Israel’s Silent Polio Epidemic Breaks All the Rules

The first positive sample was detected on 29 May, isolated from sewage in Rahat, a Bedouin community in the south of Israel. Next came a sample from Beer Sheva, a larger southern city that also has a sizable Bedouin population. By July, 30 environmental samples had tested positive, and it was clear that 25 years after it had been dispatched, wild poliovirus was back in Israel and spreading fast.

As of late October, more than 140 specimens from 25 sites had tested positive for poliovirus, mostly in the south but also in central and northern Israel, including Jerusalem and Haifa. Retrospective analysis of sewage samples has shown that the virus has been circulating since February but, surprisingly, has caused no cases of paralysis. Polio outbreaks are raging nearby in Pakistan and war-torn Syria. But in developed, prosperous Israel, no one saw this coming. The country has an impressively high immunization rate of at least 95%, and it uses the inactivated polio vaccine (IPV), the vaccine of choice in high-income countries, which unlike the oral live-virus vaccine used in poorer countries poses no threat of reverting to infectious virus.

Finding circulating wild virus was “totally unexpected,” says Itamar Grotto, director of public health services at the Israeli Ministry of Health. “[A] shock,” wrote the Independent Monitoring Board of the Global Polio Eradication Initiative (GPEI) in its October report. Not only could the circulating virus spread from Israel to countries now considered polio-free, but it could easily cause cases of paralysis if it infects unvaccinated people in Israel.

The country is now scrambling to quash the silent outbreak before it spreads further. It has also launched a massive scientific investigation to figure out how the virus could be so widespread yet avoid detection. And other wealthy countries, including the United States and the United Kingdom, are watching closely, hoping to draw lessons for their own vaccination and monitoring strategies.

Paradoxically, Grotto says, Israel’s high coverage with IPV is what has allowed the virus to circulate silently for so long. In many countries, IPV is the successor to oral polio vaccine (OPV), which has long been the mainstay of the global eradication effort because it is cheap and easy to administer in drops. OPV not only protects the individual from paralysis but also induces strong gut immunity that blocks transmission of the virus, which is shed in the stool and spread largely through fecal-oral contamination.

But OPV has a downside. The weakened live virus used in the vaccine can in rare instances regain its neurovirulence and cause paralysis. To avoid that risk, countries that have gotten rid of polio have often switched to the more expensive IPV or a combination of OPV and IPV. Israel adopted an IPV-only schedule in 2005. IPV provides excellent protection against disease, but because it elicits only weak mucosal immunity, it is much less effective than OPV at blocking transmission.

In the face of the virus’s reappearance, however, Israel has resurrected the earlier vaccine. After an initial response with IPV in August Israel began vaccinating all children under age 10 with OPV. In October, the government decided to reintroduce OPV along with IPV into the routine immunization schedule. “Israel has made clear that switching to IPV-only at a time when wild virus is still circulating is a risky strategy,” says Nicholas Grassly of Imperial College London. It also dispels the notion that IPV by itself might be sufficient to stop an outbreak post eradication. “After Israel, we need to be clear that OPV is the one to use [in outbreaks] and the role for IPV may be limited,” Grassly says. “This episode shows us we should not give up the benefits of OPV lightly,” adds Roland Sutter, who coordinates polio research at the World Health Organization (WHO) in Geneva, Switzerland.

Not all IPV-only countries need to rethink their vaccination strategies. Israel may be a special case, Grotto says—a possibility that Grassly’s research suggests. Well before the reports from Israel, he designed a model to see whether IPV could actually foster the spread of the virus in a vaccinated population by masking an outbreak until it was large and hard to stamp out. In a paper published online on 7 October in the American Journal of Epidemiology, Grassly and colleagues concluded that it could, but only in a “very, very rare” circumstance, Grassly says—when
immunization rates are very high and some portion of the population lives in conditions where the virus transmits very efficiently. “It turns out Israel is one,” says Bruce Aylward, WHO’s assistant director-general who leads GPEI and is a co-author on the paper.

As soon as the virus was detected, Israel expanded its environmental surveillance and began analyzing stool samples to see who was carrying it. They’ve found it predominately in the poor Bedouin population, who mostly live in squalid conditions in the southern part of the country. The children found to be carrying the virus so far have all been fully vaccinated, which is why there have been no cases, but poor sanitation, overcrowding, and migration have enabled the virus to spread.

“It’s a first-world country with a third-world population,” Sutter says.

Israel’s experience does make clear that every country should have ready access to a supply of OPV to respond to emergencies like this and should use it fast, says Hamid Jafari, director of GPEI at WHO. And countries at risk that don’t monitor the environment for circulating poliovirus—the only way this outbreak was detected—should consider starting, he adds.

Meanwhile, Israeli researchers and their collaborators at WHO and the U.S. Centers for Disease Control and Prevention are trying to figure out where the virus came from. Early phylogenetic analysis linked it to a strain that circulated in Pakistan in 2012, and investigators initially thought it had jumped from Pakistan to Israel via Egypt, where it was briefly detected in sewage samples late last year. Further sequencing by Lester Shulman of the Ministry of Health’s Central Virology Laboratory in Tel Hashomer suggests a single introduction from Pakistan into the broader region sometime in 2012, after which the virus diverged, with some branches going to Egypt, Israel, and now, presumably, Syria, where an outbreak began in October.

Despite the vaccination campaigns, the virus is still circulating in Israel. The most pressing question now is how much OPV is needed to stop transmission—Israel is gearing up for another national vaccination round with OPV—and how long it will take. “We are inventing the wheel,” Grotto says. “There is no experience to learn from.”

—LESLIE ROBERTS

INTELLECTUAL PROPERTY

California Moves Shake Up Prenatal Gene Testing Market

Two decisions in California last week promise to give a boost to a new technique for prenatal genetic testing, opening the field to increased competition and expanding the market for the tests.

On 30 October, a federal district court judge in San Francisco invalidated a patent owned by Sequenom of San Diego on a novel test for Down syndrome that sieves fetal DNA from a mother’s blood and checks it for risky abnormalities. Three other companies planning to offer similar blood tests, which obviate the need for taking samples from the womb, now won’t worry as much about being sued over patents. In a separate windfall, California agreed on 1 November to subsidize these fetal DNA tests—known as noninvasive prenatal testing—through the state’s genetic diseases program, which screens about 400,000 women a year.

The decision to nullify Sequenom’s U.S. patent (number 6,258,540) seems to have rattled investors, with the company’s stock price dropping 23% on 31 October. Company executives issued statements saying that they “vigorously” disagree with the ruling, which “misapplies or ignores the controlling law,” and will appeal.

In her opinion, Judge Susan Illston of the federal court for northern California wrote that, in light of recent U.S. Supreme Court decisions, Sequenom should never have received a patent in 2001 on its prenatal testing methods. They are based on work done in the late 1990s by Yuk-Ming Dennis Lo of the Chinese University of Hong Kong and James Stephen Wainscoat, then of the University of Oxford in the United Kingdom, who developed a way to use paternal DNA to isolate cell-free fetal DNA circulating in a pregnant woman’s bloodstream, making invasive procedures such as amniocentesis unnecessary. The DNA can then be checked for chromosomal abnormalities such as trisomy 21—the cause of Down syndrome.

But Illston wrote that Sequenom’s patent was built on discoveries that for the most part were not very inventive, citing the Supreme Court’s 2009 rejection of a blood test patent held by Prometheus Laboratories of San Diego. Sequenom was trying to claim ownership of lab processes such as amplifying DNA fragments that were already “well-understood” and “routine” when the patent was issued, she wrote. The exception was Sequenom’s novel use of paternal DNA as a screening tool. But DNA is “a natural phenomenon,” she decided, and therefore not patentable. In June, the Supreme Court had denied claims on the BRCA1 breast cancer genes held by Myriad Genetics of Salt Lake City for the same reason, and Illston cited the Myriad decision to buttress her conclusion.

“This will help keep the prices down and provide a driver for general competition.”

—HENRY GREENLY, STANFORD UNIVERSITY

“It’s a huge victory for us and for the entire field,” says Ken Song, CEO of Ariosa Diagnostics of San Jose, California, the firm that started this legal brawl. Ariosa, Sequenom, and two other California companies are offering similar cell-free prenatal tests. Ariosa was the first to sue, in 2011, seeking to prevent Sequenom from coming after it for patent infringement. An initial decision favored Ariosa, was appealed to a higher court, and came back to Illston’s court for a second review in light of recent Supreme Court decisions.

If Illston’s decision stands, the court ruling is a “big deal for the field” of DNA testing, says Henry Greely, an expert on law and bioethics at the Stanford University Center for Law and the Biosciences in Palo Alto, California. Limiting the reach of patent claims in this way will be good for public health, he argues. “This will help keep the prices down and provide a driver for general competition,” Greely predicts.

Some worry that the decision could scare potential investors away from the diagnostics industry. Ariosa’s Song doesn’t think so. A former venture capitalist, he says he’s confident investors can live with the rule changes. They won’t “give you a bunch of money because you have a patent on a protein or marker,” Song suggests. Instead, he says, they will have to vet the feasibility of business plans more carefully. Song acknowledges that he has patents, too, but insists they’re solid ones, based on “technology we developed ourselves.”

—ELIOT MARSHALL