize that the RTS,S malaria vaccine has an acceptable safety profile, is not an "experimental vaccine" and is undergoing "phased introduction". These statements seem at odds not only with prior WHO statements, like "Other questions that should be addressed as part of pilot implementations include the extent to which RTS,S/AS01 vaccination impacts all-cause mortality (including gender-specific mortality)"(1), but also what EMA writes about the pilot implementation study: "The study will address the following safety concerns listed in the safety specification: febrile convulsions, meningitis, rebound effect, cerebral malaria, gender-specific mortality and vaccine effectiveness/impact. It will also evaluate the feasibility of implementing a fourth dose" (2).

If the task is to evaluate whether the 2-fold higher female mortality observed in the Phase III trials (3) represents a real phenomenon, then it should be carried out with due diligence. However, the pilot implementation study is designed in ways that make it possible to overlook if the RTS,S vaccine truly increases female mortality.

Despite numerous request WHO has not provided the protocol for the pilot implementation study, but based on what has been written in other documents, the pilot implementation study suffers from the following design weaknesses:

1) The study does not register individual participants. Hence, there is no follow-up of neither vaccine exposure nor outcome at an individual child level in the areas receiving or not receiving RTS,S vaccine;

2) Deaths are captured through village key informants. Such a system is unlikely to be perfect. Hence, mortality is likely to be underestimated;

3) The study does not have exact information about the number of children living in the areas receiving or not receiving RTS,S. Hence, nobody knows the exact denominator when calculating mortality risks;

4) The RTS,S vaccine coverage in the pilot study is now reported to be very low, down to 25% with the 3rd dose (4). If the study is comparing areas where <25% received the vaccine with areas where nobody received the vaccine, a real negative effect on female mortality would be diluted;

5) WHO has now changed the original plan to follow participants for 4-5 years for mortality and decided to make a preliminary assessment of the effect on mortality based on a surrogate outcome, severe malaria, after 24 months. There are two major problems with that decision: first, severe malaria was not associated with overall mortality in the phase III trials (5) and severe malaria can therefore not serve as a marker of overall mortality; second, as the negative effects or RTS,S in females increased with increasing follow-up time, an assessment 24 months after study start will limit the possibility of observing negative effects (5).

These five design decisions work in the same direction: they increase the likelihood of overlooking a true negative effect of RTS,S on female mortality.

The worrying prospect is that based on flawed data, the WHO may wrongly conclude after 24 months that there was no safety concern in relation to female mortality (measured as severe malaria), and then roll-out the vaccine in the unvaccinated regions of Ghana, Kenya and Malawi and the rest of Sub-Saharan Africa. Once rolled out, we may only discover potential harms after years of accumulation, since very few places have routine data collection to capture an increase in female mortality.

In the Phase III trials, RTS,S was associated with 2-fold higher female mortality between 5 months and 4-5 years of age (3). If this is a true finding and if it is overlooked in the pilot implementation study, and the vaccine is then rolled out over all of Sub-Saharan Africa, it may result in half a million excess female deaths/year if the vaccine coverage

reaches 70% (assumptions from UNICEF's State of the World's children 2019: females vaccinated/year=18 million; female mortality from 5 months-5 years=40/1000).

According to us, the pilot implementation study is not a "phased introduction" but a very important safety research project. We hope the WHO will share the study protocol and make it possible to suggest if and how the study can reliably assess sex-differences in mortality.

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Competing interests: Christine S. Benn was quoted in the article that WHO is criticizing.

10 March 2020
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The WHO Malaria Vaccine Trial: a bioethicist responds

Dear Editor,

In its response [1] to Peter Doshi's article on the malaria vaccine trial,[2] the WHO does not challenge the facts presented. They do, however, dispute the ethical conclusions drawn from these facts, asserting the malaria vaccine trial was "conducted in accordance with established and recognized national and international ethical standards."[1] In the following, I examine the WHO's claims about the ethical ramifications of the study.

The WHO consistently denies that the malaria vaccine trial as a whole is research, describing it instead as a "systematic evaluation of programmatic implementation" that is "good practice—not medical or scientific experimentation."[1] Data collection is described as "independent of the vaccine implementation by the EPI programme."[1] In fact, from the start the WHO designed this study as cluster randomized trial to address the effectiveness, safety and feasibility of the novel malaria vaccine. In their March 2017 presentation to the WHO's Malaria Policy Advisory Committee, David Schellenberg and Mary Hamel described the study as using a "cluster randomized design."[5] The use of a cluster randomized design indicates that it was always intended to be research. Further, since the malaria vaccine program and data collection are constituents of a randomized trial, they both constitute research and are subject to international ethical guidelines.

This puts the WHO's claims about the use of randomization in a new light. Citing a scarcity of vaccine supply, the WHO contends that the rollout of malaria vaccine to districts in Ghana, Kenya and Malawi was randomized as a "fair

way to allocate limited vaccine doses."[1] In his response, Peter Doshi finds the claim "at odds with every other WHO document I have reviewed."[3] He notes that the WHO's website reports "GSK is donating up to 10 million doses of RTS,S [malaria vaccine] for use in the pilot programme"[4]—more than enough for the 360,000 children enrolled in the malaria vaccine trial annually. If vaccine supplies are indeed scarce and randomization was not for research purposes, why didn't the WHO choose one of the more obvious paths of either vaccinating all children in one country, so that no child is denied access to a government program, or providing vaccine to districts across several countries with the highest rates of malaria in children? Indeed, it is plain that districts were randomized to receive the malaria vaccine program or not because the WHO and its host country partners were conducting research.

International ethical guidance specific to cluster randomized trials is found in the Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials[6] and the CIOMS/WHO International Ethical Guidelines for Health-related Research Involving Humans (especially guideline 21).[7] The WHO malaria vaccine trial violates ethical requirements in both international ethics guidance documents.

The Ottawa Statement says that "[r]esearchers must submit a CRT [cluster randomized trial] involving human research participants for approval by a REC [research ethics committee] before commencing."[6] "This includes CRTs conducted outside health care settings, such as…public health research."[6] The CIOMS/WHO guidelines add that in "externally sponsored research, ethical review must take place in both the host and the sponsoring institution."[7] In its response, the WHO makes clear that only "observational studies to evaluate the routine use of the vaccine" were submitted for research ethics committee review.[1] Randomized implementation of the malaria vaccine was approved by the Ministries of Health of Ghana, Kenya, and Malawi and not the research ethics committees.[1] Thus, host country research ethics committees were not given the opportunity to review questions of equipoise or consent for vaccination for the WHO malaria vaccine trial.

Why would the WHO not submit the full cluster randomized trial for research ethics committee review? It appears that the WHO is labouring under the misapprehension that government programs do not require research ethics committee review even when these are part of a cluster randomized trial. After all, governments have a democratic mandate to provide routine public health programs to citizens. But in randomizing districts to receive malaria vaccine or not, the government was not implementing the vaccine routinely; it was conducting research. As we explain elsewhere, the "government is collaborating with researchers to randomly allocate provinces [or] communities…to intervention or control…so the program may be evaluated."[8] "Even if the government is the author of the program, researchers are the authors of the study design. And it is the design that triggers equipoise [and consent] issues… that must be assessed by the research ethics committee."[8]

Further, both the Ottawa Statement and the CIOMS/WHO International Ethical Guidelines require consent for drug or vaccine interventions in cluster randomized trials.[6,7] Indeed, the CIOMS/WHO guidelines consider a hypothetical cluster trial of a school-based vaccination program and analyze the role of parental consent. They say, "parents will not be able to consent to their children's school being randomized to a vaccination program or to being allocated to that cluster, but they could consent or refuse to consent to their child's vaccination at school."[7] This same reasoning applies to the WHO malaria vaccine trial. Parents cannot meaningfully consent to health districts being randomized to the vaccine program, but they can—indeed they must—consent to their child receiving the malaria vaccine.

In their response, the WHO tells us that "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." But there is no requirement that parents attend a community information session. Crucially, no parent is informed that their child is to be a research participant in a cluster randomized trial. Thus, the response from the WHO only provides further confirmation that the malaria vaccine trial represents a serious breach of international ethical standards.

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Competing interests: I was quoted in the article that the WHO is criticizing. I receive consulting income from Eli Lilly & Company.

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Response from the author

I thank the WHO for its response [1] to my article [2].

In its letter, the WHO states that the decision to use randomization in the allocation of malaria vaccine "was taken in conjunction with national authorities as a fair way to allocate limited vaccine doses in the first part of a phased, sub-national introduction. This has the added benefit of strengthening the robustness of the programme evaluation." [1]

I have not seen any documentation that supports this statement. WHO's suggestion that the decision to use randomization was driven by a social justice aim of fairness, and not research aims—and therefore just happens to be an added perk that helps strengthen programme evaluation—is at odds with every other WHO document I have reviewed.

Regarding vaccine supply, the WHO's website says that "GSK is donating up to 10 million doses of RTS,S for use in the pilot programme." [3] This seems sufficient for a pilot that is vaccinating 360,000 children per year.

Regarding the use of randomization, a 2015 background paper states: “There is a need to evaluate initial introductions before wider scale-up is considered to address a number of issues that remain following the conclusion of the trial. The primary issues are: … The safety signals of most concern (i.e. imbalances in meningitis and cerebral malaria) in the trial may be chance findings, but further evaluation is necessary when the vaccine is given to larger numbers of children” [4]

The document goes on: “It is likely that several hundred thousand vaccinated children will be included in each setting and that phased introduction would need to be randomized to ensure comparability of vaccinated and unvaccinated groups.” [4]

A 2019 policy document similarly outlines the evaluation of “safety signals” as a key reason for the pilot, and states that “the division into vaccine implementation or comparison areas has been completed through randomization to generate the strongest possible evidence on the impact and safety of the vaccine.” [5] The document makes no mention of limited vaccine doses.

Peter Doshi

References

[1] Swaminathan S, O’Brien K, Alonso P. The WHO Malaria Vaccine Implementation Program: clarifying misconceptions. March 2, 2020. https://www.bmj.com/content/368/bmj.m734/rr-1

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[3] WHO. Q&A on the malaria vaccine implementation programme (MVIP). https://www.who.int/malaria/media/malaria-vaccine-implementation-qa/en/ (March 2020)

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[5] Framework for Policy Decision On RTS,S/AS01 Working Group and the WHO Secretariat. Proposed framework for policy decision on RTS,S/AS01 malaria vaccine. https://www.who.int/immunization/sage/meetings/2019/april/1_Session_7_Fr...(for_print).pdf (March 13, 2019)

Competing interests: I authored the article that the WHO has criticized. See https://www.bmj.com/about-bmj/editorial-staff/peter-doshi for a general statement of competing interests.

04 March 2020
Peter Doshi
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The BMJ
Baltimore, MD, USA

Re: WHO’s malaria vaccine study represents a “serious breach of international ethical standards”

Dear Editor,

To give one group of individuals an intervention and to refrain from giving it to another comparable group of people without telling them that it is for the purpose of determining which course of action has the better outcome is unacceptable, unethical and disrespectful of a person`s right to autonomy. It is unjust, disrespectful of a person`s dignity, It flouts human rights. For trialists and any individuals in public authority, financed by others, to turn a blind eye to this fundamental tenet of ethical research must be challenged.

There is a parallel here [1] with what is happening in the AgeX Breast Screening Trial [2] where many thousands of women are unaware that they are being used as mere counters in an experiment under the guise of testing a hypothesis with an intervention that has known harms..

There seems to be a curious reluctance to expose these malpractices, seemingly for legal reasons. Why is there reluctance to call these powerful organisations to account? Rather, there seem to be attempts to justify using unsuspecting citizens without their knowledge, full understanding or consent for all participants. The phrase “speaking truth to power” springs to mind. Unfortunately, what is legal may sometimes be neither ethically nor morally right.

[1] Peter Doshi. WHO’s malaria vaccine study represents a “serious breach of international ethical standards” BMJ 2020;368:m734

[1] Bewley S, Blennerhassett M, Payne M. Cost of extending the NHS breast screening age range in England. BMJ 2019;365:l1293

Competing interests: No competing interests

03 March 2020
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The WHO Malaria Vaccine Implementation Program: clarifying misconceptions

Dear Editor,

We strongly disagree with the assertion that the Malaria Vaccine Implementation Programme (MVIP) is at odds with international ethical standards. The systematic evaluation of programmatic implementation of a newly approved product is considered good practice - not medical or scientific experimentation.

The RTS,S/AS01 malaria vaccine has been authorized for use in the pilot areas by the National Regulatory Authorities of Ghana, Kenya and Malawi and has received a positive scientific opinion from the European Medicines Agency; it is not an experimental vaccine. These regulators concur in their assessment that the vaccine has an acceptable safety profile and that the benefits of the vaccine outweigh the risks. The vaccine has been shown to significantly reduce malaria, including life threatening severe malaria. Modeling suggests that, if introduced broadly, the vaccine could save tens of thousands of lives per year [1]. Given the 228 million malaria episodes suffered every year, and the 405,0000 premature deaths attributed to malaria every year, it is important to take all steps to tackle this disease.

The imbalance in female mortality in the Phase 3 trial was identified by a post-hoc analysis and was considered by the national regulators and the EMA. The EMA concluded that there is insufficient information to classify the finding

as a “potential risk” (a formal EMA classification) and that this was likely to be a chance finding, but one that should be monitored during vaccine introduction. Accordingly, mortality is being carefully monitored and action will be taken should the need arise.

The vaccine is now being provided to children through the routine immunization services of the Ghana, Kenya, and Malawi Ministries of Health as part of childhood vaccination programmes. The consent process used for administration of RTS,S is the same as that used for all vaccines provided through these programmes – an “opt-out” approach that is otherwise referred to as “implied consent”[2]. This means that 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. The EPI programmes in the three countries have used a variety of communication approaches to inform the communities about the pilot introductions, the reasons for the pilots, and the risks and benefits of vaccination with RTS,S.

The decision to allocate the vaccine to randomly selected communities in each country was taken in conjunction with national authorities as a fair way to allocate limited vaccine doses in the first part of a phased, sub-national introduction. This has the added benefit of strengthening the robustness of the programme evaluation.

Independent of the vaccine implementation by the EPI programme, groups of researchers in each country are conducting observational studies to evaluate the routine use of the vaccine – specifically to evaluate the impact and feasibility of delivering the four vaccine doses and to consolidate its safety profile. Written informed consent is sought from all participants in the observational studies for activities that are beyond routine care. The programme evaluation protocols were submitted for full ethical review and received approval both at WHO and from the national ethics review boards in the participating countries. The evaluation has been registered on clinicaltrials.gov as an observational study, defined as a study “in human beings in which biomedical and/or health outcomes are assessed in pre-defined groups of individuals. Participants in the study may receive diagnostic, therapeutic, or other interventions, but the investigator does not assign specific interventions to the study participants. This includes when participants receive interventions as part of routine medical care, and a researcher studies the effect of the intervention”[3]. Such registration is considered good practice and nearly 69,000 (21%) of the studies registered on clinicaltrials.gov are observational studies.

In summary, the RTS,S vaccine is undergoing phased introduction by the MoH of Malawi, Ghana, and Kenya. The evaluation of the pilot implementation is being conducted in accordance with established and recognized national and international ethical standards and with respect to human subjects regulations. The evaluation protocols have been reviewed and approved by four ethical review boards. The information gained from the evaluations will help to inform the broader use of the RTS,S vaccine, within the countries piloting the vaccine and across Africa, as part of the global effort to reduce suffering and deaths from malaria.

[1] Penny M, Verity R, Bever C, et al. Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. Lancet 2016; 387: 367–75
[2] WHO, 2014. Considerations regarding consent in vaccinating children and adolescents between 6 and 17 years old. Available at https://www.who.int/immunization/programmes_systems/policies_strategies/...
[3] ClinicalTrials.gov. Protocol Registration Data Element Definitions for Interventional and Observational Studies. Available at https://prsinfo.clinicaltrials.gov/definitions.html#StudyType

Competing interests: WHO provides scientific and technical leadership to the MVIP.

02 March 2020
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Re: WHO's malaria vaccine study represents a "serious breach of international ethical standards"

Dear Editor

I was interested to read Peter Doshi's article [1]. I also note with concern the comments of Elhadj As Sy, Secretary General of the International Federation of Red Cross and Red Crescent Societies (IFRC), at the European Commission Global Vaccine Summit, last September which I have transcribed as best I could [2]:

"Simple example. So, if we have big headlines that we are going to be having an experimental vaccine in this community which is a thousand miles away - so here we understand what we mean but the community level there would be all sorts of multiple misinterpretation ("Here we are the guinea pigs, here we are being the experiments for the world, is it the vaccine which is not for us, it is to protect others") so we have to change that it is protecting public health, it is not protecting people people outside the community, but it is something which is first good for the community, there for its own sake and to protect its own needs..."

The question is whether they are to be told it is an experimental vaccine or not: we surely have to be clear both at the global level and the community level, so no one is misinformed.

[1] Peter Doshi, 'WHO's malaria vaccine study represents a "serious breach of international ethical standards" BMJ 2020; 368 doi: https://doi.org/10.1136/bmj.m734 (Published 26 February 2020)

[2] STREAMING SERVICE OF THE EUROPEAN COMMISSION: GLOBAL VACCINE SUMMIT, 12 September 2019, On-Demand 14.22.55-14.23.33, https://webcast.ec.europa.eu/global-vaccination-summit-12-09-19#

Competing interests: AgeofAutism.com, an on-line daily journal, concerns itself with the potential environmental sources for the proliferation of autism, neurological impairment, immune dysfunction and chronic disease. I receive no payment as UK Editor

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