and even which vaccine—OPV, the more expensive inactivated vaccine used in wealthy countries, or a still-to-be-invented one—should be used. But any scenario, they agree, involves incorporating polio vaccine into routine immunization—which would need to be strengthened considerably and augmented with one or several special immunization weeks a year to keep up immunity. And vaccination would need to continue indefinitely, they agree. Arita and colleagues recommend continuing emergency campaigns with OPV until global cases drop below 500 and the number of nations with polio drops below 10 and then switching to a control strategy. Which vaccine to use would be reassessed in 2015.

Even if transmission of wild poliovirus could be stopped, vaccination will still be needed, adds Chumakov. One problem, as Henderson points out, is the difficulty of ever knowing for sure that the virus is gone. What's more, if immunization ceased, the world's population would soon become profoundly vulnerable to a reintroduced poliovirus, whatever its origins—whether a vaccine-derived strain, or one that escaped from a vaccine manufacturing plant, or a synthetic version released by a terrorist.

The risks are well understood and are manageable, responds Heymann. He adds that policies on whether to vaccinate posteradication are still wide open to debate, which he welcomes, noting that both Henderson and Arita were his bosses in the earlier smallpox campaign. "Nothing is cast in stone," Heymann says.

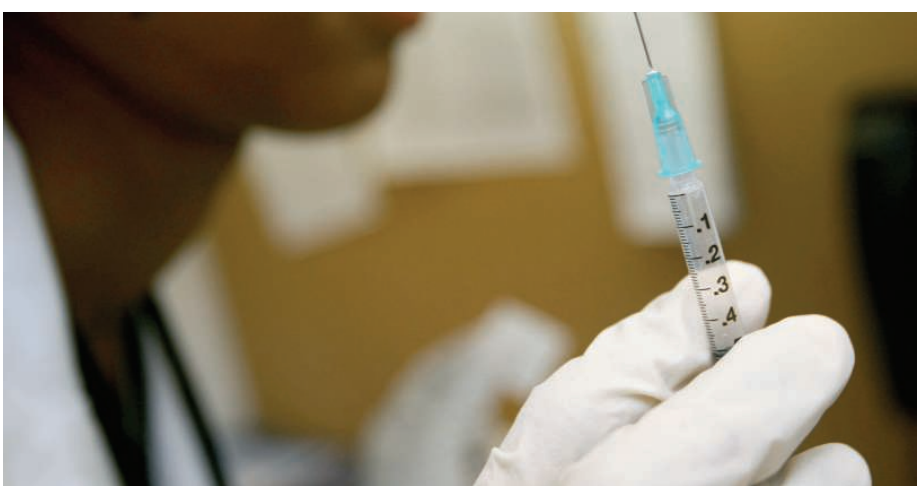
As for stopping transmission of wild poliovirus, there is no question. "We have to finish," he insists. "It would be injurious to the world's population and to its $4 billion investment to throw up our hands and say we are going back to routine immunization. … As long as the partners and countries are willing to make the effort, it is not for Isao [Arita] or me to say that eradication is not feasible."

And although it would be wonderful if polio could be controlled through routine immunization, as Arita and others propose, Heymann argues that it's simply not feasible. To keep polio in check, routine coverage would have to be maintained at consistently high levels—90% if IPV were used—and many parts of the world are not even close to achieving that. "If we had 90% or greater coverage, polio would probably have disappeared on its own," says Heymann.

Meanwhile, Heymann and his colleagues say they have an eradication program to run, and things are looking up. Not only are most countries committed and making progress, but "there are a whole series of things we are doing to improve" as well. For instance, the program is supporting development of a rapid diagnostic test that would enable countries to respond to outbreaks much more quickly. The state of Uttar Pradesh, India, will be testing a birth dose to see whether it boosts immunity. On the political front, Heymann just came back from Kabul, where the Afghani president reiterated his support, and the United Nations' Kofi Annan is committed to helping with security.

"As long as there are things we haven't tried, the polio team remains optimistic."

–LESLIE ROBERTS



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SCIENTIFIC PUBLISHING

A Cure for the Common Trial

A new journal aims to alleviate bias in clinical trials reporting, but some question whether it's the remedy the field needs

On the excitement spectrum, results from the LOTIS trial rank right alongside "New soil fungus identified." In the study, a Dutch team takes 402 85-year-olds and gives half access to an occupational therapist, who teaches them how to use walkers and apply for household help. The point is to see whether such interventions slow the onset of age-related disabilities. They do not.

Ordinarily, a study with negative results like this wouldn't see the light of day in a medical journal—at least not a top-tier one. But the Public Library of Science (*PLoS*) aims to be different. It's using the LOTIS study to launch its new journal, *PLoS Clinical Trials*, which begins publishing on 19 May.

The journal's credo is simple: Disappointing results can still be good news. Its editors have explicitly stated that all clinical trials submitted—regardless of outcome or significance—will be published, as long as they are methodologically sound. The policy takes aim at a pervasive problem in the clinical trials literature: a heavy skew toward studies with positive outcomes. Some say there's a "black hole" where studies with negative or ambiguous outcomes should be.

This bias can cost lives. In a particularly lethal example, a 1980 clinical trial that indicated that a prophylactic heart attack drug did more harm than good went unpublished because the drug was abandoned. Thirteen years later, the researchers involved in the trial published the study to illustrate the warning it might have provided: Estimates suggest that—in the intervening years—hundreds of thousands of people may have died prematurely from effects associated with this class of drugs, known as antiarrhythmics. More recently, industry-sponsored trials of Paxil and Vioxx have also highlighted the dangers of not reporting negative results (*Science*, 14 January 2005, p. 196).

"Science has been letting the public down very badly by not getting to grips with this problem," says Iain Chalmers, a clinical trials expert and editor of the James Lind Library in Oxford, U.K. "*PLoS Clinical Trials* is sending a message that it won't contribute to this bias." Still, Chalmers and others wonder how effective such "catch-all" journals can be—especially given that much of the bias seems to be coming from the authors. And some worry that flooding the literature with negative or ambiguous studies could itself do more harm than good.

Leveling the field

The *PLoS Clinical Trials* philosophy is hardly unique. Several medical journals, including *The New England Journal of Medicine*

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(*NEJM*) and *The Journal of the American Medical Association* (*JAMA*), claim to place a high priority on methodology.

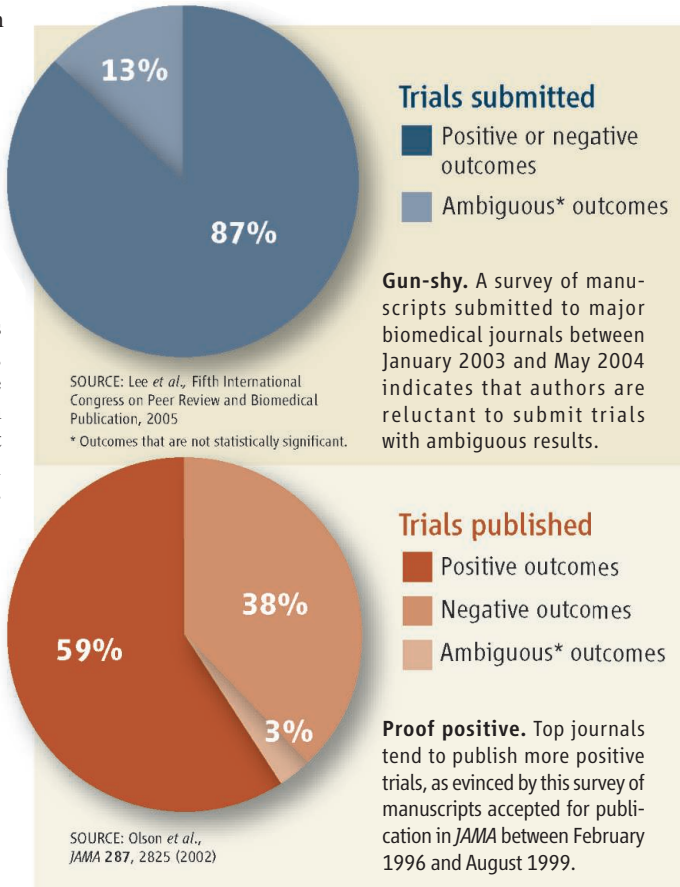
But even the big guys admit to factoring in issues beyond study design. "Our editors are looking for research that is important" and "defines new treatments or resolves major controversies," says *NEJM* spokesperson Karen Pederson. And in meetings at which *JAMA* editors debated the merits of manuscripts, editors have frequently mentioned "journalistic goals" such as "readership needs and timeliness," according to an on-site analysis by Kay Dickersin, director of the Center for Clinical Trials at Johns Hopkins University in Baltimore, Maryland.

Such standards may give pause to authors of trials with negative or ambiguous results. Reluctance to submit such papers is a huge problem, says Kirby Lee, a clinical trials expert at the University of California, San Francisco (UCSF); it's one of the biggest drivers of publication bias. In a preliminary report presented last September at the Fifth International Congress on Peer Review and Biomedical Publication in Chicago, Illinois, Lee and UCSF colleague Lisa Bero showed that only 13% of manuscripts submitted to major biomedical journals contained ambiguous outcomes. Although these trials may not seem important on their own, they help scientists design better future trials and can be vital when combined with similar trials in so-called meta-analyses, which help determine a drug's safety or efficacy.

Getting ambiguous or negative trials into the literature can also prevent needless and potentially harmful duplicate studies. In the early 1980s, researchers at the National Cancer Institute in Bethesda, Maryland, showed that retinoic acid could turn acute myeloid leukemia (AML) cells into normal cells. Soon after, many doctors apparently began testing the acne drug Accutane—then the only clinically available form of retinoic acid—on their AML patients. The treatment didn't work, but no one reported that. Toward the end of the decade, a Chinese clinical trial showed that only a particular isomer of retinoic acid had the effect. In the interim, patients were exposed to unnecessary side effects, and alternative treatment routes were not pursued as vigorously as they might have been.

Industry suppression of unfavorable results likely plays some role in author bias, says Lee, but a lot of it comes down to human nature. "Authors don't think their studies are important, or they think editors won't be interested," he says, so they don't take the time to write them up. As a result, adds Dickersin, only about half of the studies that should be published actually are.

PLoS Clinical Trials could change that. Other journals say they are interested in methodology, but "it's a defining part of what *PLoS Clinical Trials* is," says Dickersin, who also sits on the journal's advisory board. "The editors don't care if something's hot or not." The approach "removes uncertainty on the author's end," says *PLoS Clinical Trials* publication manager Emma Veitch. And *PloS*'s open-access policy, which makes all of the papers freely available online at the time of publication (authors pay a negotiable $2500 fee upon acceptance), assures investigators that their research will reach a much wider audience than it would at a specialty journal, she says. A number of manuscripts are coming in: "We're getting a good mix of all types of trials," says Veitch.



No panacea

But will getting more of these negative and ambiguous trials into the literature really address the bias problem? "Journals can help encourage the right atmosphere," says the James Lind Library's Chalmers, "but the fundamental problem is with the scientists themselves." If authors don't want to be associated with a negative trial, he says, they're still not going to submit their work. And, most say, the strategy is unlikely to stop drug companies from sitting on negative results.

The real change, says Chalmers, has to come from within the scientific community. It is "scientifically and ethically unacceptable to invite people to participate in these studies and then not publish the results," he says. The fact that medical societies have not stated this, he thinks, is "disgraceful."

Other experts worry that inundating the literature with negative and ambiguous studies could compromise patient care. "Physicians and the public rely on top-tier journals to filter out studies that are not easily interpretable or that may be misleading," says Celia Fisher, director of the Center for Ethics Education at Fordham University in New York City. "Having access to these studies could cause patients to go off medications that could be helpful" or vice versa, she says.

Publishing such trials could also hurt a journal—by marginalizing it—says Marcia Angell, a senior lecturer in social medicine at Harvard Medical School in Boston and former editor-in-chief of *NEJM*. "It sounds like a recipe for a lot of 'so-what' studies," she says, "and who wants to read a study that says the world is not flat?" UCSF's Lee agrees that readership needs to be a concern for *PLoS Clinical Trials* and any other journal that publishes such a wide range of results. "A journal that doesn't appeal to its readers won't survive," he says. That may explain the demise of a similar online journal, *Current Clinical Trials*, which began publishing in 1992 but eventually went defunct. Nevertheless, Lee is optimistic about *PLoS Clinical Trials*. "It's a great idea," he says, "and it could change the way clinical trials are published."

Robert Califf, director of the Duke Clinical Research Institute in Durham, North Carolina, believes that the new journal will encourage more authors to submit their trials, "although, personally, I'd probably try a few specialty journals before I went to *PLoS Clinical Trials*," says Califf, because the work would be more likely to reach those in his field. "Putting everything online is a good idea," he says, "but not everyone knows how to use Google." Still, he says, "if the new journal catches on, it's the right way to do things."

–DAVID GRIMM

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