



The RTS,S/AS01 candidate vaccine offers poor protection against severe malaria.

GLOBAL HEALTH

Malaria vaccine results face scrutiny

Experts question early release of incomplete trial data.

BY DECLAN BUTLER

“Malaria vaccine could save millions of children’s lives”; “World’s first malaria vaccine works in major trial”; “Malaria vaccine almost here”. To judge from last week’s headlines, scientists had made a big breakthrough in the long campaign to create a malaria vaccine, proving its effectiveness with interim results from a huge phase III clinical trial in Africa¹.

Yet several leading vaccine researchers, who are critical of the unusual decision to publish partial trial data, argue that the results raise questions about whether the RTS,S/AS01 candidate vaccine can actually win approval.

RTS,S has been in development for some 25 years, initially by the US military, and since 2001 by a public–private venture between the PATH Malaria Vaccine Initiative (MVI) and the drug-maker GlaxoSmithKline (GSK), supported by US\$200 million in funding from the Bill & Melinda Gates Foundation. Bill Gates himself announced the interim results at the Gates Malaria Forum in Seattle, Washington.

Gates’ speech and the MVI’s public-relations material were suitably circumspect about the results, but they were “immediately translated into headlines about [reductions] in death and mortality”, says Andrew Farlow, an economist at the University of Oxford, UK, who has previously assessed the RTS,S programme². “But the data are not telling you that at all.”

Some researchers question whether the results should have been published before all

the data were available; full results are expected in 2014. Interim trial data are usually reported only to regulatory authorities, and clinical trials published only once all the data are in, noted Nicholas White, a malaria expert at Mahidol University in Bangkok, in an editorial³ accompanying the interim results. “There does not seem to be a clear scientific reason why this trial has been reported with less than half the efficacy results available,” he wrote.

The publication presents vaccine-efficacy data for infants aged 5–17 months, but not for those aged 6–12 weeks, who are the stated target of the trial: it is this group that would receive the malaria vaccine alongside routine immunizations. The aim of the trial is to provide the World Health Organization (WHO) with the information it needs to consider licensing the vaccine, and recommend it for use in that age group. “What is the point of publishing the interim data on the 5–17-month-olds?” asks Stephen Hoffman, a veteran malaria researcher and chief executive of a rival vaccine effort, Sanaria, based in Rockville, Maryland.

The MVI’s director, Christian Loucq, argues that the results were “robust enough to be published. We decided this before we knew the results; we felt it was our scientific and ethical duty to make the results public when they become available.”

One of the biggest claims made in the paper is that RTS,S reduced the total number of episodes of clinical malaria in the older group by 55.1%, ▶

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► compared to controls. This measure of efficacy is recommended for assessing a partially effective vaccine⁴. But the public expects vaccine efficacy to describe protection over a period of time, argues Judith Epstein, a captain and paediatrician at the US Military Malaria Vaccine Program in Silver Spring, Maryland. Recalculating the trial data shows that RTS,S protected just 35–36% after 12 months, she says, adding that the paper should have presented both numbers. The study also showed no detectable impact on mortality, and it is too early to tell whether RTS,S actually protects against malaria, or merely delays infection.

The paper did report that RTS,S reduced severe malaria by 47% in the older group. But combining that result with available data from the younger age group cut that number to 34.8% — meaning that for the youngest children, the benefit must be even smaller. “The real question mark is the 34.8% efficacy in severe disease,” says Blaise Genton of the Swiss Tropical and Public Health Institute in Basel, and a member of the WHO technical advisory group for RTS,S. The results suggest that the vaccine might fall short of expectations, laid out in 2006 by a WHO-led consortium⁵, that it should have a “protective efficacy of more than 50% against severe disease and death and lasts longer than one year”. “If it doesn’t reduce deaths, and has only a modest effect on severe malaria, these are going to be big questions for decision-makers at WHO, GSK and the Gates Foundation,” says Hoffman.

Another worrying finding is that the frequency of serious adverse events, such as convulsions and meningitis, was significantly higher in the vaccinated group, although the data are too preliminary to draw firm conclusions. “The severe disease findings are a concern,” says Genton.

But Hoffman, like many researchers contacted by *Nature*, says that RTS,S still marks a significant achievement. It is the first vaccine against a parasite, *Plasmodium falciparum*, to consistently show a significant protective effect in large-scale trials. The phase III trial of RTS,S resulted in groundbreaking cooperation with African scientists, who led the 11 trials in 7 countries, says Hoffman. “I think that those teams deserve an incredible amount of recognition and congratulation.” ■

1. The RTS,S Clinical Trials Partnership *New Engl. J. Med.* <http://dx.doi.org/10.1056/NEJMoa1102287> (2011).

2. Farlow, A. In *The Science, Economics, and Politics of Malaria Vaccine Policy* (2006). Chapter available at <http://go.nature.com/8oxle3>

3. White, N. J. *New Engl. J. Med.* <http://dx.doi.org/10.1056/NEJMe1111777> (2011).

4. Moorthy, V. S., Reed, Z. & Smith, P. G. *Vaccine* **27**, 624–628 (2009).

5. World Health Organization et al. *Malaria Vaccine Technology Roadmap* (2006). Available at <http://go.nature.com/i1jdf7>

GENETICS

Fetal gene screening comes to market

Non-invasive procedure could make prenatal testing easier, but it comes with ethical problems.

BY ERIKA CHECK HAYDEN

Until last week, scrutinizing a fetus’s DNA for indications of genetic abnormalities meant tapping into the mother’s womb with a needle. Now there’s a test that can do it using a small sample of the mother’s blood. MaterniT21, a Down’s syndrome test that Sequenom of San Diego, California, launched in major centres across the United States on 17 October, is the first of several such tests expected on the market in the next year. It signals the arrival of a long-anticipated era of non-invasive prenatal genetic screening, with its attendant benefits and ethical complications (see *Nature* **469**, 289–291; 2011).

With the technology in place to sequence the fetal DNA carried in a pregnant woman’s bloodstream, geneticists predict the list of conditions that can be detected by non-invasive means will grow rapidly. Another company, Gene Security Network of Redwood City, California, says its forthcoming test will also check for other genetic abnormalities, and Sequenom is studying the feasibility of expanding its test.

“There’s every reason to think that in the future you’ll be able to extract an enormous amount of information from that sequencing data,” says Peter Benn, director of the Diagnostic Human Genetics Laboratories at the University of Connecticut Health Center in Farmington.

Sequenom’s test sequences 36-base-pair fragments of DNA to identify sections from chromosome 21. Normally, the chromosome contributes 1.35% of the total maternal and fetal DNA in the mother’s blood. An overabundance of this material indicates the genetic abnormality that marks Down’s syndrome.

Sequenom is marketing its test as an add-on to current screening methods, which estimate the chance that a woman is carrying a fetus with Down’s syndrome from ultrasound results and protein markers in the blood. Such non-genetic screening can detect 90–95% of Down’s syndrome cases, but falsely indicates that up to 5% of women are carrying a baby affected by the condition. Sequenom’s test could be taken after a positive screening result to help a woman decide whether to undergo amniocentesis, a test that extracts amniotic fluid with a needle and carries a small risk of miscarriage. A study published this month, and paid for by

Sequenom, found that the company’s test has a false positive rate of 0.2% (G. E. Palomaki et al. *Genet. Med.* <http://dx.doi.org/10.1097/GIM.0b013e3182368a0e>; 2011).

It could spare some women from having amniocentesis after a false-positive screening result. But Benn says that the test will also pose difficulties. For instance, because it would take 8–10 days to get the results of Sequenom’s test, if a woman did still opt for amniocentesis, and the result confirms that the baby has Down’s syndrome, there would be little time left to decide whether to terminate the pregnancy. And some women who test positive on MaterniT21 will probably choose to terminate pregnancies immediately rather than have amniocentesis.

“Inserting this new test in the way that Sequenom is proposing is very difficult, from the patient perspective, and difficult for physicians and counsellors to manage,” Benn says.

Ethicists also caution that using such easy screening methods ever earlier in pregnancy might worsen the gender imbalance seen in countries such as China and India. And if it becomes routine to check for many different kinds of genetic abnormalities, ethicists predict that more couples may face the quandary of whether to carry an ‘unhealthy’ fetus to term.

“The idea that couples have choices about whether to continue their pregnancies may become strained because parents may be seen as irresponsible for allowing ‘defective’ pregnancies to go to term,” says Mildred Cho, an ethicist at Stanford University in Palo Alto, California. Other ethicists worry that fears of eugenics will be raised if testing can be done for less-serious conditions.

Sequenom is solely focused on developing tests for conditions that are already part of prenatal screening programmes, says Mathias Ehrlich, the company’s senior director for research and development diagnostics. “We do not want to invent new applications. Our focus is on making existing clinical applications safer,” he says. “I don’t think that we are in a position to say that we should determine what hair colour the baby has.” ■

“In the future you’ll be able to extract an enormous amount of information from that sequencing data.”