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EXPERTS IN GLOBAL INVESTING

Superbugs are outsmarting antibiotics

A market failure means pharmaceutical companies are failing to address the threat.

In 1938, Ernst Chain,[1] a German-born biochemist working at Oxford University, found an article on penicillin written nine years earlier by UK bacteriologist Alexander Fleming.[2] In 1928, by fluke, Fleming noticed a zone around an invading fungus on an agar plate in which the bacteria did not grow. After isolating the mould, Fleming identified it as belonging to the Penicillium genus.[3]

But doing anything more with the unstable compound was beyond Fleming's skills, which is where Chain stepped in. He proposed to his supervisor, Australian pathologist Howard Florey,[4] that they isolate, purify and test the compound to see if it could kill microorganisms without harming their host. Florey, seeing penicillin's potential, assembled a team that in 1939 oversaw experiments where only treated mice survived.

By 1941, the group was experimenting on sick people. Because a UK stretched by war was incapable of producing enough penicillin, Florey travelled to the US to convince drug companies and officials to produce penicillin. When the US was drawn into World War II later that year, the government took over the mass production of penicillin to ensure the drug would be available for Allied forces. (It was by 1943).[5]

In 1942, Fleming, who obtained some of the Oxford team's scarce penicillin, saved a UK woman who was dying of an infection. The Times of the UK published the feat, without referring to Fleming or Florey. Fleming's boss wrote to the newspaper praising Fleming who boasted in press interviews while Florey refused to speak to the media. Thus, many people today wrongly believe Fleming gifted penicillin to the world, even though Chain, Fleming and Florey equally shared the Nobel Prize for Physiology or Medicine 1945 and those in the know thought a self-promoter stole the credit from Florey.[6]

What matters more is Florey's vision led to one of history's key medical feats. The drug's breakthrough advantage was how cheap it was to produce. The antibiotic became a worldwide cure and boosted life expectancy, mainly by reducing childhood deaths. By 1954, for instance, pneumonia's death toll on US toddlers had plunged 75% from 1939 levels.[7]

Penicillin's wonders inspired the development of other affordable antibiotics that could combat an ever-wider array of ailments.[8] As antibiotics, antifungals, antiviral and other drugs that are grouped as antimicrobials were developed, optimists dared talk of a world without deadly infections.

What could go wrong? Four things. First, in the advanced world where prescriptions are regulated, doctors overprescribed and misused antimicrobials. Second, in the unregulated emerging world, people can buy antibiotics (many counterfeit)[9] at pharmacies without prescriptions and even find them at markets and shops. People thus mistreat or overtreat themselves with these medicines because it's cheaper and easier than seeing a doctor. The result is that up to 70% of human use may be inappropriate.[10] Third, 80% of antibiotic use worldwide is to fatten farm livestock and prevent livestock infections.[11] Efforts to curb such misuse have failed.[12] The fourth problem is that antibiotic and antifungal residue is too prevalent in third-world drug-making hubs such as India's Hyderabad.

The result? The natural immunity microbes develop over time has accelerated. 'Superbugs' have built resistance to antimicrobials and global deaths from drug-resistant bugs are mounting. Before antibiotics, only about one in 10 million bacteria would prove resistant to antibiotics. Now, given that bacteria vulnerable to antibiotics can't survive, it is estimated that up to 90% of bacteria causing infections are immune to previously effective antibiotics.[13]

As for deaths, a study led by researchers from the University of Washington out in January attributed 6.22 million deaths worldwide in 2019 to drug-resistant microbes (of which 1.27 million were a "direct result" of superbugs).[14] A 2016 UK-government-commissioned study predicted that as "routine surgeries and minor infections will become life-threatening once again" deaths would reach 10 million annually by 2050 – by when the accumulated cost of superbugs would be US$100 trillion due to the need to use costlier treatments and longer hospital stays to save lives.[15][16]

The University of Washington study suggested five ways to combat superbugs. First, improve sanitation and hygiene, especially for water, to limit infections. Second, prevent infections through vaccinations where possible. Third, reduce antimicrobial use in animals. Fourth, minimise the misuse of these drugs with people. Fifth, boost investment to find drugs that can defeat superbugs.[17]

Here lies a key handicap in the battle against infections that fail to respond to treatment. Few superbug-busting drugs are appearing because investment in the field is minimal compared with other spheres of public health. Only about US$1 billion a year worldwide is spent on research to combat superbugs compared with US$50 billion a year tackling HIV/AIDS in low- and middle-income countries[18] or an estimated US$157 billion to be spent on covid-19 vaccines through to 2025.[19]

Pharmaceutical companies, which rely on prescription-based sales for revenue, aren't investing enough because they can't recoup an adequate return for three reasons. First, the cheapness of antimicrobial generics makes hospitals reluctant to pay high prices for superbug stoppers. Another problem is that medical facilities use new superbug-busters as a fallback when generic treatments fail. A third hitch is that antimicrobials are taken for a short time only, whereas profitable drugs are usually ones that people take daily for years. The outcome is that sales volumes are too small to make new drugs profitable. As a sign of how fragile are the economics in this sphere, Big Pharma players have abandoned the superbug fight and smaller antibiotic-development companies struggle to survive, even after gaining approval for their finds.

A crisis around superbugs is building. A market failure means capitalism can't yet derive a solution to diffuse a foreseeable catastrophe. Governments need to do more when it comes to funding research and offering financial incentives for private enterprise because only alarming levels of deaths will improve the economics. Even though the pharmaceutical industry is likely to solve the problem in extremis, it would be too late for millions of people.

To be fair, policymakers are trying to stop the misuse of antibiotics – but with little success in the emerging world. To be fair again, authorities have tried to help develop superbug-busters. The PASTEUR Act of 2021 before US Congress provides incentives for research.[20] The Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator, or CARB-X, which is a public-private initiative, is spending US$480 million from 2016 to 2022 to solve the problem.[21] A UK initiative unveiled in April could become a global template for encouraging research because it offers to pay drug companies a fixed fee for supplying antibiotics.[22] Success might come but moneywise these efforts don't compare with the billions Big Pharma spends on research in lucrative areas. Some superbugs arise out of nature so antibiotic misuse and overuse are not to blame for all of them.[23] Doctors are finding novel ways to combat superbugs. Phage therapy, the use of specific viruses to target bacterial infections, is one of them.[24]

But greater efforts are needed. Surely in the medtech age, someone can discover a cure for superbugs. No one will care if self-promoters pinch the credit.

A FLAWED MODEL

Before 1870, US pharmacies were virtually unregulated. Chemists sold remedies without prescriptions, heavily promoted quack cures and sold drugs now illegal such as cocaine, heroin and opium. Doctors overprescribed doses to be obtained from pharmacies because they knew chemists watered down medication. Newspapers so relied on advertising by drug companies they downplayed medical mishaps. By 1906, the harm to society was prominent enough to warrant the passing of the Pure Food and Drug Act, the first step in the US to regulate drug marketing.[25]

The act gave rise to the Food and Drug Administration, the US's oldest consumer-protection agency. Tougher laws in 1938 meant new drugs required the body's approval and some medicines required doctor prescriptions.[26] This doctor oversight meant the big drug companies founded after World War II aimed their advertising at doctors, not the public – by 1961, about 60% of the advertising budgets of the 22 biggest drug firms was targeted at doctors.[27] Thus formed the pharmaceutical business model, whereby drug companies identify promising molecules, test them, and, once gaining approval, target the medical industry for sales. Success is a 'blockbuster drug' that reaps annual sales topping US$1 billion year after year.

The model has provided the world with many wonder drugs but it's flawed at the same time. A major disadvantage is that many discoveries are so expensive as to be unaffordable. Another is a slowing rate of discovery of effective medicines – most of the breakthroughs such as antibiotics, the polio vaccine, heart treatments, chemotherapy and radiation for cancer were discovered between 1940 and 1980.[28] In terms of antibiotics, no major advances have come since the 1980s[29] – new drugs are variations rather than breakthroughs.[30]

A third disadvantage with the pharmaceutical business model is that the economics of certain spheres of medical research are so poor Big Pharma avoids the area and specialist start-ups can't survive. Such is the fate of research against superbugs.

In 2018, Novartis joined Allergan of the US, AstraZeneca of UK-Swedish origins, GlaxoSmithKline of the UK, The Medicines Company of the US and France-based Sanofi in quitting the fight against infections.[31]

One comfort when Big Pharma companies dodge the superbug fight is they often sell their infection-disease research units to small biotechs. The Medicines Company, for instance, in 2017 sold its portfolio to Melinta Therapeutics of the US,[32] while AstraZeneca in 2018 hived off part of its antibiotic research to Entasis Therapeutics[33] (which just announced a promising cure).[34]

But Little Pharma is besieged. The World Health Organisation says the smaller and mid-sized companies that dominate the preclinical and clinical antibiotic pipeline are "struggling to find investors to finance late-stage clinical development up to regulatory approval". As such, many companies disappear and so do their finds. Of 15 new antibiotics approved in the US in the decade to 2020, five were shelved as companies applied for bankruptcy or were sold.[35]

Take, for example, the experience of Achaogen. The US company collapsed in 2019 after spending about US$1 billion over 15 years to win Food and Drug Administration approval for Zemdri, a drug for hard-to-treat urinary tract infections and one the World Health Organization classes as an essential medicine.[36]

Somehow Zemdri is still available. To overcome the overall market failure that prevents the discovery of similar feats, the OECD said in 2017 it would take an extra US$500 million per year over a decade to make available four new 'first-in-class' antibiotics. Governments need to make this happen, just like the US government, thanks to Florey's efforts, ensured enough penicillin for the military in World War II.[37]

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