pairs, which harbor a dense object such as a black hole and an ordinary star, are undetectable—except when they suddenly flare, or outburst. Observing in wavelengths longer than x-rays can help researchers get a handle on the size and shape of the accretion disks responsible for emissions. In the past, astronomers have marshaled multiple ground- and space-based telescopes to observe outbursts across the spectrum, but doing so entails "a lot of coordination and difficulty," says K. Suryanarayana Sarma, Astrosat's project director at ISRO in Bengaluru. It's hard to free up telescopes on short notice, meaning observations often lag the initial burst.

"To study these sources, it is necessary to detect them as early as possible in the outbursting phase," which lasts only a few months, says Somasundaram Seetha, program director in ISRO's space science program office. The new spacecraft should make that possible by lying in wait, tracking x-ray emissions across the sky. When it catches an outburst, she says, Astrosat's instruments will swing into action, and ISRO will also send out a worldwide alert.

In another first, a U.S. firm will hitch a ride on an Indian launch. Piggybacking on Astrosat's heavy lift rocket are four LEMUR CubeSats, designed for Earth observation and as a technology demonstration by Spire Global, Inc., based in San Francisco, California.

Astrosat's anticipated mission life is 5 years. Observing time will be opened to the global community 1 year after launch, says Kiran Kumar, chairman of ISRO. Kasturirangan is confident that the long delay has not dimmed the observatory's prospects. "There is no doubt," he says, "that Astrosat is still very relevant for the world." ■

Pallava Bagla is a science journalist in New Delhi.

Astrosat is jam-packed with telescopes and imagers.

CLINICAL TRIALS

Ebola vaccines face daunting path to approval

Triumph in a clinical trial is no guarantee a vaccine stock will be available in the next outbreak

By **Jon Cohen** *and* **Martin Enserink**

No vaccine in history has moved forward more quickly than the one against Ebola made by Merck. The first person received the vaccine last fall; in July, 9 months later, an unusual clinical trial conducted in Guinea under the most unforgiving conditions—remote villages, suspicion of researchers, dwindling cases—proved that the shots actually worked. The estimated efficacy was between 74.7% and 100%—such solid protection that the control arm of the study was abandoned and all participants were offered the vaccine (*Science*, 7 August, p. 569). Many say the Merck vaccine may have helped curb the epidemic in Guinea, and it is now also being used in Sierra Leone, in an extension of the trial.

But will this remarkable efficacy translate into a desperately needed stockpile of vaccines ready to quash the next outbreak? The answer will depend on whether developers can persuade regulatory agencies including the U.S. Food and Drug Administration (FDA) that their vaccine is safe and effective enough for widespread use. The Merck vaccine and a different one made by London-based GlaxoSmithKline (GSK), which has not yet proven itself in a clinical trial but looks promising, face multiple hurdles. The unconventional clinical trial of the Merck vaccine may not have generated enough data to satisfy regulators, acknowledges Mark Feinberg, who headed the vaccine project until he left Merck on 7 September. And with the epidemic finally on the wane, collecting more convincing efficacy data on either vaccine has become practically impossible. After 22 gruesome months, more than 28,000 cases, and 11,291 deaths, Liberia is officially Ebola-free, and during the week ending on 6 September, Guinea and Sierra Leone only had one case each.

There are sure to be future outbreaks, making it a "huge priority" to approve an Ebola vaccine so that it can be stockpiled and deployed fast, says Luciana Borio, the acting chief scientist at FDA in Silver Spring, Maryland. "A vaccine that's proven safe and effective for Ebola would be a monumental event," adds Borio, who says the agency will speedily review any application manufactur-

PHOTOS: (TOP TO BOTTOM) ISRO; IDRISSA SOUMARE/AFREECOM

Baldé Thierno Boubacar, a hospital worker in Conakry, in Guinea, takes part in a study of Merck's vaccine.

ers submit. But neither Merck nor GSK has yet filed anything to FDA or key regulatory agencies in other countries. Both companies are gathering more data in human and animal trials, hoping to take advantage of approval routes that do not require massive, controlled trials in the midst of an outbreak.

The Merck vaccine, which contains the gene for an Ebola virus surface protein stitched into a harmless livestock pathogen, vesicular stomatitis virus (VSV), was originally developed in 2003 by the Public Health Agency of Canada. The Canadian government then licensed the vaccine to NewLink Genetics, a small biotech in Ames, Iowa, which relied on funding from the U.S. Department of Defense to develop it. The company had difficulty drumming up interest in the vaccine until the outbreak hit. But last November, when it became clear that hundreds of thousands of doses might be needed in short order, NewLink licensed the vaccine to Merck.

After the VSV-based vaccine quickly passed muster in safety studies, the World Health Organization began the unusual "ring vaccination" trial—a strategy reminiscent of the one used to eradicate smallpox by creating a ring of immunity around infected people. The concept had never been tried in a clinical trial. Standard efficacy studies randomly assign participants to receive either a vaccine or a placebo; in this study, researchers gave the Merck vaccine to clusters of people in Guinea who might have been exposed to a confirmed Ebola case. They then compared Ebola cases in these clusters, which averaged about 80 people each, with those in similarly sized clusters of people who had also potentially been exposed but were randomly assigned to receive the vaccine 3 weeks later. The delayed arm essentially served as a control group. Ten days after receiving one shot, no one in the 48 clusters of immediately vaccinated people had developed Ebola, compared with 16 cases in the 42 delayed clusters.

The study originally had planned to compare 95 immediate clusters with 95 delayed ones, and the early termination of the control arm of the study decreased the statistical "power" of the results. But if the data are not robust enough to obtain FDA's standard efficacy approval, Merck could pursue either of two alternative approval processes in place for drugs and vaccines designed for "serious or life-threatening conditions" that for practical or ethical reasons cannot meet the traditional efficacy requirements. So could GSK, whose vaccine uses a chimpanzee adenovirus with the Ebola surface protein gene.

Both vaccines already appear to satisfy the first of these, the animal rule: They have proven to be safe in humans and have protected vaccinated monkeys that were injected with the virus to "challenge" their immunity. But FDA will not consider the animal rule if a vaccine possibly can meet what's known as the accelerated approval requirements, which fall midway between demonstrating formal efficacy and the animal rule. Accelerated approval has been used for drugs but not vaccines, so when FDA suggested it in May, "a light bulb went off," says Ripley Ballou, head of the program developing GSK's Ebola vaccine. "I don't think anyone had thought of it before."

In essence, accelerated approval demands that researchers determine which immune responses protect vaccinated monkeys and then show that the product triggers similar responses in humans. To figure out which immune responses in vaccinated monkeys correlate with protection, researchers compare animals that get sick after a viral challenge with those that stay healthy. But both the GSK and Merck vaccines had 100% success in monkey tests, which makes it difficult to tease out the immune mechanisms behind their efficacy. To find the correlates of immunity, both companies are now giving lower doses of the vaccines to monkeys before challenging them, which theoretically should reveal the immunologic breaking points between success and failure.

Both companies also want more data about the immune responses in vaccinated humans. A massive trial planned in Liberia of both vaccines was suspended because the epidemic there ended; researchers plan to take blood from the people enrolled in the study—500 for each of the two vaccines—for a full year. Similar studies of the Merck vaccine alone are taking place in Guinea and Sierra Leone. And GSK in June launched new studies in five West African countries near this epidemic—three of which had spillover Ebola cases—to assess safety and immune responses.

At this point, FDA says it remains open to all three approval options. "Each and every one of these pathways has uncertainties," Borio says. But if the companies receive licensure via the animal rule or accelerated approval, FDA will require postmarketing studies in future outbreaks. Just what those would look like "is not entirely clear," Feinberg says. It would be unethical to withhold a licensed product to create a control group, and if more than one vaccine receives approval, trials become more complex still.

If another outbreak erupts in the interim, countries may well request to use one or both of these vaccines experimentally. But a far better option is to have an approved vaccine in hand at the start of an outbreak that can be used in conjunction with traditional containment efforts such as isolation of cases, contact tracing, and safe burial, says Clifford Lane of the U.S. National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, who is running the Liberian vaccine study. "If things are able to be mobilized quickly enough," Lane adds, "we probably won't find ourselves in the situation that we're just leaving." ■

The winding road to an Ebola vaccine

These phase II and phase III trials may yield additional information needed for regulatory approval.

VACCINES/LOCATION	TARGET ENROLLMENT	START DATE	DESIGN	STATUS
Merck, GSK/Liberia	27,000 in general population	February 2015	Randomized controlled with placebo arm	Stopped at 1500. Blood collection continues
Merck/Sierra Leone	8700+ frontline workers	April 2015	Immediate versus deferred	Immediate arm vaccinated, deferred in fall
Merck/Guinea	190 clusters of potential contacts	April 2015	Ring vaccination, immediate versus deferred	Control arm halted after analysis of first 90 clusters, all offered vaccine
Merck/Guinea	1200 frontline workers	March 2015	Safety and immune responses	May add 2000 more
GSK/Mali, Senegal, Ghana, Cameroon, Nigeria	3000 adults	June 2015	Safety and immune responses	Plan to add 600 children in October

DATA: NIH, CDC, MSF, WHO, GSK, MERCK