Aleksandra Zofia Szymczak. 2305 words.

**Introduction.**

As society and the environment progress, the vulnerability of mankind to the ever-widening spectrum of infectious diseases becomes more apparent (1). Extensive population growth, escalating poverty, increasing urban migration and numerous other factors inevitably affect our exposure to the infectious agents which inhabit the Earth, leading to further demands for medicine to protect the populations from new and resurgent infectious diseases (1). However, our attempts to shield ourselves from the inevitable deterioration of health and suffice our desires, pertaining agriculture in particular, has come at an ever-larger cost. With antibiotic resistance being just one of mankind’s effects, we desperately need to understand that the “post-antibiotic era” (1) is seemingly approaching, and so must adapt with knowledge to prevent the possibility of further pandemics and famines.

**Mutations, Anti-microbial resistance, and distribution.**

The World Health Organisation has declared antibiotic resistance as one of the three most important public health threats of the 21st century (2). When exposed to an antibiotic, most bacteria are destroyed, however, mutations may arise in the genome that lead to a resistant bacterium. As a result, the molecule may, for instance, undergo structural changes, preventing the binding of the drug, and reducing membrane permeability (3). A new population of resistant bacteria can now emerge from the fission of this bacterium, likewise, horizontal gene transfer can also provide neighbouring bacteria with the DNA coding for resistance (3). This renders the antibiotic ineffective when battling this particular strain of bacteria, take, for instance, some strains of mycobacterium tuberculosis bacteria that are resistant to all current treatment drugs (3).

Most clinical antimicrobial agents derive from natural products, with which bacteria share an environment, meaning some may possess intrinsic genetic resistance (4). However, mankind has a large play in the emergence of antibiotic resistant bacteria. Unregulated access to cheap antibiotics promotes overuse, and the implementation of antibiotics for growth supplements in livestock is equally dangerous (5). These both unnecessarily expose humans to anti-microbials and promote the emergence of more virulent, resistant bacteria. For instance, 80% of antibiotics sold in the U.S. are used in animals (6). Whilst not affecting humans as directly as the resistant consequences of 50% of patients with coughs and viral sore throats being prescribed antibiotics that won’t, in these cases, render significant effects (7), the antibiotics used in livestock are ingested by humans during food consumption (8). Up to 90% of the antibiotics used in livestock disperse into the surroundings via natural processes, such as excretion, which further fuels resistance (9) (10).

Virulence of pathogens could also be fuelled by the use of vaccinations in livestock, which provide the conditions for hypervirulent strains (11). In unvaccinated birds, hypervirulent strains of MDV kill before they have the chance to be transmitted, whereas, in imperfectly vaccinated birds, the birds remain alive and can easily transmit (12), though it must be noted that direct causation between the direct development of hypervirulent strains and vaccinated flock is still incompletely proved, requiring further research (11). There is a clear trend however - take, for example, the 1950 myxoma virus in Australian rabbits, which developed hyper-immunosuppression as the rabbits developed resistance, the transmission of which fuelled more virulent evolution and lead to vast mortality among the populations of immunologically weaker rabbits (11). Frank Fenner, an Australian microbiologist, set up an experiment regarding this phenomenon, highlighting the evolution of pathogens as host cells gain resistance (13). It also provides insight into how pathogens could react when the important developments in agricultural and human medicine of vaccination and genetic engineering make hosts more resistant to infections (11). Thus, this means that continuous study is vital in, despite how currently inexplicably rare the event would be in humans, ensuring that those who cannot be reached by vaccines, e.g. immunosuppressed patients, are not contended with a largely virulent pathogen due to a leaky or “imperfect” vaccination (11) (12) (14).

The issues of agriculture also extend to the resistance of fungal infections. Fungi behave in a similar way to bacteria regarding HGT and rapid reproduction (15). Azoles are a particular group of AFDs, which have accelerated the emergence of resistant strains (15). Migrations of pathogenic diseases are emerging more, and as global warming gives rise to pathogen-friendly conditions in more areas of the world, it is not a surprise that exposure to insect vectors, animal reservoirs and resurgent resistant diseases that span wider areas becomes more common (16). For instance, V. cholerae 0139 emerged in southern Asia from 1992, replacing the known V. cholerae 01 strain, and being unaffected by the vaccines (17). The monitoring and studying of these diseases, which we seem to have under control, is thus shown to be vital as pathological medical advances are exploited more and more often, with the rise of new, mutated strains, rendering prior vaccines and overused antibiotics ineffective.

**The effects on Public Health.**

Once again, without effective treatment, the human race is exposed to newer, deadlier pathogens. The dire consequences are perhaps most pertaining when looking at the COVID19 Pandemic, which has resulted in over 4.8 million confirmed cases as of May 19th 2020 and over 300,000 deaths globally (18). Fears of an economic crisis and recession are ripe following decreases in the workforce and increasing unemployment (19), with mental health issues being overwhelming for many. Pandemics entail unfathomable demands regarding healthcare, pushing healthcare workers further to the brink of exhaustion and placing them in direct danger of infection, often with insufficient equipment due to poor preparation- over 100 healthcare workers have died due to COVID19 in the UK (20).

The effects of pandemics should not be taken lightly. For instance, examining the strain on healthcare systems also shows reductions in the health workforce due to nosocomial COVID19 infection and burnout (21), subsequently leading to less effective treatment and further cases of health deterioration, with LMICs being most seriously impacted as a result of low provisions and less developed healthcare systems (22).

Pandemics can be caused by any disease - take for instance, a potential MRSA pandemic following antibiotic resistance. If unprepared for due to a lack of studying this could indeed become a devastating reality, with prior treatments being rendered ineffective, a potentially more virulent strain will be increasingly harder to halt (23). The increased virulence is indeed probable with communicable diseases (11) (12). For instance, concern has risen over strains of HIV resistant to antiviral drugs, infection with which have resulted in prolonged hospitalization and higher death rates, requiring more expensive and toxic drug prescriptions (24). When considering highly infectious diseases, it becomes ever more important to study prior pathogens that could emerge due to changes in behaviour and re-emergence elsewhere. Contagious illnesses are often carried home and transmitted to constituent members of the household, leaving a smaller possibility to control the outbreak (1). Surveillance with laboratory support is thus vital for defence (1).

It is also important to look beyond direct consequences. Mortality rates for COVID19 appear to be low for children and women of reproductive age, however, these groups could later be greatly impacted by the disruption of routine health services, emphasised by the decreased healthcare workforce (25) (22). According to the WHO, the shift of medicine and effort towards the emergency often causes neglect of basic and regular essential health services (22)- it is harder for patients with health problems to access healthcare services, and the fear of infection could cause many to avoid services, especially those who are vulnerable (26). For instance, the 2014 Ebola virus epidemic resulted in a 27.6% decrease in service use and 44.3% decrease in inpatient services in high-incidence areas (27). Unfortunately, those who are vulnerable, e.g. a patient who is immunosuppressed due to organ transplantation (1), are also most at risk of developing complications by not attending.

More than 30 LMICs could experience widespread famine as a further consequence of the pandemic (executive director of the World Food Programme, David Beasley, 2020) - (28). The UN and other organisations have previously released a report highlighting that more than 265 million people are being pushed to the brink of starvation during the COVID19 pandemic, a secondary effect influenced by export bans and other restrictions (UN study report)- (28). Thus, healthcare systems of predominantly developing countries will be unable to cope, after shortages and casualties during the pandemic and following (28), with the health deterioration of millions who may starve offstage. The economic collapse following will further stretch resources (28), putting larger strain on exhausted healthcare systems.

The potential for famine due to pathological disease is often “under-appreciated” (Anon, University of Exeter, 2014) (15), however, it too could have severe effects, as common fungal infections become increasingly resistant to treatment - escalated by monoculture and other agricultural techniques (29)- and could one day become uncurable (15). For instance, the Irish Potato Famine of 1845/46 led to 1 million deaths and 1 million cases of emigration, which heavily depleted workforce, leading to economic burden (30). Caused by a single plant disease, the Potato Late Blight, through Phytophthora infestans (30), it establishes the possible consequences of fungi, which are currently responsible for perennial yield losses of 20%, and 10% postharvest (31) (29). The effects of famine are undeniable, with weakness and hypotension being factors that can effortlessly cause a depleted workforce, leading to shortages of income and a strained healthcare system with a lower capability to treat patients who will come with increased communicable disease due to the implications of starvation on the immune system. Permanent organ failure, which can lead to death isn’t uncommon (32).

The health-threatening effects of fungi do not end with famine, as the number of human deaths from fungal diseases is said to exceed those from malaria and breast cancer (33). With moulds that can damage both crops and compromised immune systems, such as Aspergillus fumigatus fungi, studying fungi becomes more important as anti-fungal resistance increases. Hospitals will become most at risk with open wounds and invasive treatments. For instance, Candida auris is responsible for rapidly increasing hospital-acquired invasive infections worldwide (34) and is now resistant to all clinical antifungals (35), as well as being able to survive normal decontamination protocols (36), causing further diseases and infections for patients, and inflicting the most damage upon those who are less capable of responding to diseases due to prior treatments, i.e. surgery or chemotherapy. Therefore, without studying currently treated pathogens, it cannot be said that mankind is prepared for an outbreak of a mutated, resistant strain.

**How research can provide a solution.**

Monitoring the development of antimicrobial drug resistance and virulence allows early intervention and prevents excessive suffering and mortality, with studies also providing the potential to understand the distribution of vaccinations and antimicrobials, allowing for identification of shortages where diseases can thrive, and the likelihood of resistance occurring (37). It decreases the risk of economic troubles and guides clinicians to undertake the most effective path of treatment possible (38). For instance, this could halt the development of anti-fungal fungi by shifting perspective to not only limiting the use of antifungals, as with antibiotics, but also developing further treatments to prevent emergence (15). Partly due to high costs, there has been a significant decrease in the development of new antibiotics, with the loss of development from 15 of the largest pharmaceutical companies (10). Thus, a modern shift to new studies on previously treated pathogens is highly important as antibiotics lose their effect – the fading effort of antibiotics and lack of availability of vaccines in certain scenarios has spurred the exploration of host-targeted treatments with antibacterial agents (39).

Regarding vaccinations, studying antigenic structure changes can facilitate necessary alterations (38). Take, for instance, antigenic drift in measles virus (38). Increased virulence is also a key aspect of studying these pathogens, and can allow for the development of new vaccinations, and, as virulence can increase alongside resistance (11), additional medical advancements to protect those whom are vulnerable due to a lack of immunisation if necessary (12). New medical advancements and technology to combat pathogens in innovative ways are becoming ever more important, with the potential to revolutionise treatments in more sustainable ways. For instance, studying the interactions between virulence factors and host cells advances understandings of immunity, developing immune-based therapies for infection (39). Cellular molecules that the pathogen relies on for infection can also be identified and thus used as drug targets to halt and treat infections (39).

The study of infectious pathogens isn’t limited to specific treatments for a specific disease, but also broadens understandings of interactions between diseases. For example, it has been acknowledged that human papillomavirus is linked to cervical cancer, highlighting interactions between communicable and non-communicable diseases (40). Heavily accelerated by the study of viruses is the contribution of signal pathways to diseases, such as cancer (41), for instance advances have already been made with Abelson murine leukaemia virus which leads to lymphosarcoma in mice (39). The discovery of further complications with diseases is vastly important for intervention and developments of further treatments for the effects. Take, for instance, the connection between parkinsonism and encephalitis lethargica, the effects of which could first emerge up to a year after initial infection (42), which shows the role studying has in potentially understanding the progressions of highly debilitating non-communicable diseases, such as Parkinson’s, perhaps leading to a greater understanding and thus prevention.

**Conclusion**

From 1943, Alexander Fleming, who discovered penicillin, noted the presence of penicillin-resistant bacteria and thus warned against excessive use (3). It too becomes increasingly apparent, approaching the “post-antibiotic era” (1) that the study of pathogens for whom mankind seems to currently hold treatments is vital in the analysis of resistance and host interaction to allow the identification of potential future issues, such as pandemics and famines among many, as well as facilitating the advancement of medicine towards treatments of countless other diseases- communicable and non-communicable. Thus, ensuring that medicine progresses parallel with threat.

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