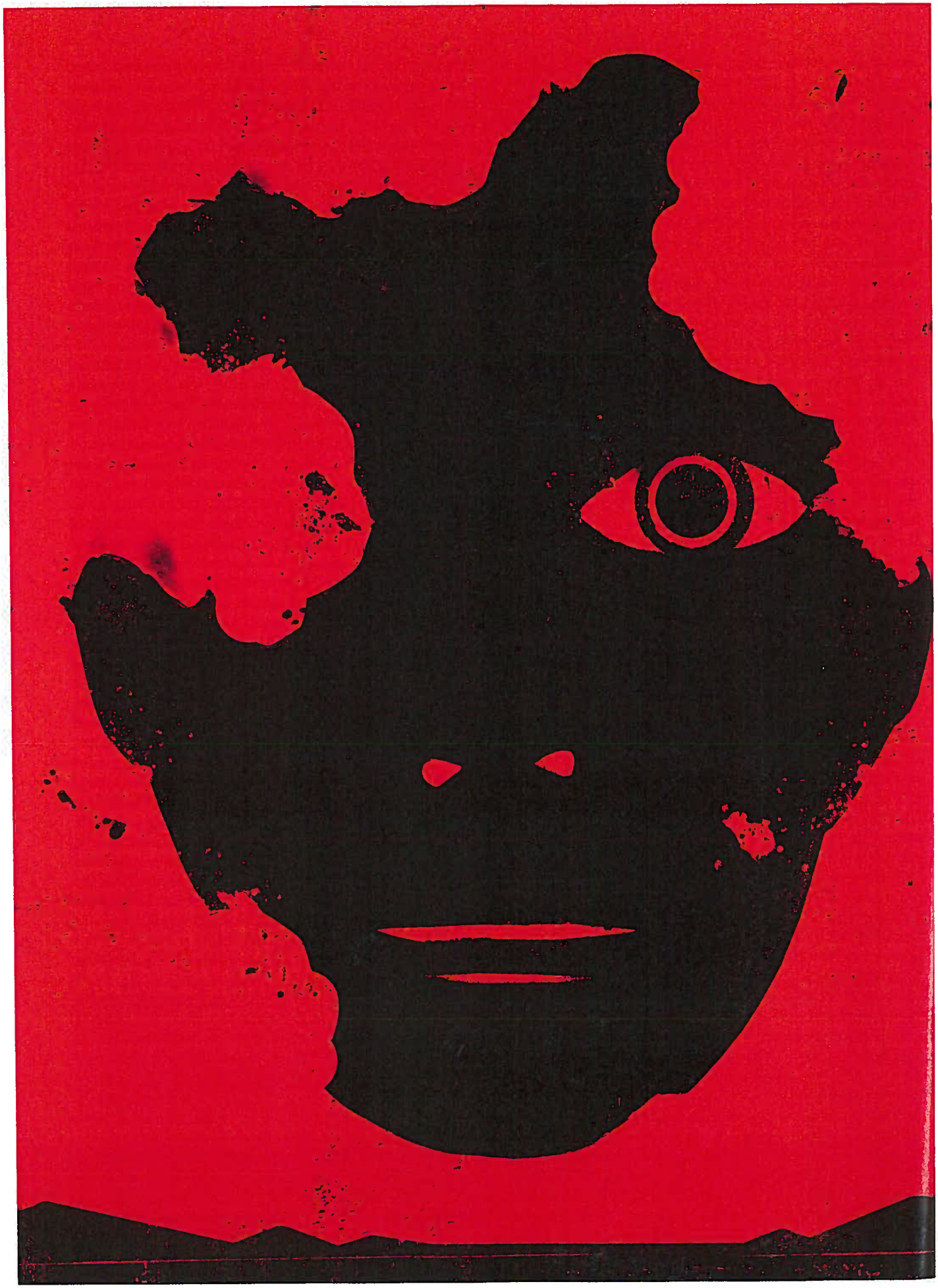


PUBLIC HEALTH

EBOLA'S SECOND COMING

Brain deficits and more torment many virus survivors in Liberia. The top suspects are hidden viral remnants and immune system overreactions

By Seema Yasmin

Illustration by Edel Rodriguez

Seema Yasmin, a writer and medical doctor, reported for *Scientific American* from Liberia. Travel was supported by the Pulitzer Center on Crisis Reporting.

JOSEPHINE KARWAH STEPPED OUT OF THE EBOLA TREATMENT UNIT AND CRADLED HER pregnant belly. She had hobbled into the white tent in Monrovia, Liberia, two weeks earlier, during August of 2014, her knees burning with pain and threatening to buckle every fourth step.

Josephine's mother had died in this unit. Her body had been carried away in a white body bag that nurses had prepared with her name written neatly on the side. Her father, too, had died from Ebola, as did her aunt and uncle. But Josephine, though she got sick from the virus, lived. She and her unborn child were survivors, unlike 40 percent of the patients in the 2014–2016 African Ebola epidemic. Josephine decided she would name the baby Miracle.

Then the nightmares began. Back at home in her village, Smell No Taste, an hour's drive east of the Liberian capital, Josephine dreamed of the family members she had lost to Ebola and the horrors of the treatment unit. Throbbing headaches interrupted her dreams, and her hips and knees ached as she tried to fall back asleep. During the day she helped her older sister make soap to sell at the market. But her right eye burned, and her left eye made the world appear cloudy, as if drops of dew had settled on a camera lens. At the money changer's booth, she walked away with the wrong change, unable to recall how many Liberian dollars were in her purse when she left the house.

Josephine is one of 1,500 Ebola survivors in Liberia. Like Josephine, many today suffer memory loss, joint pains, muscle aches and eye problems. These are not isolated anecdotes and vague reports. In February, reporting findings from the largest-ever study of Ebola survivors at a conference in Boston, Mosoka Fallah, an epidemiologist from Liberia, said more than half of the patients who lived through an acute attack later reported muscle and joint problems. Two thirds had neurological difficulties, and 60 percent reported eye problems approximately one year after Ebola infection. Although the World Health Organization declared the public emergency was over this past March, now people are living with what doctors call post-Ebola syndrome.

Post-Ebola syndrome has been spotted before. After small virus outbreaks in East and Central Africa in the past 20 years, survivors suffered joint pains, muscle aches and eye problems serious enough to prevent many from working.

But these were limited episodes of the disease and small groups of survivors. The 2014–2016 West African Ebola epidemic has left 17,000 survivors at risk of post-Ebola syndrome. Like Josephine, they stepped out of treatment units into an uncertain future. There is one thing that experts and patients do know: Ebola is not over.

EBOLA'S GHOST

FALLAH'S OFFICE sits at one end of a long corridor in the John F. Kennedy Medical Center in Monrovia. A Harvard University–trained epidemiologist who grew up in one of Liberia's largest slums, he was part of the team testing treatments and vaccines as part of the initial Ebola response. His survivor research grew out of that work.

The National Institutes of Health in the U.S. and the Liberian Ministry of Health and Social Welfare had formed a coalition in 2014 called the Partnership for Research on Ebola Vaccines in Liberia (PREVAIL). By the time the initial vaccine safety tests were completed, however, Liberia's epidemic was slowing down. The number of people becoming infected with Ebola was far fewer than expected, so the first study, PREVAIL I, was scaled back to test only for vaccine safety and immune response and not the vaccine's ability to prevent Ebola. Instead PREVAIL scientists shifted resources to Ebola's aftereffects. Reports were coming in from across West Africa of patients who survived the disease but suffered physical and psychological problems. Fallah was appointed principal investigator for the study in Liberia and switched his focus from the Ebola response to Ebola survivors.

On a Wednesday afternoon, two days before Christmas, Fallah flicked through a patient file at the Kennedy Medical Cen-

IN BRIEF

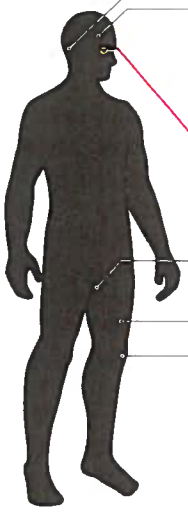
With West Africa's Ebola epidemic declared over, about 17,000 people are at risk for symptoms called post-Ebola syndrome.

In a Liberian study, 60 percent of survivors reported eye problems, 53 percent had muscle aches and joint pain, and 68 percent had neurological problems.

Supposedly virus-free people are frequently shunned by others and must wonder if the disease will afflict them again.

Suspected Hideouts

More than half of the people who live through Ebola have serious symptoms after the disease is supposedly gone, according to a study of more than 1,000 of Liberia's confirmed 1,500 virus survivors. Ailments include neurological problems and muscle pain. Physicians suspect the virus may still be hiding in parts of the body not rigorously patrolled by immune system cells, such as the eye. Or perhaps the initial immune reaction to the virus causes inflammation that damages organs. Here are commonly afflicted body parts and symptoms. The eye is a particular focus because about 60 percent of patients report troubles there.



Ears: Full or partial loss of hearing or a ringing sensation called tinnitus

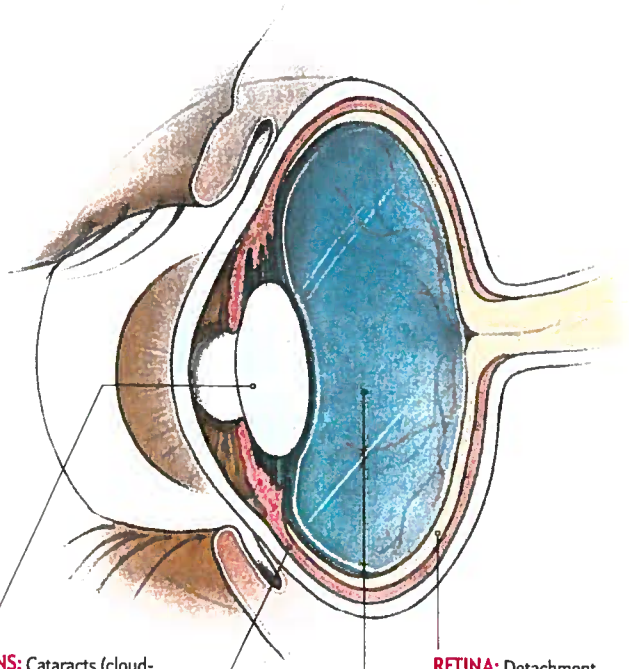
Brain: Headaches, movement-control issues resembling Parkinson's disease, memory problems, cognitive disorders, fatigue, anxiety, depression and sleep disorders
Suspected virus hiding place

Eyes:
Suspected virus hiding place

Testes:
Suspected virus hiding place

Muscles: Pain

Joints and joint cartilage: Pain
Suspected virus hiding place



LENS: Cataracts (clouding in the front of the lens instead of more typical obstructions in the middle or back), leading to blurred or lost vision, difficulty seeing in dim light, and halos around light sources

VITREOUS HUMOR: Protein clumping and particulate matter floating around, causing blurred vision

UVEA: Swelling of the middle layer, producing eye redness, pain, light sensitivity, blurred or decreased vision, and floating spots

RETINA: Detachment, disrupted cell layers, changes in pigment patterns and an inflamed area in the middle of the retina, possibly resulting in blindness or partial vision loss, inability to see in dim light, sensitivity to bright light, and seeing flashes or spots

ter. He had overseen the refurbishment of the building's second floor to include the space and equipment needed to study Ebola survivors. Outside his office and stretching up the corridor, men and women sat in chairs that lined the walls, waiting to be seen by medical staff.

Since the survivor study was launched in Liberia in June 2015, more than 1,000 of the country's confirmed 1,500 Ebola survivors have agreed to take part. Their health will be monitored at semiannual checkups for five years. Each survivor is asked to bring four friends or relatives to one of the study's three sites. These are people with whom the patients have close contact but who were not infected with Ebola. Fallah says he hopes to enroll 6,000 close contacts who will serve as controls, helping researchers separate the health problems that are part of post-Ebola syndrome from those experienced by the general population in Liberia.

When Fallah presented the first findings from the study in February, he had grim numbers: 60 percent of the approximately 1,000 virus survivors in the study reported eye problems, 53 percent said they suffered muscle aches and joint pain, and 68 percent reported neurological problems. His team dug deeper to learn what kind of damage the virus can inflict on the nervous system. At a meeting of neurologists in April, they reported that nearly three quarters of Ebola survivors suffered headaches, 72 percent had depression, and more than half suffered memory loss and difficulty walking.

One in every four or five survivors had changes to the eye affecting vision. When Fallah's team looked more closely at those survivors, they found 10 percent had uveitis, a swelling of the middle layer of tissue in the eye wall.

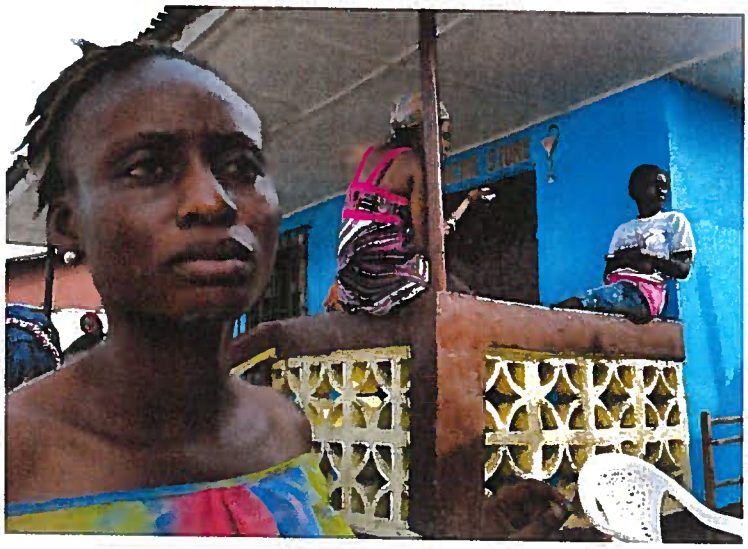
The vision problems drew his attention early in the research. "We saw as the war went on—I mean, as the epidemic went on—that there were different manifestations among survivors, and that would drive us to do more in-depth substudies," he says. "And it was clear that the first target should be the eye."

Fallah looked to previous studies of Ebola survivors dating back to the 1990s and found that many described eye problems in the convalescent phase. After an outbreak in the Democratic Republic of the Congo in 1995, doctors examined 20 survivors,

Illustration by Shizuka Aoki

some of them more than two months postinfection. Four were found to have eye pain, sensitivity to light, loss of visual acuity and uveitis. After another outbreak, this one in Uganda in 2007, 49 survivors were followed for more than two years. Along with memory loss, joint pain, sleep disorders and hearing loss, these people reported blurred vision and pain behind the eyes.

More recently, a study of eight patients who were treated for Ebola in U.S. hospitals found that all suffered various symptoms of post-Ebola syndrome up to four months after leaving the hospital. Six had psychological problems, including depression, anxiety and memory loss, and five suffered eye problems, including blurred vision and pain. There was no doubt the syndrome was real. But the existing data offered little explanation for how the virus can cause these problems.



AFTERSHOCK: Josephine Karwah, who survived Ebola infection only to be afflicted by other symptoms, stands outside a store in her village of Smell No Taste, Liberia.

UNDERSTANDING THE DAMAGE

THIS KIND OF CONFUSION has happened before, with another virus: HIV. Back in the 1980s when researchers were puzzled by this new viral threat, they tried to understand its effects by applying what they knew about other diseases. The same process is happening with Ebola, says Avindra Nath, a neurologist and scientist at the NIH who works closely with Fallah.

Nath has spent the better part of three decades studying infections of the brain. Although Ebola is not a retrovirus like HIV, Nath believes that years of research invested in studying HIV and the body's response to the infection have jump-started our understanding of how Ebola affects the nervous system. "Ebola has benefited from HIV research. A lot of us involved with Ebola made our careers with HIV, so we are quickly adapting our knowledge and techniques to studying these patients," he says.

Nath wonders if the neurological symptoms in Ebola survivors are a direct result of the virus or, instead, are triggered by the immune system's response to the infection. HIV, for instance, infects immune cells called macrophages in the brain, prompting the release of cytokines, small proteins that are toxic to nerve cells. Studies in monkeys have shown that Ebola infects macrophages and can set off a massive "cytokine storm." (Cytokines, chemical messengers between cells, trigger inflammation.) That can bring on hemorrhaging throughout the body, including the brain, which could explain the memory problems, headaches and movement disorders Nath has seen in Ebola survivors.

As the neurologist looks to HIV for clues to how Ebola affects the brain, others turn to different viruses to understand another symptom: the extreme fatigue reported by Ebola survivors. Studies have shown that up to a quarter of patients with dengue fever and close to 40 percent of Epstein-Barr patients suffer fatigue after the acute illness. Inflammatory cytokines may be to blame. They can act on receptors in the brain to induce postinfection fatigue and loss of appetite.

Painful joints seem to be one of the more common symptoms of post-Ebola syndrome. In a study of survivors of the 1995 Congo outbreak, almost two thirds experienced joint pain two years after infection, and one third of a Ugandan outbreak's survivors suffered from joint pain two years later.

Lumps of immune system proteins that sit inside a joint like the hip or shoulder could cause irritation and swelling. Other components of the immune system, including antibodies, could explain or even act as a surrogate marker for joint pain. After the Congo outbreak, survivors who complained of painful joints were found to have higher antibody levels as compared with survivors who did not report joint pain. Another protein might be at work in causing joint pain, too: D-dimers, small chunks of protein that break off from blood clots, have been linked to joint pain in people recovering from other infections. Patients suffering joint pain after infection with the bacterium *Neisseria meningitidis* had high levels of D-dimers in their blood. Studies looking for D-dimer-level changes have not been done on Ebola survivors.

HIDING PLACES

AS FOR THE EYE DISEASE seen in many Ebola survivors, experts say it, too, could be a result of the immune response to the virus. Or, more ominously, the virus could be replicating in the eye long after it has been cleared from the blood. The eyeball offers a safe place for the virus to hide out, away from detection and interference by the immune system. In one survivor the eyeball was found teeming with Ebola. In September 2014 an American physician, Ian Crozier, fell sick with Ebola while working in Sierra Leone. Less than two months after he was discharged from a U.S. hospital, he felt pain in his left eye and noticed that its color had changed from blue to green. When doctors inserted a needle into Crozier's eye, they found more copies of the virus in his eyeball than had been in his blood when he was close to death weeks earlier.

The eyeball is not the only hiding place for Ebola. The testes, central nervous system and joint cartilage can act as sanctuary sites for a number of pathogens, including HIV. These vital structures are at risk of collateral damage when the immune system wages war on foreign invaders. So to protect themselves from the inflammatory response, they have adopted such clever mechanisms as immune-suppressing molecules and physical

SCIENTIFIC AMERICAN ONLINE Listen to Josephine Karwah talk about life after Ebola at ScientificAmerican.com/jul2016/josephine

Photograph by Seema Yasmin

barriers. These protective measures make them great hiding spots for viruses. Hidden reservoirs could explain how Pauline Cafferkey, a Scottish nurse who recovered from Ebola, fell sick nine months after her blood tested negative for the virus and again a year after she was first infected.

If the testes harbors Ebola, that could explain why the virus persists in the semen of some survivors for months, even after they are free of symptoms. At the beginning of the West African outbreak, the World Health Organization cautioned people to practice safe sex for at least three months after their blood tested negative for Ebola. That advice was based on the 1995 Congo episode where the virus was found in the semen of survivors 82 days after the onset of symptoms.

But during the West African epidemic, Ebola virus lived in the semen of some survivors for a much longer time, more than a year after acute infection. At the conference in Boston, Fallah reinforced these findings, saying the virus was found in the semen of Liberian Ebola survivors 18 months after infection. In some men, the virus disappeared from the semen and then reappeared over the course of the year. (The WHO now advises male Ebola patients to practice safe sex for a year and to get their semen tested repeatedly.)

In his Monrovia office, Fallah has a patient file that belongs to a woman whose son died of Ebola in November 2015. The family reported no contact with anyone sick with Ebola or any survivors, but Fallah believes otherwise. He thinks the mother may have had sex with a survivor, not realized that she was sick with Ebola and passed the infection to her son.

Fallah had previously investigated a case of Ebola that was most likely transmitted via sex. In March 2015 a woman who died from Ebola was found to have had sex with a man who had been discharged from an Ebola treatment unit six months earlier. Blood samples from the man tested negative for Ebola, but a semen sample tested positive.

Fallah furrows his brow when talking about the woman who contracted Ebola from a survivor. That the virus can persist after many symptoms stop—even after a patient's blood appears clear—makes him anxious for two reasons: if Ebola hides out in people who seem healthy, only to reappear from compartments deep within the body to make them sick and potentially contagious, it could spark more outbreaks.

But finding the viral genome or bits of viral RNA in the bodily fluids of survivors does not prove they are contagious, he adds. What really worries Fallah is the stigma that these new findings place on survivors. "It's bad enough with post-Ebola syndrome that they have these symptoms we can't explain—and for who knows how long," he says. "Survivors are going through enough. Now imagine people are scared of them for fear of catching the virus."

TRAGEDY IN THE WOMB

A FEW DAYS AFTER Josephine left the Ebola treatment unit in Monrovia, while she was sleeping in her bed in Smell No Taste, she woke just after midnight. This time it was not nightmares or headaches; it was cramping in her abdomen. She rose to use the bathroom, and when she wiped herself she saw blood on the tissue. Then her water broke. "Ophelia!" she called for her older sister. They phoned for an ambulance but were told none were available. So they called a radio station in Monrovia for help. No one came.

Josephine paced up and down her bedroom, stopping to press her palms against the wall when it felt like her stomach was tearing. At 5 A.M., she wrapped herself in a maroon lapa, a traditional Liberian saronglike fabric, and staggered out of the house. If help would not come to her, she would find help on the streets. The village was asleep, sunrise still an hour away. Josephine walked alongside her house, clutching the walls to steady herself. As she screamed, women came out of their houses. "Help me, please help me," she cried. But no one would come near her, fearful of touching the woman who had left the Ebola treatment unit only a few days ago. When she reached the house at the corner of the dirt road, Josephine could no longer walk. She fell to the ground, her back against the wall and felt the baby between her legs.

Five women approached, unwrapping their lapas as they walked. They formed a semicircle around her so the male onlookers could not watch her give birth. Josephine pushed and screamed, and Miracle was born. What a chubby boy, she thought, lifting the silent child to her chest. But Miracle was not breathing.

No one would touch Josephine. The women stared as she rocked her baby and sobbed into her chest. Only her brother came close to her. He took Miracle from her arms and wrapped the baby and placenta in a yellow towel, ready for burial.

Josephine's mother had been a midwife before she died of Ebola. "Why isn't she here to help me now?" Josephine lamented. In the weeks that followed, there were more questions: Did Ebola kill Miracle, or was it because nobody would help? Would the baby have lived if an ambulance had come? Was the virus still lurking in her body, and would it harm any future pregnancies?

On visits to the Kennedy Medical Center for her survivor study appointments, Josephine asks Fallah these same questions. One afternoon she sits in his office wearing a leopard-print shirt and matching head wrap, waiting for his response.

Fallah worries the uterus may be another sanctuary site for Ebola, offering the virus a safe place to hide and still affect the body. Perhaps it could reappear and infect others. Then he wonders if the stress of being an Ebola survivor can cause a woman to give birth to a stillborn baby in the street with people watching but no one helping. He thinks, "When you can no longer sell soap in the market, when you have to wrap your money in tissue to buy vegetables, when your boyfriend stops loving you because you are an Ebola survivor—what impact does that have on a person's body? What could that do to the unborn child?"

This is what goes through his mind, but when Josephine asks, he says: "I don't know, Josephine. We are trying to find out."

MORE TO EXPLORE

Possible Sexual Transmission of Ebola Virus—Liberia, 2015. A. Christie et al. in *Morbidity and Mortality Weekly Report*, Vol. 64, No. 17, pages 479–481; May 8, 2015.

Persistence of Ebola Virus in Ocular Fluid during Convalescence. Jay B. Varkey et al. in *New England Journal of Medicine*, Vol. 372, pages 2423–2427; June 18, 2015.

Serious and Common Sequelae after Ebola Virus Infection. Luke Hunt and Victoria Knott in *Lancet Infectious Diseases*, Vol. 16, No. 3, pages 270–271; March 2016.

FROM OUR ARCHIVES

Ebola War. Helen Branswell; March 2015.

scientificamerican.com/magazine/sa