INNOVATION

What Happens When Antibiotics Stop Working?

More and more, many previously effective medications are no longer able to fight off the germs that are making us sick, leading to millions of deaths each year. For World Antimicrobial Awareness Week, learn what Johnson & Johnson is doing to combat this health threat around the world.

By **Barbara Brody**, November 18, 2022

If you've ever had strep throat or a urinary tract infection (UTI), chances are your doctor prescribed an antibiotic and your symptoms quickly vanished. But what would happen if the medicine designed to stop bacterial infections like these stopped working?

That's already a reality when it comes to a number of illnesses caused by antibiotic-resistant bacteria, which have evolved to outlast exposure to the drugs developed to treat them.

"In the last decade or so, the 'silver bullet' antibiotics for many infections have become less reliable," says Jan Poolman, Ph.D., head of Bacterial Vaccines Discovery and Early Development and Disease Area Stronghold Leader, Bacterial Vaccines at the Janssen Pharmaceutical Companies of Johnson & Johnson.

The biggest driver of the problem: overuse and misuse of antibiotics in humans, as well as in agriculture.

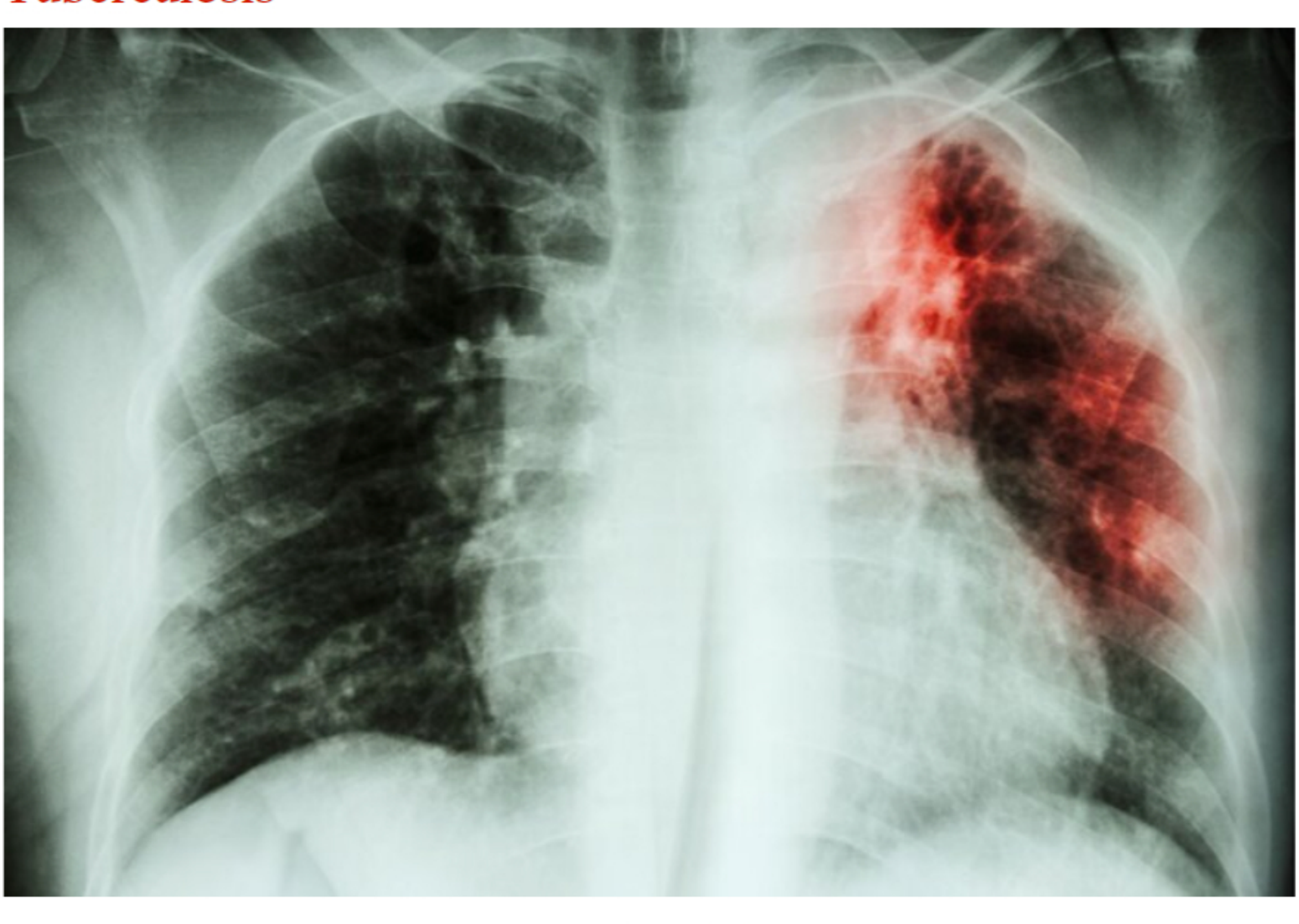
Antimicrobial resistance (AMR)—which refers to the ability of any microbe (bacterium, virus, parasite or fungus) to survive the drugs developed to kill them—is a serious and growing threat. In the United States alone, more than 2.8 million antibiotic-resistant infections and more than 35,000 related deaths occur each year. The Centers for Disease Control and Prevention (CDC) currently maintains a list of 18 treatment-resistant bacteria and fungi, including five they deem urgent threats (such as *Clostridioides difficile*, which can lead to severe diarrhea and intestinal inflammation).

Globally, the problem is even greater: AMR is one of the top 10 public health threats, according to the World Health Organization (WHO), which keeps a list of antibiotic-resistant priority pathogens. Annually, 1.2 million deaths are attributable to AMR, and 4.9 million deaths are associated with AMR.

"If we don't tackle antimicrobial resistance now, by 2050 we could find ourselves facing a new pandemic of sorts with serious drug-resistant infections impacting people on multiple continents," says Martin Fitchet, M.D., Global Head, Global Public Health at Johnson & Johnson.

The promising news? Johnson & Johnson is already hard at work tackling this threat, from developing new treatments and vaccines to collaborating with other companies innovating to fight AMR. Here's a look at this work in action.

Developing a Multipronged Plan to Curb Drug-Resistant Tuberculosis



An X-ray of TB in the lungs

Despite an existing tuberculosis (TB) vaccine, drug-resistant tuberculosis (DR-TB) has become one of the biggest contributors to AMR worldwide, especially in resource-limited settings. In India, China, Eastern Europe and beyond, it is no longer unusual to find strains of TB that are multidrug-resistant, meaning they're resistant to two of the most important first-line drugs. Some forms are considered "extensively drug-resistant," which means they've acquired mutations that enable them to survive even many newer, second-line drugs, says Alexander Pym, M.D., Ph.D., Senior Director, Global Public Health R&D, Janssen.

"If you go back 10 years, the treatment regimen for DR-TB lasted 18 months and required taking six or seven drugs. It caused a lot of side effects, and it didn't work at all against certain forms," says Dr. Pym. Many patients died as a result.

Then, in 2012, the U.S. Food & Drug Administration (FDA) approved the first new medicine for TB as part of a combination therapy to hit the market in 50 years. The medication, developed by Janssen, allows many patients with DR-TB to take fewer drugs in combination and be treated for a shorter duration, leading to better outcomes with fewer side effects.

The medicine is now approved in over 70 countries, and the WHO recommends its use as part of a core component of all-oral DR-TB treatment regimens. Now, three out of every four DR-TB patients treated are enrolled on an all-oral regimen containing Janssen's medicine. "It has revolutionized the treatment of DR-TB," says Dr. Pym.

Of course, the fight is far from over. An estimated 1.5 million people per year die from TB—more than the number who die from HIV/AIDS and malaria combined. One part of the challenge is getting treatment to people in underserved areas where access to healthcare is limited—and ensuring its appropriate use to prevent resistance from developing.

"We have taken innovative steps to scale access to our medicine for multidrug-resistant TB worldwide, including through the Stop TB Partnership's Global Drug Facility, where it is available to more than 135 low- and middle-income countries," says Ana-Maria Ionescu, Global TB Franchise Lead, Johnson & Johnson Global Public Health. "To date, we have delivered more than 500,000 courses of our treatment to 157 countries around the world. As part of our broader stewardship efforts, we have also supported the training of more than 80,000 healthcare providers to ensure our medicine is being used safely and correctly, with the goal of enabling children and adults diagnosed with DR-TB to continue to receive effective care."

Of course, medication can only help if you know you have TB. The disease often goes undiagnosed—and therefore untreated—leading to millions of people with TB putting themselves, their families and their communities at risk. So Johnson & Johnson is taking part in several key initiatives that aim to resolve that problem. These include launching a youth-focused behavior-change campaign in India called "Be the Change for TB" to raise awareness about TB symptoms and encourage people to seek early care, working with Aquity Innovations in South Africa to better identify and diagnose children and adolescents with DR-TB and serving as a founding partner of the Ending Workplace TB initiative, which was launched in January 2020 to help combat TB through the influence of private businesses in countries impacted by the disease.

Pioneering New Vaccines That Protect Against Resistant Bacteria

E.coli colonies in a petri dish

You've probably heard of *E. coli* (short for *Escherichia coli*), a bacterium that colonizes the healthy gut and can provide functions to the human body, such as the production of vitamin K. Approximately 90% of people carry *E. coli* without any noticeable negative effects.

On the other hand, there are pathogenic strains of *E. coli* that can cause disease in the digestive system, such as diarrhea and inflammatory bowel disease. *E. coli* strains that cause diarrhea often produce toxins and are usually caused by ingestion of contaminated food. *E. coli* strains that cause disease outside of the digestive system are called extraintestinal pathogenic *Escherichia coli* (ExPEC), which most commonly causes urinary tract and intra-abdominal infections.

ExPEC can cause bloodstream infections that can lead to sepsis, which is the body's extreme and dangerous reaction to infection. Sepsis can be fatal—particularly in older adults, since the immune system naturally becomes less effective with age. *E. coli*-related bloodstream infections and sepsis are referred to as invasive *E. coli*/ExPEC disease (IED).

ExPEC can be multidrug resistant, which means that what starts as a bladder infection could escalate to an infection that damages the kidneys, enters the bloodstream and becomes life-threatening.

Staphyloccous aureus (S. aureus) is another bacterium that's commonly found in the body—in this case, on the skin or in the nose—but can become dangerous if it makes its way into the bloodstream. *S.aureus* often starts as a skin infection. And some strains, such as MRSA (Methicillin-resistant *S. aureus)*, are drug-resistant. In general, *S. aureus* bloodstream infections are less common than ExPEC, but the severity of invasive *S.aureus* disease (ISD) is higher as compared to the already high severity of IED.

"The antibiotic crisis is increasing, and in some countries we're now seeing resistance to the 'last resort' antibiotics for *E. coli*," says Poolman. "We really need to act as a society. Vaccines, in addition to antibiotic stewardship and new therapeutics, can be part of the solution."

Janssen researchers have already created an investigational vaccine designed to ward off ExPEC-related IED. The vaccine, which is currently in phase 3 clinical trials, uses the outer coating of sugar-like components in an optimized vaccine formulation to maximize the immune response. It's targeted at people age 60 and older and strives to prevent infection by the strains most likely to lead to IED.

Research into an *S. aureus* vaccine isn't quite as far along—"this is a very smart bacterium," Poolman says—but his team is committed to using its deep understanding of the science related to *S. aureus* infectious disease mechanisms to bring a vaccine to fruition.

Using Medical Device Innovation to Reduce the Risk of Surgical Site Infections

Ethicon's PLUS Antibacterial Sutures

Your skin serves as a protective barrier, and any time it's compromised—as it is when you have a surgical incision—the door is open to the possibility of infection. "The operating room and equipment are made sterile, but whenever there are human beings around, complete sterility is a challenge. It is impossible to sterilize a person," says Liza Ovington, Ph.D., consulting Franchise Medical Director for Ethicon, a Johnson & Johnson MedTech company.

On average, 2 to 4% of patients who have an inpatient surgical procedure in the United States will develop a surgical site infection (SSI).

That might not sound like much, but it adds up to hundreds of thousands of infections each year in just one country.

Additionally, there is a growing risk of AMR infections that are a cause for concern. As AMR rates rise, the chance that a post-surgical infection could be caused by a resistant pathogen also increases, and those infections become more difficult to treat.

"Infection prevention and control is essential in curbing AMR. If you reduce the risk and number of SSI, you may reduce the need to treat patients with antibiotics, and the most significant cause of AMR is the overuse of antibiotics," says Ovington.

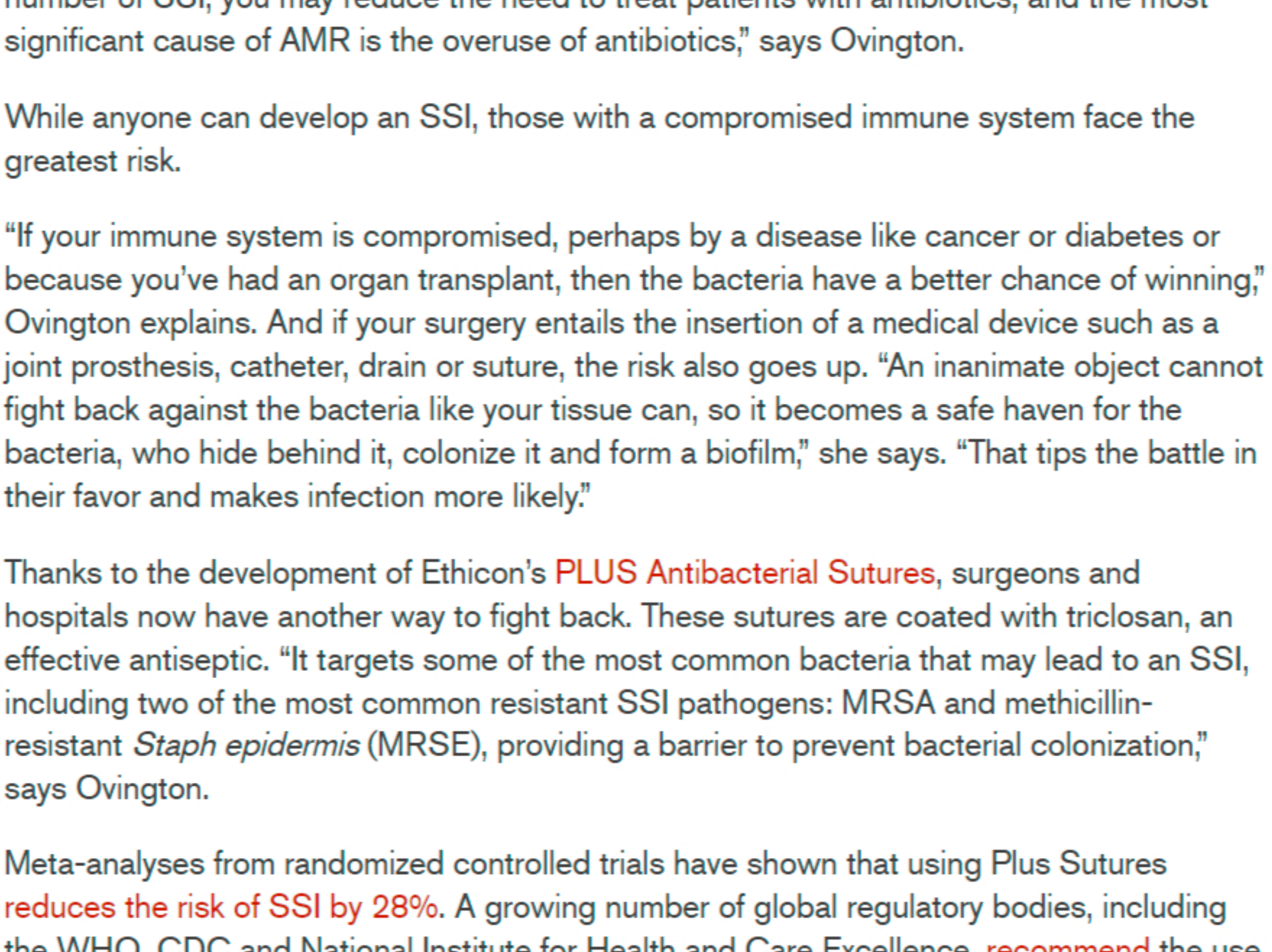
While anyone can develop an SSI, those with a compromised immune system face the greatest risk.

"If your immune system is compromised, perhaps by a disease like cancer or diabetes or because you've had an organ transplant, then the bacteria have a better chance of winning," Ovington explains. And if your surgery entails the insertion of a medical device such as a joint prosthesis, catheter, drain or suture, the risk also goes up. "An inanimate object cannot fight back against the bacteria like your tissue can, so it becomes a safe haven for the bacteria, who hide behind it, colonize it and form a biofilm," she says. "That tips the battle in their favor and makes infection more likely."

Thanks to the development of Ethicon's PLUS Antibacterial Sutures, surgeons and hospitals now have another way to fight back. These sutures are coated with triclosan, an effective antiseptic. "It targets some of the most common bacteria that may lead to an SSI, including two of the most common resistant SSI pathogens: MRSA and methicillin-resistant *Staph epidermis* (MRSE), providing a barrier to prevent bacterial colonization," says Ovington.

Meta-analyses from randomized controlled trials have shown that using Plus Sutures reduces the risk of SSI by 28%. A growing number of global regulatory bodies, including the WHO, CDC and National Institute for Health and Care Excellence, recommend the use of triclosan-coated sutures as an effective way to reduce the risk of SSIs as part of a care bundle.

Joining Other Companies to Invest in the AMR Action Fund



A close-up look at bacteria

While Johnson & Johnson is clearly making strides against AMR, this isn't a problem that any one company can solve by itself. That's where the AMR Action Fund comes in.

Since its launch in 2020, the Fund has "assembled over $1 billion ready to invest in the development of novel antibiotics," says Dr. Fitchet, who serves as a board member.

At first glance, the Fund's goal of spurring the creation of two to four novel antibiotics by 2030 might seem modest. But creating novel antibiotics is no easy feat, in part because current global market conditions do not incentivize their development.

"About 20 years ago, interest in producing antibiotics started to wane because of guidelines aimed at stemming drug resistance," Dr. Fitchet explains. "Many companies no longer want to invest in antibiotics, yet antibiotics are becoming increasingly hampered by resistance," which means developing new ones is critical, he adds.

To accelerate their development, the Fund is sharing money and scientific expertise with select biotechnology companies. It's also seeking ways to make it easier and more profitable for companies to bring new antibiotics to market, such as by encouraging regulatory agencies to prioritize review of potential new antibiotics.

Global collaboration is key, Dr. Fitchet adds, citing COVID-19 vaccines as an example. "Scientists shared the genetic code of the virus; regulators came together and worked very closely with innovators to get really effective vaccines to market very quickly. The message is clear: If you work together, amazing things can be done. When it comes to fighting AMR, or any urgent healthcare need, no one can do this alone."