# NEWS IN FOCUS



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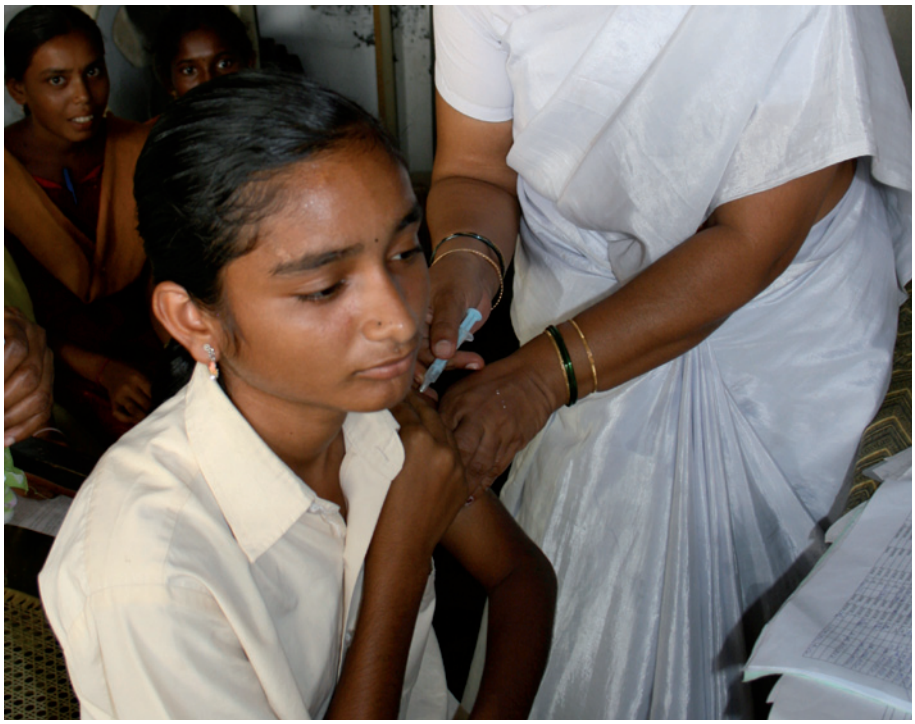

A schoolgirl receives human papillomavirus vaccine as part of a feasibility study in India.

DRUG DEVELOPMENT

# Vaccine trial's ethics criticized

*Collapsed trial fuels unfounded vaccine fears.*

BY PRIYA SHETTY

A clinical trial that came under fire in India threatens to have a dual legacy: inflaming unfounded fears about a lifesaving vaccine and raising new questions about the management of medical research in the country. After four teenage girls taking part in a test of human papillomavirus (HPV) vaccines died last year, the Indian government faced accusations that its citizens were being used as guinea pigs to test dangerous vaccines. A scientific investigation has exonerated the vaccines but uncovered a more familiar problem in India: ethical irregularities.

The study, funded by the Bill & Melinda Gates Foundation and run by the international health charity PATH and the Indian Council of Medical Research (ICMR), vaccinated more than 23,000 girls aged 10–14 against HPV, which can cause cervical cancer. The vaccines — Merck's Gardasil and GlaxoSmithKline's Cervarix — are already in widespread use in the developed world, and the study was designed to assess the feasibility of launching an HPV-immunization programme in the Indian health system. The researchers hoped to gauge public acceptance of the vaccines and assess the costs of administering it in different parts of the country.

A committee of three scientists from the All India Institute of Medical Sciences (AIIMS) in New Delhi, commissioned by the government to look into the trial, confirmed that the deaths were not linked to the vaccines — two of the girls died of poisoning, one of drowning and the fourth of a fever. But its report, leaked to India's media last month, said that the study involved several serious ethical violations. According to media reports, participants were recruited from vulnerable tribal populations, consent was improperly obtained — headmasters of the girls' schools signed the forms — and adverse events were poorly recorded.

The scientists also criticized Indian regulators for classifying the HPV study as an observational rather than a clinical trial, which meant that it was subject to different regulations, including looser reporting of side effects. The expert committee deemed it to be a clinical trial because it was a "study of a pharmaceutical product carried out on human participants" and "4 of 5 primary outcome measures proposed related to evaluation of the safety of the vaccine".

Vivien Tsu, director of PATH's HPV vaccines project, says that the procedures criticized in the report had all been approved by state ethics boards in India and an independent review board in the United States. "The problems the report raises, over the poor reporting of adverse events, for instance, were the sorts of issues that the study was intended to tease out," she says. Vishwa Katoch, director-general of the ICMR, says that his organization "had advised on ethical issues when the study was being planned. All necessary ethical approvals were there; the problem was how different individuals or teams implemented it."

Still, the verdict could pose a setback to the country's ambitions to become a hub for international clinical trials, luring drug developers with its large patient population and low costs. Rani Kumar, dean of the AIIMS, who assisted the investigating committee, declined to speak to *Nature*. But India's weak ethical infrastructure has been heavily criticized in the past for having few well-trained ethicists, and poorly run ethics boards. A clinical-trials registry was introduced in 2007 in a bid to better regulate clinical research, but "India still needs clear national guidelines on the ethical ▶

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conduct of clinical trials", says Ramanan Laxminarayan, vice-president of policy and research at the Public Health Foundation of India in New Delhi. Shortly after the HPV report hit the headlines, the Drugs Controller General of India produced, for the first time, draft guidelines on the reporting of adverse events in clinical trials.

Heidi Larson, an anthropologist at the London School of Hygiene & Tropical Medicine who studies the social acceptance of vaccines, says that the collapse of the HPV trial highlights one of the key problems in research collaborations between developed and developing countries. Ultimately, she says, international researchers are obliged to work within the ethics capacity of the host country, regardless of whether or not it is robust. Trying to align different expectations over research ethics can be especially tricky, Larson adds. "How do you negotiate local versus national versus international tensions?"

Meanwhile, India's vaccination plans could suffer collateral damage from the controversy. India decided in 2008 to roll out a new pentavalent vaccine against diphtheria, pertussis, tetanus, *Haemophilus influenzae* type b (Hib) and hepatitis B. Public objections over fears of dangerous side effects reported in Sri Lanka and the vaccine's high cost delayed the programme. Vaccination is finally due to start next month, but only in Tamil Nadu and Kerala, southern states chosen because their routine immunization coverage is already high, says Ajay Khera, deputy commissioner of India's Universal Immunisation Programme.

Vaccination fears that have made headlines in the West are now taking hold in countries such as India, says Larson (H. J. Larson *et al. Lancet* doi:10.1016/S0140-6736(11)60678-8; 2011). Because most of the vaccines now in development are aimed at diseases common in the developing world, such as malaria, tuberculosis, leishmaniasis and helminth infections, anti-vaccination movements in such countries could have a major impact on public health, adds Richard Moxon, a paediatrician at the John Radcliffe Hospital in Oxford, UK.

Jacob Puliyel, head of paediatrics at St Stephen's Hospital in Delhi, has been a vocal opponent of both the HPV vaccines and the pentavalent vaccine. He does not endorse the vaccine fears that gripped the public after the four girls' deaths, but he told *Nature* that too little is known about the prevalence of Hib and HPV-related cervical cancer in India to justify the new vaccines. At a time when India is already struggling to achieve universal coverage with existing vaccines — coverage for basic childhood immunizations is just 63%, according to Khera — the country simply cannot afford them, Puliyel says. ■

JOURNALS

# Open access comes of age

*Publishing model enters phase of slower but steady growth.*

BY JOHN WHITFIELD

A study of open-access publishing — published last week in the open-access journal *PLoS ONE* — has found that the number of papers in freely accessible journals is growing at a steady 20% per year (M. Laakso *et al. PLoS ONE* **6,** e20961; 2011). To many, the growth confirms the health of the free-access, author-pays model. But to a few it is a discouraging sign that open access is not about to take over the world of scholarly publishing.

The analysis, by information scientist Mikael Laakso of the Hanken School of Economics in Helsinki and his colleagues, also found that the number of fully open-access journals is growing at around 15% every year as new journals are founded and subscription journals switch to the open-access model (see 'Opening up'). By contrast, subscription journals are growing at about 3.5%. "Most indicators suggest growth is not slowing," says Laakso. "The open-access publishing model has proven itself to work."

Laakso divides the history of open access into three phases. First came the pioneering years of 1993–99, during which most open-access journals were, he says, "home-brew" efforts, set up by individuals and hosted on university servers. Next were the innovation years, which saw the birth of publishers such as the Public Library of Science and of software infrastructure that makes it much easier to launch a digital journal.

Since 2005, Laakso says, innovation has slowed but growth continues — the consolidation phase. Following this trend, last week Nature Publishing Group (NPG) launched *Scientific Reports*, an author-pays, open-access, online-only journal, which reviews papers on technical soundness rather than impact.

NPG's acknowledged inspiration is *PLoS ONE*, which in 2010 published 6,749 papers, making it the world's largest journal. It has been a "phenomenal success", says Jason Wilde, business development director at NPG. "It shows that authors and readers like the model of a broad-based journal with light peer review." *Scientific Reports* will provide *PLoS ONE* with a rival and help drive up standards, says Wilde. "In any market there should be competition."

The trends "show the success of open access", says Peter Suber, director of the Open Access project at the non-profit lobby group Public Knowledge in Washington DC. So far, he adds, the open-access movement has not imperilled commercial publishers. "The predictions of harm are being proven to be false."

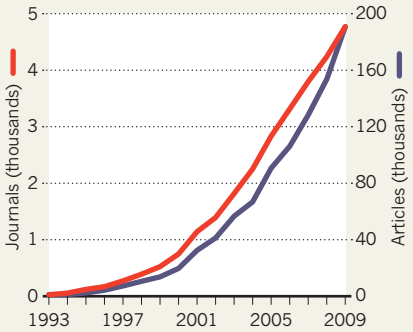
But not all advocates of open access are satisfied with its progress. "The growth rate is portrayed as dramatic, but it's not dramatic at all if the goal is 100% open access," says Stevan Harnad, a cognition researcher at the University of Southampton, UK. Other ways to make papers freely accessible, such as self-archiving and hybrid journals, which allow authors to choose whether to pay for open access, are also growing only linearly, he says. "The rate is much too low for the needs of research."

What is not known is whether open-access journals are competing with subscription journals, or whether they have opened up a publishing niche. Harnad believes that most open-access journals are new ventures. Because nearly all the must-have journals still charge subscription fees, the rise of the author-pays model actually imposes an extra expense on research funders, he says.

To escape this catch-22, says Harnad, institutions and funders — who have led the demand for open access — must mandate grantees to deposit papers published in subscription journals in open repositories. This would free up resources to support author-pays open access. "Publishers won't convert until the money is available to pay them," he says. ■

**OPENING UP**

The number of open-access articles and journals has been steadily increasing since 2000.




SOURCE: M. LAAKSO *ET AL. PLOS ONE* **6,** E20961 (2011)