Intended for healthcare professionals

Feature Informed Consent

WHO's malaria vaccine study represents a "serious breach of international ethical standards"

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WHO's rollout of malaria vaccine in Africa: can safety questions be answered after only 24 months?

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Experts are troubled by the apparent lack of informed consent in a large, cluster randomised study of the malaria vaccine. **Peter Doshi** reports

A large scale malaria vaccine study led by the World Health Organization has been criticised by a leading bioethicist for committing a "serious breach" of international ethical standards. The cluster randomised study in Africa is already under way in Malawi, Ghana, and Kenya, where 720 000 children will receive the RTS,S vaccine, known as Mosquirix, over the next two years.[1][2][3]

Mosquirix, the world's first licensed malaria vaccine, was positively reviewed by the European Medicines Agency, but its use is being limited to pilot implementation, in part to evaluate outstanding safety concerns that emerged from previous clinical trials.[3] These were a rate of meningitis in those receiving Mosquirix 10 times that of those who did not, increased cerebral malaria cases, and a doubling in the risk of death (from any cause) in girls.[2]

Charles Weijer, a bioethicist at Western University in Canada, told *The BMJ* that the failure to obtain informed consent from parents whose children are taking part in the study violates the Ottawa Statement, a consensus statement on the ethics of cluster randomised trials, of which Weijer is the lead author, and the Council for International Organizations of Medical Sciences' International Ethical Guidelines. "The failure to require informed consent is a serious breach of international ethical standards," he said.

Implied consent

WHO contends that the study is a "pilot introduction" and not a "research activity." It says that those children living in areas randomised to receive the new vaccine will do so as part of each country's routine vaccination schedule and that consent is "implied."

"An implied consent process is one in which parents are informed of imminent vaccination through social mobilisation and communication, sometimes including letters directly addressed to parents. Subsequently, the physical presence of the child or adolescent, with or without an accompanying parent at the vaccination session, is considered to imply consent," said a WHO spokesperson.

Christine Stabell Benn of the University of Southern Denmark, professor in global health and a vaccine expert who recently published concerns about WHO's study in *The BMJ*,[4] added her concerns: "I think parents should be made aware of this doubled female mortality. Imagine that this mortality was a true finding (and remember that it comes on top of five other non-live vaccines being associated with increased female mortality[5][6][7][8][9]). If true, then how will this be perceived by the participants—that their children were unknowingly involved in a huge experiment by the authorities? This could be a disaster for public trust in vaccines and health authorities."

In the study, areas are being randomly assigned to either receive malaria vaccine or not. After two years, WHO intends to analyse the data between the two groups to make a decision about whether to recommend wider rollout of the vaccine to other countries.[4]

Recipients of the malaria vaccine are not being informed that they are in a study. And the extent to which parents are being given information about the known safety concerns before vaccination is unclear. "Information on vaccination is provided to the community and to parents through health talks and community outreach—among other methods, and parents who present for vaccination do so with the option to vaccinate their children or not," WHO says.

Weijer says that so called implied consent is "no substitute for informed consent. Indeed, implied consent is no consent at all. We have no assurance that parents in fact received information about the study let alone that they understood it."

Safety signals

What information parents are provided with in practice is hard to judge. WHO sent *The BMJ* some training information that it says it has shared with country partners about Mosquirix's potential risks. The material lists the increased rates of meningitis and cerebral malaria observed in trials and states that they will be monitored. But the potential for increased risk of death among girls is not mentioned.

In a post hoc analysis of the GlaxoSmithKline phase III trial, WHO reported that the all cause mortality rate was "about twofold higher in females" given malaria vaccine versus those in the control arm.[10] A more detailed analysis of the data showed that at study end, 67 of 2967 female children (2.3%) in the malaria vaccine group and 17 of 1503 female children (1.1%) in the control group had died (relative risk 2.00 (95% confidence interval 1.18 to 3.39); risk difference 1.1%, (0.4% to 1.9%); P=0.009).[4][11]

When asked why the female mortality signal was not included, WHO cited "insufficient evidence to classify gender specific mortality as a known or potential risk."

Anders Björkman, a malaria expert at the Karolinska Institute who coauthored the recent analysis published by *The BMJ*,[4] rejected WHO's characterisation of gender specific mortality as not even rising to the level of a "potential risk." "Whether the evidence to call it a known risk is sufficient or not," he said, "it remains a potential risk, so that is a wrong statement according to me."

Questionable ethics

It is unclear whether any ethical bodies specifically reviewed and signed off on the "implied consent" process already under way. *The BMJ* asked WHO whether the agency's Research Ethics Review Committee, which approved the study protocol in February 2018, waived the requirement for individual informed consent.

WHO did not answer the question directly, instead referring to the process as one used by the ministries of health in Ghana, Kenya, and Malawi. “The vaccine deployment is led by the countries and it is done in the context of routine vaccinations, where there is no requirement for written individual consent.” It said that “care givers are free to decline if they do not wish their child to receive the vaccine.”

McGill bioethicist Jonathan Kimmelman commented, “If an activity is classified as research, then all sorts of rules and oversight mechanisms are activated. For example, the activity must receive prospective ethical review. Unless certain conditions are met, human subjects must provide informed consent.” He added, “The fact that the activity has been registered in clinicaltrials.gov [NCT03806465] amounts to an open declaration that this is research.”

Weijer doubted a research ethics committee would have ever given permission for waiving the need for informed consent. “It is difficult to see how a research ethics committee could have approved a waiver of consent for the WHO malaria vaccine pilot cluster randomized trial,” pointing out that neither the Ottawa Statement[12] nor the CIOMS international ethical guidelines (that WHO says it follows[13]) support the use of waivers of consent in cluster trials of drugs or vaccines.

He also noted that the human rights provisions of the Malawi constitution include a specific provision prohibiting the use of a waiver under any circumstances: “No person shall be subjected to medical or scientific experimentation without his or her consent.”

Footnotes

- Competing interests: See https://www.bmj.com/about-bmj/editorial-staff/peter-doshi
- Provenance and peer review: Commissioned; not externally peer reviewed.

References

1. Mahase E. Malawi launches first malaria vaccination programme for children. *BMJ*2019;**365**:l1901. doi:10.1136/bmj.l1901 pmid:31023647 FREE Full Text Google Scholar
2. World Health Organization. Proposed framework for policy decision on RTS,S/AS01 malaria vaccine. 2019 Apr 10. https://www.who.int/malaria/mpac/proposed-framework-for-policy-decision-on-rtss-as01-malaria-vaccine.pdf
3. Framework for Policy Decision on RTS,S/AS01 Working Group, WHO Secretariat. Malaria vaccine implementation programme (MVIP): proposed framework for policy decision on RTS,S/AS01 malaria vaccine. 2019 Mar. https://www.who.int/immunization/sage/meetings/2019/april/1_Session_7_Framework_for_Policy_Decision_on_RTSS-AS01_-_MALARIA_VACCINE_(for_print).pdf
4. Aaby P, Fisker AB, Björkman A, Benn CS. WHO’s rollout of malaria vaccine in Africa: can safety questions be answered after only 24 months?*BMJ*2020;**368**:l6920. doi:10.1136/bmj.l6920 pmid:31980436 FREE Full Text Google Scholar
5. Garly M-L, Jensen H, Martins CL, et al. Hepatitis B vaccination associated with higher female than male mortality in Guinea-bissau: an observational study. *Pediatr Infect Dis J*2004;**23**:1086-92.pmid:15626943 PubMed Web of Science Google Scholar
6. Aaby P, Garly M-L, Nielsen J, et al. Increased female-male mortality ratio associated with inactivated polio and diphtheria-tetanus-pertussis vaccines: Observations from vaccination trials in Guinea-Bissau. *Pediatr Infect Dis J*2007;**26**:247-52. doi:10.1097/01.inf.0000256735.05098.01 pmid:17484223 CrossRef PubMed Web of Science Google Scholar
7. Aaby P, Ravn H, Fisker AB, Rodrigues A, Benn CS. Is diphtheria-tetanus-pertussis (DTP) associated with increased female mortality? A meta-analysis testing the hypotheses of sex-differential non-specific effects of DTP vaccine. *Trans R Soc Trop Med Hyg*2016;**110**:570-81. doi:10.1093/trstmh/trw073 pmid:27856947 CrossRef PubMed Google Scholar
8. Fisker AB, Biering-Sørensen S, Lund N, et al. Contrasting female-male mortality ratios after routine vaccinations with pentavalent vaccine versus measles and yellow fever vaccine. A cohort study from urban Guinea-Bissau. *Vaccine*2016;**34**:4551-7. doi:10.1016/j.vaccine.2016.07.034 pmid:27475473 CrossRef PubMed Google Scholar
9. Andersen A, Fisker AB, Rodrigues A, et al. National immunization campaigns with oral polio vaccine reduce all-cause mortality: a natural experiment within seven randomized trials. *Front Public Health*2018;**6**:13. doi:10.3389/fpubh.2018.00013 pmid:29456992 CrossRef PubMed Google Scholar
10. Malaria vaccine: WHO position paper-January 2016. *Wkly Epidemiol Rec*2016;**91**:33-51.pmid:26829826 PubMed Google Scholar
11. Klein SL, Shann F, Moss WJ, Benn CS, Aaby P. RTS,S malaria vaccine and increased mortality in girls. *mBio*2016;**7**:e00514-6. doi:10.1128/mBio.00514-16 pmid:27118593 CrossRef PubMed Google Scholar
12. Weijer C, Grimshaw JM, Eccles MP, et al., Ottawa Ethics of Cluster Randomized Trials Consensus Group. The Ottawa statement on the ethical design and conduct of cluster randomized trials. *PLoS Med*2012;**9**:e1001346. doi:10.1371/journal.pmed.1001346 pmid:23185138 CrossRef PubMed Google Scholar
13. World Health Organization. Research ethics review committee. 2020 https://www.who.int/ethics/review-committee/en/

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