Commentary

Megatrends in Infectious Diseases: The Next 10 to 15 Years

Sin Yew Wong,[1] *MBBS, MMed (Int Med), FAMS*, Ban Hock Tan,[2] *MBBS, MRCP, FAMS*

Abstract

It has been about 100 years since the Spanish influenza pandemic of 1918-19 that killed an estimated 50 million individuals globally. While we have made remarkable progress in reducing infection-related mortality, infections still account for 13 to 15 million deaths annually. This estimate is projected to remain unchanged until 2050. We have identified 4 megatrends in infectious diseases and these are "emerging and re-emerging infections", "antimicrobial resistance", "demographic changes" and "technological advances". Understanding these trends and challenges should lead to opportunities for the medical community to reshape the future. Further inroads will also require broad approaches involving surveillance, public health and translating scientific discoveries into disease control efforts.

Ann Acad Med Singapore 2019;48:188-94

Key words: Antimicrobial resistance, Demographic changes, Emerging infections, Technological advances

Introduction

Microbial threats to human health have existed for thousands of years.[1,2] In the past, infectious diseases presented some of the most defining challenges of human existence.[3] Great pandemics and local epidemics have influenced wars and the fate of countries and empires.[4] As recently as 30 years ago, the human immunodeficiency virus (HIV) epidemic caused devastating loss of at least 1 generation of adults in some African countries, setting back years of progress.[5]

Infectious diseases have long been associated with poverty. Rapid economic and scientific progress of the 1960s and the subsequent reduction in infectious disease mortality likely prompted the infamous quote: "It is time to close the book on infectious diseases and declare the war against pestilence won." Though often attributed to William H Stewart, the 10th United States (US) Surgeon General, the source remains controversial. Controversy notwithstanding, the resulting complacency in public health efforts has been blamed for antimicrobial resistance, emerging and re-emerging infections.

More than 1400 species of pathogens cause diseases in humans.[6] With global effort, we have eradicated just 1 (smallpox) but have made significant progress controlling many others. However, microbial threats continue to emerge and re-emerge. Under "favourable" conditions, the previously obscure Zika virus—first discovered in the 1960s—emerged in 2015 to infect millions in Central and South America, resulting in thousands of cases of congenital Zika syndrome and is expected to be a long-term public health challenge.[7]

Nowhere in the world have infectious diseases become negligible.[8,9] Outbreaks and epidemics will continue to grab headlines. The Ebola epidemic that began in 2013 ravaged many countries in West Africa. It captured global attention prompting the World Health Organization (WHO) to declare the infection a public health emergency of global concern.[10] Even as the world catches its breath, a new Ebola outbreak

[1]Infectious Disease Partners Pte Ltd, Gleneagles Medical Centre, Singapore
[2]Department of Infectious Diseases, Singapore General Hospital, Singapore
Address for Correspondence: Dr Wong Sin Yew, Infectious Disease Partners Pte Ltd, 6 Napier Road, #05-13, Gleneagles Medical Centre, Singapore 258499.
Email: symswong@singnet.com.sg

was declared in the Democratic Republic of Congo in May 2018—and it rages on. Clearly, investing resources and time in the prevention and control of infectious diseases need to be ongoing.

In this article, we review the significant historical events in infectious disease, primarily the scientific progress that have enhanced our understanding of pathogens, their epidemiology, prevention and treatment. We emphasise that significant changes have occurred and that there has been an epidemiological transition in infectious diseases globally.[11] The direction of these changes and the forces they unleash will define the future world. We express what we know and put forward 4 important "megatrends" in infectious diseases that will be ongoing challenges in the next 10 to 15 years. These trends, if harnessed well, will also serve as opportunities to reshape the future.

Megatrend 1: Emerging and Re-Emerging Infections

The Institute of Medicine (now called Health and Medicine Division at the National Academies of Sciences, Engineering and Medicine, United States of America) published a landmark report entitled "Emerging Infections: Microbial Threats to Health" in January 1992 and brought global attention to the ongoing threat of infections to human health.[12] Since then, many new pathogens have been identified. Some of the newly identified viruses that caused outbreaks in Singapore are Nipah virus in 1999,[13] severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003[14] and *H1N1* influenza virus in 2009.[15]

There are many drivers of emerging and re-emerging infections.[16,17] These can be broadly categorised into "microbial factors", "human host factors", "environmental factors" and "others". For "microbial factors", genetic adaptation of the microbe may allow it to infect a different host or result in the development of antimicrobial resistance. "Human host factors" that drive emerging and re-emerging infections include individuals with increased susceptibility to infection (such as those who are immunocompromised and the elderly) and individuals with occupational exposure. Spread within healthcare facilities, human migration and lifestyle issues (including travel for business or leisure) are also implicated. "Environmental factors" include increased population density, climate change (impacting vector habitats and population), changes in land use and development, international trade, changing ecosystems and changing animal populations. Wars, famines, poverty are also other external factors that can impact on emerging and re-emerging infections.

International travel and the global food chain are factors especially relevant to Singapore. The SARS-CoV outbreak in Singapore was linked to a Singaporean who acquired the infection during travel to a North Asian city.[18] More recently, the first Zika case notified in Singapore in April 2016 was a traveller who returned from a business trip to Brazil.[19] Interestingly, the subsequent outbreak of over 400 cases that started in August 2016 was linked to the Southeast Asian strain of the Zika virus.[20] In recent years, our healthcare system has been on heightened alert against the introduction of avian influenza, Middle East respiratory syndrome coronavirus (MERS-CoV) and Ebola.

International travel has also been associated with the spread of multidrug-resistant bacteria.[21] In late 2008, a Swedish diabetic visiting India developed a gluteal abscess and required hospitalisation in New Delhi. A day after his transfer to a Swedish hospital, urine cultures grew a carbapenem-resistant *Klebsiella*. This led to the characterisation of the New Delhi metallo-lactamase gene, which had been unknown hitherto.[22] In Holland, a Dutch man developed fever 2 weeks after returning from a 2-month stay in the Philippines. Blood cultures grew *Salmonella typhi* that carried the SHV-12 extended-spectrum beta-lactamase (ESBL).[23] Indeed, multiple studies demonstrate that travel can be associated with acquisition of ESBL-producing organisms.[24]

With Singapore importing most of its food, the country is vulnerable to infections transmitted by food. A recent example was the Listeria outbreak that occurred in Australia in early 2018 that was linked to infected rock melon. In April 2018, Singapore's Ministry of Health (MOH) reported that 2 out of 5 persons infected with Listeria in Singapore since the beginning of 2018 were in fact infected with the strain that had caused the outbreak in Australia.

In December 2015, the WHO led a panel of experts and published a priority list of 8 pathogens that were expected to cause severe outbreaks in the future. These were Ebola, Marburg, Lassa, Rift Valley, Crimean-Congo, Nipah, MERS-CoV and SARS-CoV.[25] The priority pathogens are all viruses and are zoonoses. This list will be reviewed annually in response to any "new" threats that emerge. Clearly, we need to pay greater attention to the threat of zoonotic infections. The concept of "One Health" is a collaborative and inclusive effort involving human health, animal health and the environment.[26]

The issues of climate warming and environmental perturbation are also critical factors in emerging infectious diseases.[27,28] Climate change will increase exposure to Aedes-borne viruses and the risk of the resurgence of dengue, Chikungunya and Zika infections.[29] Recently, there have been large outbreaks of measles and mumps in developed and developing countries. Vaccine hesitancy— especially with the measles, mumps, rubella (MMR) vaccine—has been implicated[30] but the issue is likely to be much more complex with waning immunity and other considerations.[31,32]

Somewhere out there, there are emerging or re-emerging microbial threats lurking. When the "right" conditions converge, it will unleash itself onto the global population who will have no immunity to this "new" pathogen. This will present as a "black swan" event as with SARS-CoV, or more insidiously, as with HIV.[33]

Adequate preparations will prevent an "incident" from escalating into a "crisis". In Singapore, it is likely that the pathogen will be imported. Whilst these "imported" infections may be daunting, especially if "unknown", the possible routes of transmission are well defined and measures to prevent the spread of "unknown" infections can often follow a broad range of standard procedures. Our restructured hospitals are regularly put through outbreak simulation exercises where such procedures are practised.

Active surveillance for such threats is critical to ensure that outbreaks are quickly detected and contained. Containment will involve a multi-agency effort that will include the restructured hospitals as well as the National Centre for Infectious Diseases, MOH, National Environment Agency, Singapore Food Agency and research institutes like the Genome Institute of Singapore, Defence Science Organisation Laboratories, Agency for Science, Technology and Research and the relevant departments of our local universities.

In essence, we are unlikely to see eradication of the threat of infections to humans and we need to continue with efforts in disease control and mitigation.

Megatrend 2: Antimicrobial Resistance

The discovery of penicillin and the subsequent development of antibiotics must be one of mankind's greatest triumphs. The widespread use of antibiotics has saved countless human lives. In a recent publication on lower respiratory tract infections in the Global Burden of Disease Study 2016, the authors estimated that increased antibiotic availability could still prevent 30% of lower respiratory infection deaths.[34] However, the universal use of antibiotics for lower respiratory tract infections is not tenable. Microbes adapt, resist the medication used and develop antimicrobial resistance (AMR). In the past few decades, antibiotic resistance—a subset of AMR—has emerged to the extent that some bacterial infections are becoming untreatable. The dramatic increase in the proportion and absolute numbers of bacterial pathogens resistant to multiple antibiotics in recent years has prompted many regulatory agencies including the US Centers for Disease Control and Prevention, the WHO and the European Centre for Disease Prevention and Control to highlight this issue. At the 68th World Health Assembly in May 2015, the WHO declared AMR a global health threat and proposed a multiyear action plan to reduce AMR. The "Global Action Plan on AMR" has 5 strategic objectives: 1) To improve awareness and understanding of AMR; 2) To strengthen surveillance and research; 3) To reduce the incidence of infection; 4) To optimise the use of antimicrobial medicines; and 5) To ensure sustainable investment in countering AMR.

Without exception, all antibiotics, antivirals, antifungals and antiparasitic agents have inherent weaknesses that allow microbial pathogens to evolve and develop resistance mechanisms.

Emergence of resistant micro-organisms by mutation and acquisition of mobile transferable genetic elements carrying resistant genes may take place spontaneously or under selective pressure in the presence of antimicrobial agents. In recent decades, the driving force has been the use and misuse of antibiotics in humans and livestock and leakage into the environment. It has been estimated that antibiotic consumption increased 30% from 2000 to 2010. Antibiotic use has amplified the development of AMR.

If AMR is left unchecked, common bacterial infections will become difficult to treat and "simple" infections will once again kill many. Sophisticated medical interventions such as organ transplantation, joint replacement and cancer chemotherapy will become more dangerous to perform.

Clinical trials on new antibiotics and combination therapy have failed to keep up with the rapid emergence of drug-resistant bacterial, fungal and viral pathogens. Hence, improving how we prescribe antibiotics is critical. Antimicrobial stewardship programmes are now well established in the restructured hospitals in Singapore and many developed countries. These programmes have been demonstrated to be safe and effective in improving appropriate antimicrobial use.

AMR is a widespread and complex issue. The factors have been identified and the measures proposed to reduce AMR are not novel and have shown measurable success in selected settings. Successful implementation requires all stakeholders—policymakers, public health officials, regulatory agencies, pharmaceutical companies and scientific community—to work together. We also need to improve public awareness (Table 1). This may galvanise concerned citizens to work towards avoiding the worst-case scenarios where the end of modern medicine occurs as a result of AMR.

Table 1. Important Public Health Messages on Antimicrobial Resistance

• Antibiotic resistance is one of the biggest threats to global health, food security and development today.
• Antibiotic resistance can affect anyone, of any age, in any country.
• Antibiotic resistance can occur naturally, but misuse of antibiotics in humans and animals is accelerating the process.
• A growing number of "common" infections—such as skin infections, pneumonia, tuberculosis and gonorrhoea—are becoming harder to treat as the antibiotics used to treat them become less effective.
• Antibiotic resistance leads to longer hospital stays, higher medical costs and increased mortality.

Megatrend 3: Demographic Changes

Demographic changes in the next 10 to 20 years will have a major impact on infectious diseases. The 3 global demographic trends worthy of note are: 1) Increase in the elderly population; 2) Increase in the number of immunocompromised patients; and 3) Increase in the migrant population, especially refugees and asylum seekers.

Globally, the elderly—defined as those above 65—is expected to reach 2.1 billion in 2050. In Singapore, this is keenly felt with the elderly projected to reach 20% of the population by 2030. It was 9.4% in 2007 and 14.4% in 2017.[35] With multiple comorbidities and immunosenescence, they have a higher risk of acquiring infections and the diseases resulting from the infections are often more severe. Furthermore, recovery will often be slow and incomplete, resulting in physical deconditioning, impairment of activities of daily living and loss of independence.

Advances in medicine have improved the survival of patients with cancer, organ failure and autoimmune diseases. This patient population will continue to grow but their immunocompromised state puts them at higher risk for infections.

The clinical course of some malignant diseases, once thought to be fatal, is being transformed by new therapeutic approaches. A shining example is multiple myeloma which has become a chronic disease through the combination of novel therapeutics and haematopoietic stem cell transplantation.[36] For practising physicians, this transformation has necessitated a change in the approach towards "infections in myeloma". Older review articles emphasised the importance of encapsulated organisms in untreated patients and nosocomial gram-negatives in those receiving chemotherapy, but the newer therapies have led to infections such as aspergillosis and varicella zoster.[37,38] In fact, viral infections have been reported to assume increased importance in myeloma patients treated with daratumumab, a recently approved drug.[39]

The entry of a migrant population may significantly change a previously stable incident infection rate. The wave of asylum seekers into several European countries has raised not only social anxieties but also concerns about the transmission of infectious diseases to the indigenous population. In reality, infectious diseases in the refugee population usually reflect poor living conditions, especially in transit areas. Hence, "outbreaks" are more likely confined to the migrant communities. One point to note is that the "migrant population" is heterogeneous and the infections they carry or suffer from can vary considerably between students, skilled and unskilled workers and refugees. The disease epidemiology of the country of origin will help to determine the type of screening that the migrants should undergo. In a recent review, Eiset and Wejse reported that latent tuberculosis, hepatitis B and malaria were the major concerns.[40] Outbreaks due to measles, cutaneous diphtheria and shigellosis have also been reported in refugees and asylum seekers.

While we do not have a refugee issue in Singapore, we have a sizeable migrant worker population (estimated at 1.4 million). In a recent article, Sadarangani et al reported that a large proportion of malaria, enteric fevers, hepatitis A and E and tuberculosis involved migrant workers.[41]

Megatrend 4: Technological Advances

Technological advances have made a huge impact in the way we work, live and interact with each other. Similarly, technology has been a major force in the evolution of healthcare. In the context of infectious diseases, we highlight the following: 1) The revolution in microbiological diagnosis especially in "hard-to-culture" infections; 2) Novel advances in therapeutics; and 3) Data mining and artificial intelligence (AI).

Microbiological diagnosis has undergone a revolution with the use of nucleic acid amplification tests. The increasing use of syndromic multiplex polymerase chain reaction (PCR) tests has helped us diagnose viral infections more readily. Multiplex PCR tests in common use include those for respiratory tract, gastrointestinal and central nervous system infections. These platforms are being miniaturised and will increasingly become available as point-of-care tests. Improved diagnosis of viral infections in febrile illnesses may reduce empiric antibiotic use and hopefully reduce the development of AMR. Indeed, the promotion of rapid diagnostic kits was one of the major suggestions made for reducing AMR in the report of a study on AMR commissioned by the British government.[42] However, in practice, the use of rapid diagnostic kits has yielded mixed results. In 1 study, though antibiotic prescriptions fell in the presence of a positive result for influenza, 62% of patients with influenza were still prescribed an antibiotic.[43] Similarly, 40% of patients with sore throat and a negative test for Group A *Streptococcus* still received antibiotics.[44]

Next-generation sequencing (NGS) is likely to play a significant role in several areas of medicine. In clinical infectious diseases, it may find a niche in the diagnosis of "hard-to-grow" organisms. In the field of emerging infections, it has already distinguished itself by helping researchers in "first human cases" reports.[45] In epidemiology, its discriminatory power has helped to upend conventional thinking on "epidemiological links".[46]

NGS platforms are now less expensive, more readily accessible and hence are likely to be increasingly deployed in the diagnostic microbiology laboratory in the coming years. Whole-genome sequencing (WGS), in particular, may well revolutionise outbreak investigations. Snitkin et al have described how WGS helped them understand transmission routes in a prolonged outbreak of carbapenemase-producing *Klebsiella pneumoniae* in their hospital. It turned out that the temporal sequence in which patients manifested as being colonised/infected was not the sequence by which infection was transmitted.[46] They also emphasised the importance of integrating genomic information with epidemiological data, showing that sagaciously combining cutting-edge technology with established methods could lead to impressive results.

As our understanding of the human microbiome improves, therapeutics involving manipulation of the microbiome will increase. We are familiar with faecal microbiota transplant (FMT) for recurrent *Clostridium difficile* infections. Recently, FMT has also been used selectively for patients colonised and infected with resistant organisms.[47] Clinical trials now being planned may confirm if FMT can treat other diseases. Beyond FMT, there is also research on microbiome manipulation in patients with atopic dermatitis and dysbiosis on their skin.[48] We envisage more microbiome manipulation in other areas of medicine.

It would be remiss of us not to touch on the changes that will be wrought by the massive increase in computing power. The impact that data mining and AI will have on the practice of medicine cannot be dealt with in a few paragraphs. We are also not the appropriate experts to comment on these advances. However, we offer a clinician's analysis.

Mining "big data" gives researchers unparallelled statistical power. We will cite just 1 example. Investigators wanted to understand the interaction between trimethorprim-sulfamethoxazole (TMP/SMX) and spironolactone. Randomised-controlled trials recruiting more than 10,000 patients are rare and massively costly. In this exercise, however, the researchers were able to identify 206,319 patients who were prescribed spironolactone over a 17-year study period. They tapped into several large databases—Ontario Drug Benefit Database, Canadian Institute for Health Information's Discharge Abstract Database, Ontario Health Insurance Plan Registered Persons Database, National Ambulatory Care Reporting System and Ontario Office of the Registrar General's database. They were able to conclude that compared with amoxicillin, TMP/SMX use did increase the risk of sudden death[49] in persons on spironolactone.

With the digitisation of medical records, our hospitals also now contain a wealth of information. Mining the data intelligently will enable us to monitor outcomes, track infection rates and do many other things that are currently unimaginable (or that currently require expensive manpower to manually obtain the information by sampling, for example).

AI is both promising and worrying. At the moment, available technologies are still human-driven. Watson for Oncology (WfO), for example, is a programme developed in conjunction with oncologists at Memorial Sloan Kettering (MSK). After an oncologist keys in patient information, WfO will suggest a treatment regimen, based on published literature, as well as the experience at MSK (all taught to WfO). A hospital in Bangalore compared Watson's decisions against those of a multidisciplinary tumour board and found 93% concordance.[50]

Although exciting, WfO is, in a sense, limited by humans. One of the oncologists who helped to develop the software (in effect, training Watson), mentioned that it had been a struggle.[51] But will it necessarily always be as difficult? Our vision of the future is limited by our minds. Perhaps there is some technology that will mine the data in our hospital's database and also all the studies in PubMed®, and then dish out a recommendation for a patient's breast cancer. As we know, the problem of long queues at taxi stands was not solved by any number of incentives or disincentives but by Uber and Grab, and without rocket scientists. AI does promise disruption. For a detailed analysis of how AI will affect the professions, including ours, we recommend the book, "The Future of the Professions: How Technology Will Transform the Work of Human Experts".[52]

Discussion

Megatrends are transformative global forces that define the future world and have far-reaching impact on businesses, societies, the macroeconomy and the individual. Megatrends have been identified in business, investment and technology and will have different meanings for different industries. In the context of infectious diseases, megatrends represent fundamental sustained forces in the future that will impact infections in mankind.

A fundamental question is: why have we not been more successful in controlling infectious diseases? With access to clean water, sanitation and antibiotics, there has been a steady decrease in infection-related mortality in most segments of the population, except possibly the elderly. Thirteen to 15 million persons are projected to die every year due to infectious diseases up to 2050.[8] This high mortality reflects some of the concerns we have raised in this article. Global population growth has certainly contributed to these high numbers and the challenge is how to push these mortality figures down.

The megatrends that we have outlined may not be exhaustive or mutually exclusive. They serve as a blueprint for the future as healthcare planning and investments often lag behind impact. Often, focus is lost after the hype surrounding a new outbreak like Zika. Instead, ongoing preparations including investment in infrastructure should permit a comprehensive response that ensures quick interruption of transmission. Beyond infrastructure, equipment and training, previous outbreaks have taught us that the medical community needs more than "research and response".[53,54] We need better organisation, leadership, communication and community action.

Conclusion

We have made remarkable progress in diagnosing, treating and preventing infectious diseases. Our successes in meeting the threats of pathogens come not only from scientific breakthroughs but also from broad approaches on many fronts including surveillance, public health efforts and translating new discoveries into disease control efforts. The future is not a given. We must continue to improve our processes, enhance our tools and infrastructure. The challenges of infectious diseases are perpetual and so must our efforts.

REFERENCES

1. Zink AR, Sola C, Reischl U, Grabner W, Rastogi N, Wolf H, et al. Characterization of Mycobacterium tuberculosis complex DNAs from Egyptian mummies by spoligotyping. J Clin Microbiol 2003;41:359-67.
2. Cunha B. The death of Alexander the Great: malaria or typhoid fever? Infect Dis Clin North Am 2004;18:53-63.
3. Fauci AS, Morens DM. The perpetual challenge of infectious diseases. New Eng J Med 2012;366:454-61.
4. Stearn EW. The Effect of Smallpox on the Destiny of the Amerindian. Boston: Bruce Humphries; 1945. p. 44-5.
5. Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative reanalysis. Collaborative Group on AIDS Incubation and HIV Survival including the CASCADE EU Concerted Action. Concerted Action on SeroConversion to AIDS and Death in Europe. Lancet 2000;355:1131-7.
6. Woolhouse ME, Gowtag-Sequeira S. Host range and emerging and re-emerging pathogens. Emerg Infect Dis 2005;11:1842-7.
7. Colón-González FJ, Peres CA, Steiner São Bernardo C, Hunter PR, Lake IR. After the epidemic: Zika virus projections for Latin America and the Caribbean. PLoS Negl Trop Dis 2017;11:1-19.
8. GBD 2016 Causes of Death Collaborators. Global, regional and national age-sex specific mortality of 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1151-210.
9. El Bcheraoui C, Mokdad AH, Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, Morozoff C, et al. Trends and patterns of differences in infectious disease mortality among US counties, 1980-2014. JAMA 2018;319:1248-60.
10. World Health Organization. Key events in the WHO response to the Ebola outbreak. Available at: http://www.who.int/csr/disease/ebola/one-year-report/who-response/en/. Accessed on 15 July 2018.
11. Dye C. After 2015: infectious diseases in a new era of health and development. Philos Trans R Soc Lond B Biol Sci 2014;369:20130426.
12. Institute of Medicine (US) Committee on Emerging Microbial Threats to Health. Emerging Infections: Microbial Threats to Health in the United States. Lederberg J, Shope RE, Oaks SJ, editors. Washington, DC: National Academy Press; 1992.
13. Paton NI, Leo YS, Zaki SR, Auchus AP, Lee KE, Ling AE, et al. Outbreak of Nipah-virus infection among abattoir workers in Singapore. Lancet 1999;354:1253-6.
14. Goh KT, Cutter J, Heng BH, Ma S, Koh BKW, Kwok C, et al. Epidemiology and control of SARS in Singapore. Ann Acad Med Singapore 2006;35:301-16.
15. Tay J, Ng YF, Cutter J, James L. Influenza A (H1N1-2009) pandemic in Singapore – public health control measures implemented and lessons learnt. Ann Acad Med Singapore 2010;39:313-24.
16. Morens DM, Fauci AS. Emerging infectious diseases: threats to human health and global stability. PLoS Pathog 2013;9:e1003467.
17. Petersen E, Petrosillo N, Koopmans M, Beeching N, Di Caro A, Gkrania-Klotsas E, et al. Emerging infections – an increasingly important topic: review by the Emerging Infections Task Force. Clin Microbiol Infect 2018;24:369-75.
18. National Library Board, Singapore. SARS outbreak occurs in Singapore. Available at: http://eresources.nlb.gov.sg/history/events/187adc0f-841a-49cb-86e8-86734b65691a. Accessed on 15 September 2018.
19. The Straits Times. First case of Zika virus in Singapore; 48-year-old man who travelled to Sao Paulo. Available at: https://www.straitstimes.com/singapore/health/first-case-of-zika-virus-in-singapore-48-year-old-male-pr-who-travelled-to-sao. Accessed on 15 July 2018.
20. Singapore Zika Study Group. Outbreak of Zika virus infection in Singapore: an epidemiological, entomological, virological, and clinical analysis. Lancet Infect Dis 2017;17:813-21.
21. Vila J. Multidrug-resistant bacteria without borders: role of international trips in the spread of multidrug-resistant bacteria. J Travel Med 2015;22:289-91.
22. Yong D, Toleman MA, Giske CG, Cho HS, Sundman K, Lee K, et al. Characterization of a new metallo-beta-lactamase dene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in Klebsiella pneumoniae sequence type 14 from India. Antimicrob Agents Chemother 2009;53:5046-54.
23. Al Naiemi N, Zwart B, Rijnsburger MC, Roosendaal R, Debets-Ossenkopp YJ, Mulder JA, et al. Extended-spectrum-beta-lactamase production in a Salmonella enterica serotype Typhi strain from the Philippines. J Clin Microbiol 2008;46:2794-5.
24. Woerther PL, Andremont A, Kantele A. Travel-acquired ESBL-producing Enterobacteriaceae: impact of colonization at individual and community level. J Travel Med 2017;24:S29-34.
25. World Health Organization. Blueprint for R&D preparedness and response to public health emergencies due to highly infectious pathogens – workshop on prioritization of pathogens. Available at: https://www.who.int/blueprint/en. Accessed on 15 July 2018.
26. Lysaght T, Capps B, Bailey M, Bickford D, Coker R, Lederman Z, et al. Justice is the missing link in one health: results of a mixed methods study in an urban city state. PLoS One 2017;12:1-11.
27. Hoberg EP, Brooks D. Evolution in action: climate change, biodiversity, dynamics and emerging infectious disease. Phil Trans R Soc B 2015;370:20130553.
28. Dennis S, Fisher D. Climate change and infectious diseases: the next 50 years. Ann Acad Med Singapore 2018;47:401-4.
29. Ryan SJ, Carlson CJ, Mordecai EA, Johnson L. Global expansion and redistribution of Aedes-borne virus transmission risk with climate change. PLoS Negl Trop Dis 2019;13:e0007213.
30. Lo NC, Hotez P. Public health and economic consequences of vaccine hesitancy for measles in the United States. JAMA Pediatr 2017;171:887-92.

31. Phadke VK, Bednarczky RA, Salmon DA, Omer S. Association between vaccine refusal and vaccine-preventable diseases in the United States: a review of measles and pertussis. JAMA 2016;315:1149-58.
32. Béraud G, Abrams S, Beutels P, Dervaux B, Hens N. Resurgence risk for measles, mumps and rubella in France in 2018 and 2020. Euro Surveill 2018;23.
33. Gao F, Bailes E, Robertson D. Origin of HIV-1 in the chimpanzee Pan troglodytes troglodytes. Nature 1999;397:436-41.
34. GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional, and national morbidity, mortality and aetiology of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis 2018;18:1191-210.
35. The Straits Times. Singapore ageing at a faster pace than a decade ago. Available at: https://www.straitstimes.com/singapore/spore-ageing-at-faster-pace-than-a-decade-ago. Accessed on 15 September 2018.
36. Bianchi G, Anderson KC. Understanding biology to tackle the disease: multiple myeloma from bench to bedside, and back. CA Cancer J Clin 2014;64:422-44.
37. Nucci M, Anaissie E. Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. Clin Infect Dis 2009;49:1121-5.
38. Dasanu CA, Alexandrescu D. Does bortezomib induce de facto varicella zoster virus reactivation in patients with multiple myeloma? J Clin Oncol 2009;27:2293-4.
39. Johnsrud AJ, Johnsrud JJ, Susanibar SA, Kamimoto JJ, Kothari A, Burgess M, et al. Infectious and immunological sequelae of daratumumab in multiple myeloma. Br J Haematol 2019;185:187-9.
40. Eiset AH, Wejse C. Review of infectious diseases in refugees and asylum seekers – current status and moving forward. Public Heal Rev 2017;38:22.
41. Sadaragani SP, Lim PL, Vasoo S. Infectious disease and migrant worker health in Singapore. A receiving country's perspective. J Travel Med 2017;24.
42. O'Neill J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. The review on antimicrobial resistance. London: HM Government and the Wellcome Trust; 2016.
43. Tillekeratne LG, Bodinayake CK, Nagahawatte A, Vidanagama D, Devasiri V, Arachchi WK, et al. Use of rapid influenza testing to reduce antibiotic prescriptions among outpatients with influenza-like illness in southern Sri Lanka. Am J Trop Med Hyg 2015;93:1031-7.
44. Neumark T, Brudin L, Mölstad S. Use of rapid diagnostic tests and choice of antibiotics in respiratory tract infections in primary healthcare – a 6-y follow-up study. Scand J Infect Dis 2010;42:90-6.
45. Hoffmann B, Tappe D, Höper D, Herden C, Boldt A, Mawrin C, et al. A variegated squirrel bornavirus associated with fatal human encephalitis. N Engl J Med 2015;373:154-62.
46. Snitkin ES, Zelazny AM, Thomas PJ, Stock F, NISC Comparative Sequencing Program Group, Henderson DK, et al. Tracking a hospital outbreak of carbapenem-resistant Klebsiella pneumoniae with whole-genome sequencing. Sci Transl Med 2012;4:ra116.
47. Bilinski J, Grzelowski P, Sorensen N,Madry K, Muszynski J, Robak K, et al. Fecal microbiota transplantation in patients with blood disorders inhibits gut colonization with antibiotic-resistant bacteria: results of a prospective, single-center study. Clin Infect Dis 2017;65:364-70.
48. Myles IA, Williams KW, Reckhow JD, Jammeh ML, Pincus NB, Sastalla I, et al. Transplantation of human skin microbiota in models of atopic dermatitis. JCI Insight 2016;1.pii:86955.
49. Antoniou T, Hollands S, Macdonald EM, Gomes T, Mamdani MM, Juurlink DN, et al. Trimethoprim-sulfamethoxazole and risk of sudden death among patients taking spironolactone. CMAJ 2015;187:E138-43.
50. Somashekhar SP, Sepúlveda MJ, Puglielli S, Norden AD, Shortliffe EH, Rohit Kumar C, et al. Watson for Oncology and breast cancer treatment recommendations: agreement with an expert multidisciplinary tumor board. Ann Oncol 2018;29:418-23.
51. Ross C, Swetlitze I. IBM pitched its Watson supercomputer as a revolution in cancer care. It's nowhere close. Available at: https: https://www.statnews.com/2017/09/05/watson-ibm-cancer/. Accessed on 14 July 2018.
52. Susskind, Daniel SR. The Future of the Professions: How Technology Will Transform the Work of Human Experts. New York: Oxford University Press; 2017.
53. Klain R. Politics and pandemics. N Engl J Med 2018;379:2191-3.
54. Ng ES, Tambyah PA. The ethics of responding to a novel pandemic. Ann Acad Med Singapore 2011;40:30-5.