Why did Ellie in the Last of Us not succumb to Cordy, the zombie virus? Stem cells might explain it, and that could yield real-life vaccines

It’s unsettling to watch *The Last of Us*, in which parasitic fungi turn humanity into flesh-eating zombies, just as the CDC reports a new scary fungal scourge, “*Candida auris*: A Drug-resistant Germ That Spreads in Healthcare Facilities.”

*The Last of Us* recently wrapped on HBO, but is based on a video game from 2013. So, a caveat: We haven’t played the game, so our hypothesis that stem cells come to the rescue may not be original. But it does make scientific sense. Media coverage of the series has been intense. The logline for the show reads:

Out west, scientists will develop a vaccine from Ellie’s apparent natural resistance, deduced from the fact that a healed boo-boo on her arm indicates that fungi are living in her brain without killing her.

Inkoo Kang in *The New Yorker* calls the series “an anthropological travelogue of post-catastrophe subcultures, teasing out the disparate ways that survivors rebuild mini-societies and create new alignments of power.” That pretty much defines the subgenre of apocalyptic science fiction.

What will happen to the few survivors? How, exactly, have they escaped the torturous filaments of fungi that pour from orifices and burst from the brains and bodies of the zombie victims?

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Meet Cordy, the ‘Killer Fungus’

Fungi come in spectacular colors and diverse body forms. They have their own taxonomic kingdom, and at the genome level are more closely related to us than are plants. Fungi may be many-celled like mushrooms, single-celled like yeasts, or a mix. They are uncommon enemies in the sci-fi world, compared to bacteria and viruses that we can’t even see.
The enemy in *The Last of Us* is *Ophiocordyceps unilateralis*, aka cordyceps, aka “zombie-ant fungus.” An infected person can die from the infection in minutes, or walk around as a zombie for decades. The video games offer fungal types: clickers, bloaters, runners, stalkers, shamblers, and a rat king. The TV series doesn’t focus much on the zombies; their appearances are fleeting except for one scene in which a huge gang rushes up from underground.

As the series took off, media coverage trotted out mycologists, used to being consulted about fungal delicacies or hallucinogens, to reassure us that Cordy and its brethren prefer carpenter ants and spiders to burrowing into human brains. Interestingly, an article in *WaPo* reported that bits of Cordy are in health supplements, including a $200 smoothie that Gwenyth Paltrow pitches.

More seriously, a report in *Clinical Toxicology* describes 60 people in Vietnam who ate cicadas and unintentionally ingested the fungi. They experienced dilated pupils, dizziness, vomiting, salivation, a stiff jaw, inability to pee, seizures, delirium, hallucinations, sleepiness, and coma.

**Apocalypse Now**

The classic tale of humanity’s near-end is Noah’s Ark, in which a chosen few get on the boat. A natural disaster – like a flood or something celestial crashing into Earth – is one common theme. Another is us causing our own demise, such as the aftermath of nuclear war in Robert McCammon’s 1987 novel *Swan Song*. In yet another end-of-humanity plot, a pathogen or parasite decimates much of humanity.
In Michael Crichton’s *The Andromeda Strain*, from 1969, a felled satellite deposits extraterrestrial microbes in Arizona. The aliens kill people with massive instant blood clotting. A yowling infant and an old man survive because the pH of their blood lies outside the range of what the pathogen requires – the baby’s is high (alkaline) due to hyperventilation from screaming, and the man’s low (acidic) from his addiction to Sterno, the canned stuff used to warm food trays misused to substitute for alcohol.

Similarly, in Emily St. John Mandel’s haunting *Station Eleven*, people in an airport terminal are sealed off from a sudden and fast-killing flu pandemic.

Dean Koontz’s 2004 novel *The Taking* conjures a spooky fungal fog. Alas, the tale is a letdown compared to the anatomical detail of *The Last of Us*. Koontz’s website doesn’t mention fungi, and a planned miniseries never happened. The fungal invaders are checking out our planet for colonization, killing many adults. They mysteriously disappear, and society blooms anew from the young, presumably innocent human survivors. Noah’s Ark redux?

**Isaac Asimov’s Law**

*The Last of Us* follows Isaac Asimov’s law of science fiction: “change one thing.” A mutation alters the “host range,” the species that a pathogen can infect – insects and spiders for natural Cordy. David Attenborough’s *Planet Earth* depicts the fungi making infected bugs stagger around as filaments suddenly snake out of their heads and then burst from the entire body. Only stabbing or removing the victim’s head halts the fungi.

Fortunately, natural Cordy in real life doesn’t get into our heads.
The mutation that switched Cordy’s dietary preference from ants to us transpired in a grain-processing factory where workers who inhaled spores went nuts. The pathogen, infiltrating bread products, spread quickly among humans. Donuts alone could have probably doomed the world.

Another tweak was necessary for the sake of the screen. Fungi spread in spores, but that would have entailed masking the humans, which we’re all so tired of. So, instead of spores floating on a gentle breeze, reimagined Cordy is blood-borne. Zombies bite their victims, but not to drink blood. Instead, they dine on flesh, established in 1968 in Night of the Living Dead, and prefer brains, established in 1985’s Return of the Living Dead. That’s presumably why it takes a blow to the noggin, where the fungi home and gather, to fell a Cordy zombie – like killing a bunch of wildebeest around a pond.

And so Cordy lives in Ellie’s brain without killing her, like bats incubating coronaviruses without getting sick. But what is the basis of her resistance? First, the facts.

Plot recap

The Last of Us opens with a talk show, circa 1968. The topic: fear of a new disease sweeping the planet. Will it be a virus or a bacterium, the usual suspects?

Neither, holds out one expert; it'll be a fungus. “Some fungi seek not to kill but to control,” he says, evoking brain-affecting biochemicals such as LSD and psilocybin.

Fungi can infect our brains and cause hallucinations. Fungi can devour their hosts from within while preventing decomposition. Penicillin! Mutant fungi can burrow into our brains! They have one unified goal: spread to infect any human alive.

The scene fades into a backdrop of feathery mycelia, the threads of a fungal body.

Facts: Pathogens don't have goals and fungi (like Candida and Histoplasma) don’t enter human brains, just a lining membrane, causing meningitis. But the talk show guest’s warning effectively sets the stage for what will unfold.

Then it's 2003. We meet protagonist Joel Miller, a construction worker, and the initial mayhem begins. Sirens. Warnings to stay indoors. A dog howls, for non-humans always sense things first, especially aliens or mutants. Helicopters circle.

Next door, elderly Mrs. Adler devours her daughter’s neck, as mycelia meander menacingly from her mouth.

“It’s a virus! Some kind of parasite!” shouts Joel, suddenly a microbiologist.
Panic ensues. Shots are fired. Cars crash. Crowds smash windows and flee. Looting. Screaming. A plane nosedives towards main street as people stagger around. **Zombies!!!**

The world turned upside down over a weekend. On Friday, September 26, 2003, people started attacking each other. And by Monday, “everything was gone.” Over the ensuing weeks, remnants of the military herd survivors into government quarantine zones (QZs).

Then it’s 2023, in a destroyed Boston reminiscent of the dreary scenes from The Handmaid’s Tale. As military roam the destroyed streets of Beantown, a loudspeaker drones:

> Observe mandatory curfew to fight infection and insurrection.

In a clichéd abandoned subway tunnel scene plucked from *Planet of the Apes*, a fungal-exploded corpse hugs a wall, like Da Vinci’s Vesuvian Man fringed with mycelia.

A girl is wheeled into a ramshackle hospital, where signs from **FEDRA** (the Federal Disaster Response Agency) read “Report Signs of Cordyceps Infection: coughing, slurred speech …. “like warnings about COVID. Outside, descendants of zoo creatures roam, skyscrapers are rubble, and mass graves ring the destroyed cities.

Vignettes depict the societal aftermath. People who left the QZs and are captured hang. Opiates are currency. Kids go to military schools. Curfew hours are posted, as rooftop shooters enforce martial law.

Outside the cities, zombies hide. You never know where one will be lurking, always primed to leap and bite. Amid the destruction, fungal threads emanating from victims’ orifices knit the corpses into a superorganism of sorts. A quick close-up of the enemy is reminiscent of the thing that burst from Sigourney Weaver’s abdomen in *Alien*.

The rebels against FEDRA, called Fireflies, are frantically protecting Ellie. Joel must first free her from where she’s imprisoned, like Dorothy in the castle of Oz. Amid explosions, they eventually escape Boston and head west, forced to use paper maps since Google is kaput. Emotional vignettes unfold. Entire episodes focus on single stories.

Eventually Joel and Ellie continue west and meet other survivors. A glimpse of a small cult reveals chunks of red meat for dinner coming from former survivalists.

When the main narrative returns, loyalties have changed, and suddenly the Fireflies want Ellie’s brain, part unnamed, to find out how she is protected. Ellie “has a ‘purpose more than anyone imagined,” utters Firefly Marlene. **She’s been infected, but not a zombie! Ellie is immune!**

And that somehow holds the secret to developing a vaccine. How does her body keep the fungus at bay?
How Ellie became immune: Our hypothesis

The final episode depicts **Ellie’s birth**. Her very-pregnant mom Anna, played by video game star Ashley Johnson, races through woods amid zombie shrieks. She enters a farmhouse and hauls herself upstairs as her water breaks. Lodged against a wall holding a knife, she bears down as a crazed zombie crashes through the door and bites her face and neck. Baby Ellie is propelled into the world, but — and this is crucial — the pulsating, winding umbilical cord remains intact for a minute or two, linking her to Anna, who is struggling with the zombie at her throat. Stuff is getting into Ellie.

Only after Anna has stabbed the zombie in the head and it finally let’s go and backs away does she lean down, gaze at Ellie between her legs, and cut the umbilical cord. When Marlene bursts in, Anna yells, “I cut it before I was bit!” thereby protecting baby Ellie.

Clearly, hematopoietic (blood-forming) stem cells had time to flow from Anna to Ellie through the cord. Since these cells migrate to the bone marrow and give rise to all blood cell types, Ellie’s white blood cells (B lymphocytes in particular) would have been primed to crank out zillions of antibodies upon encounter with Cordy. And that’s why Ellie is immune.

Real evidence for a stem cell plot

“Training the Fetal Immune System Through Maternal Inflammation—A Layered Hygiene Hypothesis,” in *Frontiers in Immunology*, proposes that the cord and bone marrow stem cells maintain a biological “memory” of pathogens that a pregnant woman has encountered, displaying bits of fungal proteins, like flags. The idea builds on the “hygiene hypothesis” that attributes a powerful immune response to early exposures to pathogens. They write:

> We argue that the hygiene hypothesis should encompass how microbial exposure during pregnancy fosters immune development through ‘training’ immune output at the stem cell level.

In fact, lots of things happen to a fetus as the components of the future immune system catalog “self” cell surfaces so that “non-self” surfaces – such as from pathogens or transplants – can later be recognized, distinguished, and attacked.

To get Ellie’s protective stem cells, all that was needed was a blood sample! And then the festooned fungal flags could be used as a template for a vaccine.

But our young protagonist finds herself strapped down as an evil scientist wielding a drill closes in to remove her brain, explaining that her body “makes normal Cordy think she’s them. Her body makes chemical messengers to make Cordy accept her. There is no one else.” Why her brain? And what chemical messengers? Was the talk show guest yammering on about penicillin, LSD, and psilocybin prophetic after all?

Here’s what **is** logical: Transfer of stem cells at a birth during which the laboring woman is bitten by a towering fungal zombie may be a scenario so unusual that Ellie indeed may be the only source of
salvation for humankind.

We’ll have to wait for season 2 to find out.

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