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The war against evolution

Eoin Treacy, Investment Director

Penicillin has been a miraculous technological advancement.

What else can you call something that is estimated to have saved around 200 million lives?

But its widespread use – and that of other antibiotics – contains imbedded within it a bitter and potentially cataclysmic irony. As long ago as 1945, it dawned on Alexander Fleming that our greatest weapon against bacteria could give way to an incredible vulnerability.

A bacterial super-soldier...

> ***"There is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."***

Over the last five years or so, the long-feared problem of antibiotic resistance has been well documented.

But few people realise the true dangers, cost and potential opportunity it brings for whip-smart medi-tech companies.

That's what I'd like to unpack for you today.

Hyper-evolution

When my children asked me about evolution I showed them **this video** of a giant petri dish at Harvard Medical School where over the course of 11 days bacteria are shown to evolve through layers of antibiotics whose intensity increases by ten times at each fresh barrier.

It is the single best illustration of evolution at work I know of and raises some very important questions for the healthcare sector. Let me repeat it though. It took bacteria 11 days to evolve immunity to a 1,000-fold antibiotic dose. 11 days.

As noted above, by the1950s Alexander Fleming noticed that bacteria were exhibiting resistance to penicillin, tetracycline and erythromycin. **Here's a nice little primer on the rise of the super-bug.** Even so they were relatively new weapons against microbial infection and were so effective that use ballooned.

That set up the condition where microbial immunity to them could develop. The tit-for-tat arms race between bacterial immunity and the breadth of potential solutions we have available has been going on for decades and the bacteria are winning.

In a sense, this is a war against evolution itself. We are fighting one of the most powerful forces in the universe.

How bad is the problem? Two million people a year contract an antibiotic-resistant infection in the US every year and 23,000 of those people die from it. Globally that figure is 700,000 people and is expected to climb to 10 million deaths a year by 2050.

That's more people than die from cancer.

I hope that highlights what an urgent and real emergency this is. For all of us. I know it's easy to let headlines and scare stories wash over you. But I want you to see we are reaching a critical point in this war against bacterial "super-soldiers".

Antibiotic resistant tuberculosis is present in the ground water in much of India. Underdeveloped medical care systems in many developing countries mean that people tend to self-medicate. It is possible to walk into a drug store anywhere in China or India and buy the strongest imaginable antibiotics over the counter.

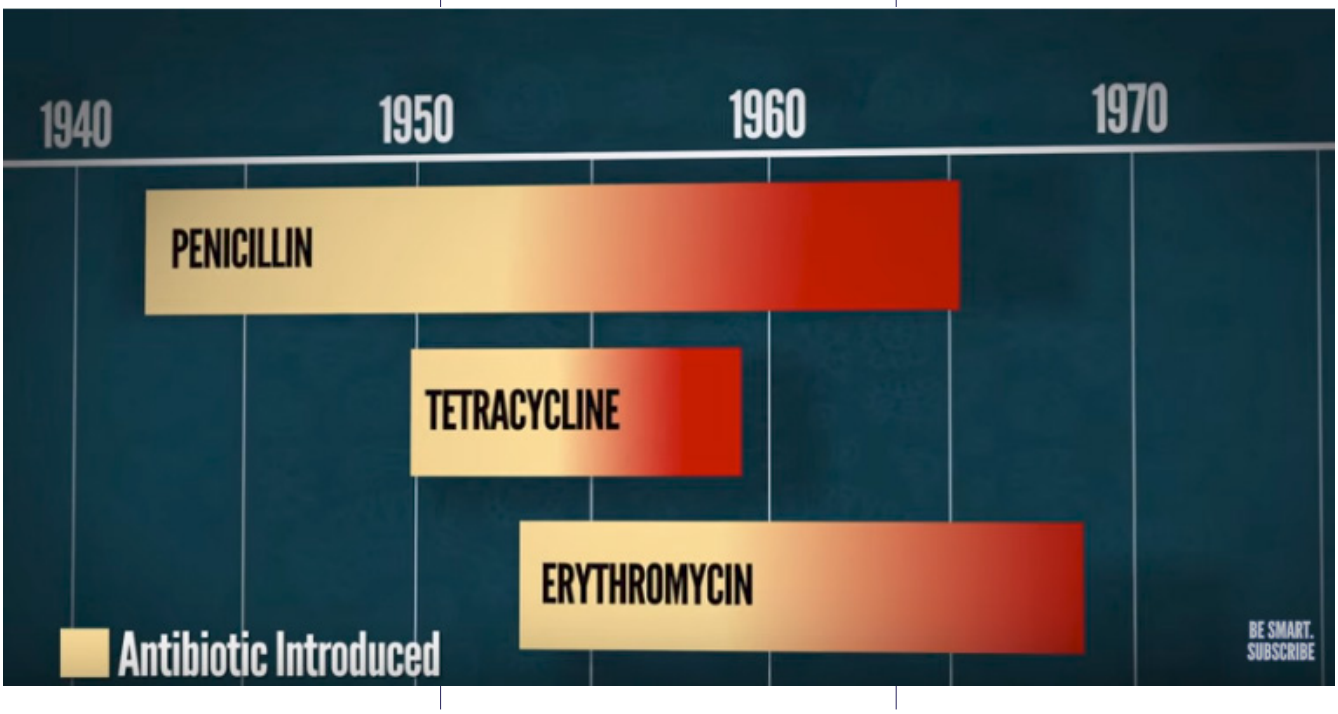
Why? It's simple, when there are no social safety nets people can't afford time off. They need a convenient solution to a health problem and it needs to work fast. It doesn't matter whether the infection is a virus or bacteria (antibiotics only work on bacteria), people take what's available anyway.

But that's just part of the problem...

Agricultural timebomb

Human antibiotic use is dwarfed by the agricultural sector where 80% of all such drugs are used.

It is commonplace to routinely dose chickens, pigs, cows and fish in factory farms with antibiotics to keep on top of infection before infections becomes a costly problem. Additionally, because many countries do not have



sophisticated water treatment measures the effluent from these factories passes into waterways and the natural environment with surprising ease.

I'm sure many people have heard about how London's water has high concentrations of oestrogen because so many women use oral contraception and their urine releases the hormone into rivers.

It is estimated that it would take £30 billion to adequately treat the UK's waste water to filter out this and other hormones. That's what we might consider a first world problem. In the emerging markets the idea of filter waste at all is aspirational, not to mind getting down to a hormonal level. The result is that much of the world is awash with antibiotic resistant bacteria.

MRSA infection has plagued the NHS for decades. Even after massive expenditure and exhaustive measures have been put in place to combat these threats, 1 in 16 NHS patients still pick up an infection when they visit a hospital. That means there is a reasonable chance you will get sicker coming out of a hospital than going in.

That's particularly worrisome when one is old or has a compromised immune system. We hear lots of good news stories about the fight against MRSA and less about the rise of antibiotic resistant salmonella and E. coli. Both of these are growing problems that are going to require very specific measures to combat.

And it's not easy.

Fighting obsolescence

The simple fact of the matter is that it costs billions to develop new drugs of any hue but new antibiotics are even more difficult to develop than just about everything else. That's because we have historically relied on nature to provide us with antibiotics.

Bacteria and viruses have been battling it out for billions of years so the focus has been on finding new microbes that already secrete antibiotic compounds. Traipsing around the globe, peaking under every rock in the hope of finding a piece of soil that has just the right little bacteria to combat a global plague is not exactly what we envisage when we think about scientific innovation.

For a company to spend the kind of money needed to develop a wholly new variety of antibiotics, it would want to have some surety that the solution it has just developed has some staying power.

The problem for antibiotics manufacturers and innovators is that bacteria evolve and new drugs become obsolete rather quickly. Then you have the simple fact that antibiotics work quickly. Drug companies like products that treat chronic diseases like cancer and diabetes that people have to take for a long time rather than just a few days for antibiotics. That's not much of an incentive to tackle the issue of antibiotic resistance in a serious way.

Back in 2014 David Cameron asked renowned Goldman Sachs strategist Jim O'Neill to chair the commissioned the Review on Antimicrobial Resistance. It made its recommendations in 2016 and the primary argument is to restrict over-marketing so that resistance to any new drugs that are developed will be slower; reduce use in agriculture; create an incentive for companies to engage in the kind of expensive research required to get the ball rolling on innovation; and finally to keep the cost down and availability high for new drugs in much the same way that vaccines are available.

Given that we seem to be

> 1 in 16 NHS patients still pick up an infection when they visit a hospital.

entering an era of a superbug apocalypse, you might be wondering:

If the situation is truly that bad, why aren't we all dead already?

There is an easy answer to that objection. Bacteria are not as transmissible as respiratory viruses. Influenza, Ebola, etc, are much more transmissible than bacteria and when they hit a region they have an almost instant effect on the economy.

That means this is a slow-motion problem by comparison. There have already been incidences of bacteria that are completely immune to all our antibiotics so this is a problem we need to tackle today before all bacteria develop the same immunity.

My friend Dr David Brown, inventor of Viagra and co-founder of Antibiotic Research UK, had this to say in an email exchange we had last year:

> *It's a broad generalisation to say there have been no new classes of antibiotics. There have been some but unfortunately not against many of the most deadly bacteria.*
>
> *Bacteria are generally divided into 3 classes, the mycobacteria (TB etc), and Gram-positives (MRSA etc) and Gram-negatives (E coli etc). There have been a few new classes of antibiotic in recent decades against 2 of the 3, though not against Gram-negatives such as E coli, K. pneumoniae, A baumannii and P aeruginosa. Gram-negatives have an extra cell coat (2 instead of just one that Gram-positives have) which makes it much more difficult for antibiotics to gain entry. And these bacteria have also developed capability to pump out our antibiotics or degrade them rapidly. Those four Gram-negatives in particular are a major cause for concern, as we have had no effective new chemical classes invented against them since the 1970s. They are increasingly gaining resistance to our best antibiotics. There have been some new antibiotics against them launched onto the market but these are minor variations on the same old chemical templates. These are easier to discover but also easier for the bacteria to resist. We desperately need new chemical templates. All efforts have failed for nearly 4 decades.*
>
> *Fingers crossed, as we need to save our antibiotics. This was brought home to me the hard way in March this year when my father died from antibiotic-resistant MRSA infection. 5 antibiotics failed to save him. Frankly, even with my expertise, if I had caught MRSA from him I could not be sure which antibiotics to choose to treat myself. The situation is getting serious very quickly.*

News in April that a team from the University of Illinois in Chicago and French firm Nosopharm have developed a new class of antibiotics is very good news.

Today multidrug resistant bacteria are primarily encountered in hospitals in the Western world and therefore represent costly risks for patients. The most successful therapies that exist right now to combat these evolved bacteria are combination approaches that attack the bacteria with conventional drugs and then with antibiotics. However, this is a stop-gap measure.

But all hope is not lost...

Nature vs nature

News in April that a team from the University of Illinois in Chicago and French firm Nosopharm have developed a new class of antibiotics is very good news and is evidence that the healthcare sector is capable of coming up with new solutions.

However, the problem is that this solution was as much about luck as all our other antibiotics. It was isolated from the biological

weapons nematode worms use to colonise insects for food. Nevertheless, new classes of antibiotics to combat multidrug resistance bacteria are essential if global wellbeing isn't going to take a major setback over the coming decades.

One of the most interesting approaches to bacterial infections is to attack them with viruses. This practice was developed in the early 1900s but fell out of use with the introduction of antibiotics. One of the only places where phage therapy, as the practice is known, is common is Russia.

Phage therapy relies on identifying individual viruses that attack bacteria without also affecting humans. The practice has some very clear benefits such as they outright kill the bacteria so there is now potential for resurgence.

Viruses infect cells and reproduce themselves so new dosages are not required. Antibiotics are the microbial equivalent of a carpet bomb and lay waste to the flora of the microbiome, which in turn creates room for immune strains to flourish. Viruses don't have this problem.

The problem with phage therapy is it is finicky. No one virus attacks all bacteria. A new one needs to be found for each fresh mutation of a bacteria. They need some very specific storage conditions and even then, they can morph so that they are no longer useful.

The additional challenge is that since viruses are proteins it is very hard to patent them individually which removes the profit potential to develop them.

At a conference last month Dr Tom Chiller, the chief of mycotic diseases at the Centers for Disease Control, called it "more infectious than Ebola".

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So...

If there are potential solutions and this is a longer-term problem then why am I writing to you about it now?

It's simple, everything I've talked about so far are bacteria. When it comes to viruses, we are dealing with wild cards. The healthcare sector has very few antivirals and the majority of companies focusing on the sector are almost exclusively working on HIV/AIDS.

However, there is an additional class of infection that no one has been worrying about for a long time, which is now a growing danger because of a fresh mutation. Let me introduce you to candida auris. It's a yeast.

Yeasts are a class of fungi and until very recently were considered to be well understood and not much of a problem. So much so, that there are only three classes of drug to treat fungal infections.

It was first identified in 2009, is now in 27 different countries and is much harder to kill than bacterial infections. Generally speaking, yeast infections are annoying but not contagious. Yeasts like warm damp locals and we only get outbreaks when the local area they reside in gets out of balance.

Candida auris is a wholly new class of yeast because it has developed the ability to reside in cool areas like the skin and hard surfaces. That means it can be passed from person to person or from chair, doorknob or computer key to person. That means it is behaving more like a bacterium than a yeast.

The complication with candida auris is that it now has different strains which have evolved in different locations internationally. Due to the prevalence of international travel these strains are finding their way in hospitals all over Europe and North America, which represents a significant cost to institutions when outbreaks are identified.

One of the primary issues is that upwards of 80% of infections are initially misdiagnosed as less risky forms of yeast. The lag in diagnosis gives it time to proliferate and makes rooting it out even more difficult.

One of infection's redeeming features, so far, is that related deaths have been confined to people who were already sick. However, its virulence and ability to survive against all known antibacterials means the cost of containment is very high.

According to results from the PHE Mycology Reference Laboratory, "very few multidrug-resistant *C auris* strains have been found in the United Kingdom, but all isolates are resistant to fluconazole, with variable resistance to polyenes (roughly 20% for amphotericin B) and echinocandins (approximately 10%)."

Therefore, candida auris is not a mass killer but it is a new class of threat that increases costs for hospitals beyond what was expected

One of the primary issues is that upwards of 80% of infections are initially misdiagnosed as less risky forms of yeast.

UK hospitals have detected more than 200 patients colonised with multidrug resistant candida auris in more than 55 hospitals. A quarter of those were clinical infections so they were picked up while in hospital.

Since 2013 there have been three major outbreaks in UK hospitals with the largest being in London's Royal Brompton Hospital. The outbreak began in 2015, involved 50 patients and 22 developed infections. Despite following the same kind of enhanced controls that have become necessary with bacterial infections, environmental sampling showed persistent presence of the fungus around beds.

from bacterial infections. I've been monitoring this sector for years and the inability of companies to profit from development of new antibacterials and antifungals has made it a fallow hunting ground for investment opportunities.

Investment in new antibiotics is progressing but the medical profession has learned from past mistakes. Any new discoveries are going to be hoarded to delay the relentless pace of resistance. That means hospitals are going to be dealing with infection protocols on a much more frequent basis, with any new drugs required brought in as a last resort. That is where the investment opportunity resides.

Cleanliness is next to godliness: how you could profit from the fight against super-bugs

It was when I remembered as a child learning about Florence Nightingale's crusade to encourage cleanliness that I turned to focusing on decontamination rather than a pharmacological solution to this issue.

That's where this month's recommendation comes in: Bioquell Inc.

Bioquell Inc is listed in the UK and headquartered in Andover. The company focuses on its hydrogen peroxide vapor technology and is a world leader in bio-decontamination. It provides modular isolators, specialist filtration and peroxide-base decontamination against bacterial, viral and fungal infections.

Ultraviolet is often used in decontamination settings not least because it is cheap, but with yeasts developing tolerance of light, dry areas its efficacy is less dependable and, in any case, ultraviolet treatment is only useful where light can shine and biological agents are hard to excise precisely because they are hard to reach. That makes vapor-based solutions superior.

Here is an explanation from its

website:

Bioquell is not meant for every room, but the right room at the right time. Our Hydrogen Peroxide Vapor's unparalleled efficacy protects your patients and lowers HAIs. This technology is a must in disinfecting critical care units, eliminating dangerous pathogens from discharged patient rooms, preparing for immunocompromised patients, stopping outbreaks and to re-zero any area in need. UV allows for quick access but low efficacy.

Bioquell has individual pieces of equipment for each individual healthcare setting:

- Its Bioquell BQ-50 is designed to sit inside patient rooms and other relatively small spaces.
- The Bioquell Pod is a pop-up patient room that is equipped with its own air handling capabilities.
- The Bioquell BQ-EMS transportation fleet is designed to fit inside ambulances and is therefore robust enough for on-the-fly implementation and can fully eliminate pathogens within transport vehicles.
- The Bioquell Qube is an aseptic work station that is designed to ensure there is no cross-contamination when mixing drugs for pharmaceutical compounding.
- The Bioquell SeQure wall-mounted unit is designed to quickly and effectively clear sensitive environments like operating rooms from pathogens.

It also maintains a rapid response bio-decontamination service where its personnel turn up on short notice to treat any size structure. This is especially useful for emergency containment and control in pharmaceutical production settings and can achieve bio safety for labs levels 2, 3 and 4.

What this demonstrates is that the company has a suite of products ready to go in the event of a multidrug-resistant outbreak. These are almost inevitably going to become more common because of the lack of wide availability of new drugs to combat them. Bioquell is therefore a well-established business in what has the clear potential to be a high-growth market.

The company generated 29.2 million in 2017, up from $26.5 million in 2016; 19.8% of that was generated in the UK, 30.1% in the rest of Europe and 50.1% in the rest of the world. 97.5% of company revenue is derived from bio-decontamination.

As of this year the company is now a pureplay on bio-decontamination following the sale of its defence contracting arm to an unnamed buyer for £400,000. That followed the sale of its airflow business in January for £240,000 to Crowthorne Hi-Tec Services.

The share has risen rather sharply over the last couple of weeks on better than expected earnings as well as the windfall from the sale of the defence business. However, while there is some near-term scope for consolidation I expect the medium-term potential for the share price to have excellent upside potential.

And here's the company's real advantage...

I've done some extensive searching both online and via Bloomberg and **I cannot identify another company that is anywhere close to a pureplay on the containment of drug-resistant bugs other than Bioquell.**

Considering how much of a growth sector this represents, I believe there is ample potential for additional upside.

The risk is that larger companies specialising in waste management or nuclear decontamination take an interest in the sector and come in as competitors. There is the additional risk, although a benefit for humanity, that multidrug resistant microbes fail to become the kind of threat I and so many more people believe they are.

On a company specific note, Bioquell has no debt and gross margins of 52.1%. However,

an additional risk is that it will make an acquisition to try and boost growth. If that is funded with additional shares, then that would be dilutive to shareholders and would represent a headwind for price appreciation.

I rate the share a buy-up-to 450p but expect perhaps a better buying opportunity at some point over the next few weeks. My 12-month target is 600p but considering the company's growth potential, 1,000p in three years is not unreasonable. There is the additional prospect that the company will be taken over, which could see these timeframes shortened considerably.

PS David Brown offers this advice should you ever find yourself with a serious infection:

> *The first assessment should be to determine if it is a virus or bacterium. Incredibly we still do not have a rapid cheap way to find out. If it is a virus then there are no effective drugs so attention to the health of our immune system is the best approach.*
>
> *If it is a bacterium then one needs to press the physician to do the following a) take a swab for skin infections or a blood sample for systemic infections b) get the bacterium cultured in a lab to identify which bacterium it is c) get a susceptibility test done in the same lab to advise which antibiotics might work.*
>
> *There are so many bacteria and not all antibiotics work against them so this last step is essential for serious infections. The barriers are that GPs and hospitals can be reluctant to do this because of the extra cost and the results will take several days to come back. Again, our technology needs improving!*
>
> ***Meanwhile the doctor has no choice but to take a guess and prescribe an antibiotic with no evidence it will work.** If it does not, then the tests listed above should guide the second antibiotic prescribed.*

Action to take:	**buy Bioquell**
Ticker:	**BQE:LN**
Price as of 03/08/2018:	**430.00p**
Buy up to:	**450p**
52-week high/low:	**213.50/440.00**
Market cap:	**$96.004m**

Figures accurate as of last market close 03/08/2018

Past performance:

Data as of 03/07/2018

Energy

Company	Ticker	Rec Date	Price Then	Price Now	Gain/ loss %
Orocobre Ltd	ORE. AX	07/04/16	A$ 2.92	A$ 4.43	51.71
Ormat Technologies	ORA on NYSE	06/06/17	$58.79	$53.37	-8.39
Smart Meter-ing Systems	SMS LN	03/10/17	735.5p	646p	-11.46
Sherritt Inter-national Corp	S CN	06/02/18	C$1.18	C$0.90	-23.73

Technology

Company	Ticker	Rec Date	Price Then	Price Now	Gain/ loss %
Cyberdyne	7779	30/05/16	JPY 2,353	JPY 1,251	-46.83
IBM	IBM LN	07/06/16	$153.33	$146.03	2.92
SAIC	SAIC US	05/07/16	$58.20	$85.84	52.29
Garmin	GRMN US	02/08/16	$55.75	$64.55	23.14
2U INC	TWOU: US	06/02/17	$33.25	$78.03	134.68
Cisco Systems Inc.	CSCO: US	03/04/17	$33.80	$43.30	33.49
Advanced Micro Devices	AMD US	26/07/17	$14.76	$19.43	31.64
Microsoft	MSFT	31/07/17	$73.04	$108.13	50.30
Northrup Grumman	NOC US	06/07/17	$301.66	$295.43	-1.04
Intel Corp	INTC	06/06/18	$56.60	$49.30	-13.03

Medical

Company	Ticker	Rec Date	Price Then	Price Now	Gain/ loss %
Autodesk	ADSK	19/07/17	$108.83	$134.35	23.45
Abcam	ABC	07/03/17	907.5p	1445p	60.73
Illumina	ILMN	04/09/17	$207.15	$332.36	60.39
PureTech Health	PRTC-L	09/01/18	155.75p	157.50p	1.12
Agios	AGIO	06/03/18	$84.23	$79.94	-3.74
Becton Dickin-son and Co	BDX	03/05/18	$221.35	$248.32	12.52
Canopy Growth Corp	WEED :CN	21/03/18	C$33.11	C$33.85	2.23
Advanced Oncotherapy	AVO	03/07/18	48p	52p	8.33
Boiquell	BQE :LN	07/08/18	430p	430p	0

Moonshot

Company	Ticker	Rec Date	Price Then	Price Now	Gain/ loss %
SolarWindow	WNDW	07/04/16	$3.96	$3.67	-7.31
Alkane Resources Ltd	ALK: AU	05/09/16	AU$ 0.31	AU$ 0.20	-34.43
Haydale Graphene Industries	HAYD	02/5/17	178.5p	48p	-73.11
Superconduc-tor Tech Inc	SCON	28/03/17	$0.95	$2.77	191.58

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