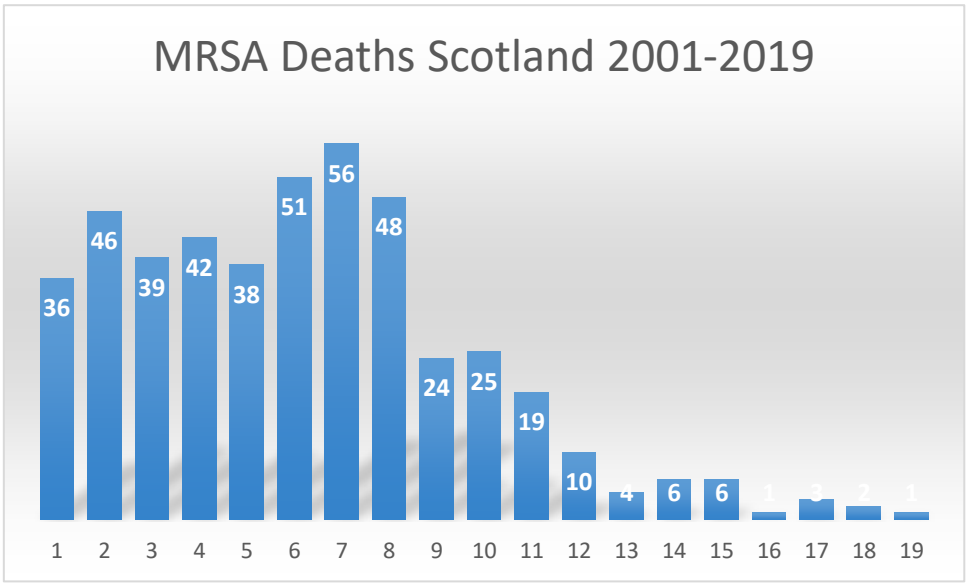
Notes on the Evolution of Resistance in Bacteria: MRSA vs. MSSA

MRSA 葡萄球菌

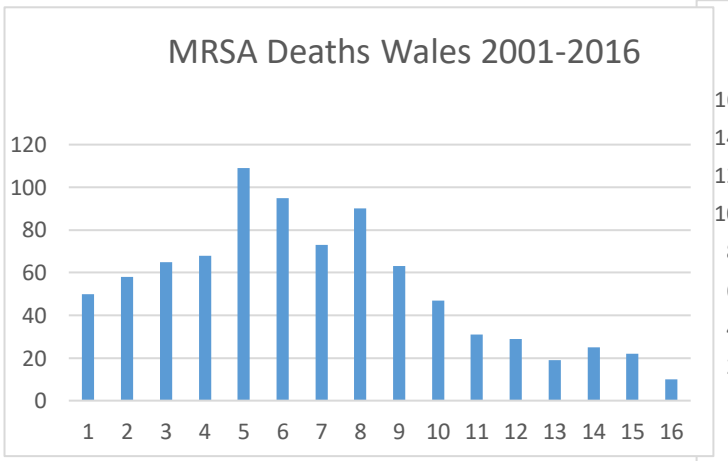
Methicillin-resistant Staphylococcus aureus (MRSA) is a bacterial strain that is resistant to beta-lactam antibiotics and cephalosporins. MRSA infections can be very difficult to treat. MRSA infections are more common in people in hospitals or care settings, but they can also occur in the community. MRSA rates have fallen in the last few years, due to increased awareness, efforts to tackle infection control in hospitals e.g. thorough handwashing and swabbing patients, and reduction of broad spectrum antibiotic use. In 2006, 1.8% of hospital patients were reported to have MRSA and this fell to 0.1% in 2012. – Public Health England (https://e-bug.eu/lang_eng/young_adult/teacher/Young_Adult_Antibiotic_Full_Pack.pdf)

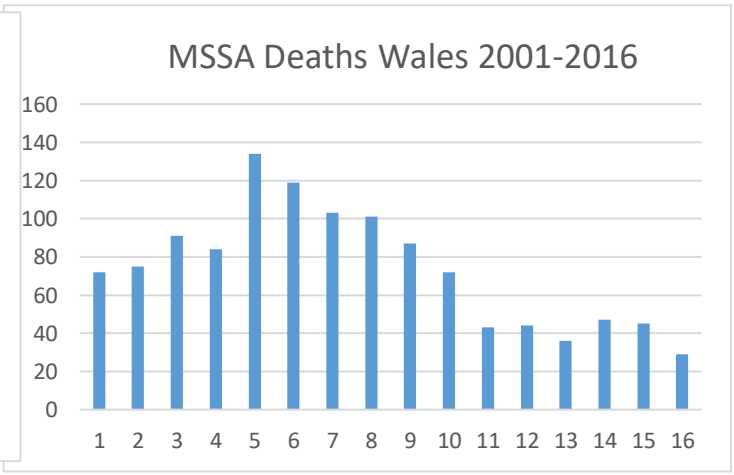


National Records of Scotland, 2020 (https://www.nrscotland.gov.uk/files//statistics/mrsa/2019/mrsa-deaths-19-all-tabs.xlsx)

Resistant

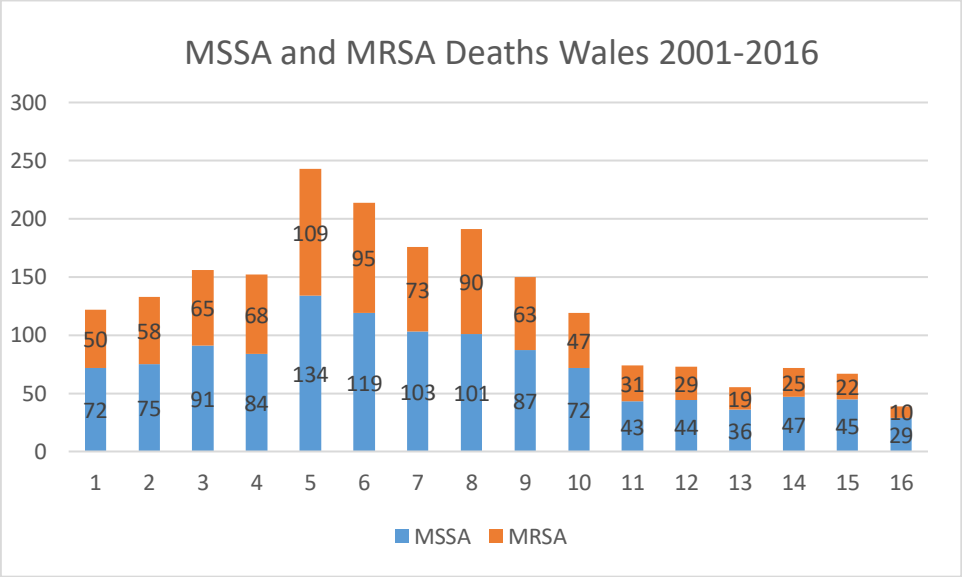
Susceptible (not resistant) 易受影响





UK Office for National Statistics, 2017 (https://www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsinvolvingmrsawales/1993to2016/mrsafinaltable.xls)

When those two graphs are stacked one on top of the other for easy comparison, the resulting graph looks like this:



P. J. Blois, 2021

The spread of antibiotic methicillin-resistant *Staphylococcus aureus* (MRSA) did go up when people used a lot of antibiotics, it is true—the growth looked like an exponential increase until about 2005. What should be clear from the above graphs, however, is that **it did not keep going up. When people became aware of the problem and began using less antibiotics, MRSA numbers reduced. Meanwhile, the non-resistant methicillin-Susceptible strain (MSSA) did not disappear and get replaced. It is possible that all this is due to greater care in hospitals and all of the effort mentioned at the top of page 1, but it is odd: if MRSA had evolved by developing an advantage, then why didn't MRSA completely take over? Why did MRSA numbers start to reduce whereas MSSA did not? Here are some research articles that may hold the answer (highlighted in yellow).**

Exploiting evolutionary trade-offs to combat antibiotic resistance
(https://www.biorxiv.org/content/biorxiv/early/2020/01/20/2020.01.20.912303.full.pdf)
With traditional therapy, the goal is to eradicate the disease by eliminating every pathogenic cell in the human body via the long-term administration of a drug at the maximum tolerable dose. A notorious drawback of this approach is that, after an initially effective treatment stage, it frequently results in the development of drug resistance during later treatment stages. In contrast, adaptive therapies aim to manage the disease without necessarily eradicating it. Evidence from studies of adaptive therapies suggest that – rather than forcing pathogenic cells into evolving elaborate forms of drug resistance during the long-term administration of antimicrobial or anti-cancer drugs – pathogens should be treated using repeated, short-term bouts of drug application that are interrupted by periods without treatment[3,5]. The rationale for this approach is that, during these periods without treatment, resistant cells will be naturally outcompeted by non-resistant cells (or cells with lower levels of resistance) either due to genetic drifts or because the resistant cells are frequently less fit than non-resistant cells in the absence of drug[1,2].

Diffusion-driven enhancement of the antibiotic resistance selection window
(https://royalsocietypublishing.org/doi/pdf/10.1098/rsif.2019.03630)
Of course, the ultimate goal of antimicrobial therapy is to drive a pathogenic population to extinction, so antibiotics must be prescribed at concentrations high enough for bacterial cells to die. Even if complete clearance of pathogens cannot be achieved, conventional wisdom states that high drug dosages suppress growth of the bacterial population and adjuvate the immune system to control the infection. Another benefit of maximizing the inhibitory effect of antibiotics is that, in principle, the mutational supply is reduced and therefore the probability that an individual in the population acquires an antibiotic-resistance mutation is lower [5] (although studies have shown that mutation rates can be density-dependant [6] and increased in the presence of antimicrobial substances [7]).
But aggressive antibiotic protocols can accelerate the rate of adaptation, for instance by suppressing susceptible competitors and releasing resources that promote growth of the resistant subpopulation [8]. Motivated by the evident failure of the current hit early, hit hard prescription strategy [9], a series of theoretical and experimental studies have argued that antimicrobial therapies should consider resistance management instead of focusing exclusively in pathogenic clearance, for example by using shorter [10] and less aggressive [11] treatments, multidrug combination therapies [12,13], sequential treatments [14–16] and increasing drug appropriateness with better point-of-care diagnostic tests [17,18].
Another problem associated with the use of high doses of antibiotics is that, even if a lethal drug concentration is administered, a heterogeneous spatial structure will produce an antibiotic gradient and thus expose the pathogenic bacteria to a range of selective pressures in favour of resistance. Indeed, it is well known that the therapeutic use of antibiotics sees in vivo drug concentrations sweep from high concentrations downwards during treatment (with a considerable time spent at low drug concentrations), producing low-dose sanctuaries that have been observed in bacterial [19] and viral infections [20], promoting the evolution of antibiotic resistance [21].

Fitness Cost and Compensation Mechanism of Sulfonamide Resistance Genes (Sul1, Sul2, and Sul3) in Escherichia Coli
(https://assets.researchsquare.com/files/rs-504582/v1/20b8840a-5f6e-4a0e-8792-e0dbc5244b99.pdf) 适当；健康
The development of antibiotic resistance often comes with a fitness cost, defined by reduced competitive ability in an antibiotic-free environment. This phenomenon usually allows the fitter, often susceptible strain to outcompete the resistant one [19].

Fatal Attraction: How the Overuse of Colistin led to the Evolution of Colistin Resistance
https://fse.studenttheses.ub.rug.nl/23889/1/mEE_2021_DesreveauxA.pdf
excessive use of colistin in human medicine and animal husbandry practices are the main reasons for the increase in colistin resistance. Bacteria can evolve colistin resistance in their genome, but it can also be acquired through horizontal gene transfer*. The horizontally transferred genes are most common in animal husbandry practices, and, by consuming contaminated food, humans can be infected or colistin resistance can be transferred to humans via the human gut microbiome. Most important now is avoiding the further evolution and dispersal of colistin resistant bacterial strains by reducing the use of colistin and limiting it to the essential cases.

*ex. through bacteria pili (菌毛) (cf. How antibiotic resistance spreads between bacteria https://www.youtube.com/watch?v=Sqr39xbDPS4)

According to points made in these academic research papers (highlighted in yellow), why might MRSA numbers have reduced whereas MSSA did not?

Can you think of a few examples of quick and easy ways that even you would be able to do to change a car in order to make it faster and more fuel efficient?

What might this tell us about how MRSA 'evolved' its resistance to antibiotics?

How to take antibiotic correctly
https://www.youtube.com/watch?v=08NJsI_D8vw

What did you learn from the video?

How can we solve the antibiotic resistance crisis? - Gerry Wright
https://www.youtube.com/watch?v=ZvhFeGEDFC8

What Causes Antibiotic Resistance - Kevin Wu's TED Ed video
http://ed.ted.com/lessons/how-antibiotics-become-resistant-over-time-kevin-wu

How could these videos be improved in light of the highlighted information?