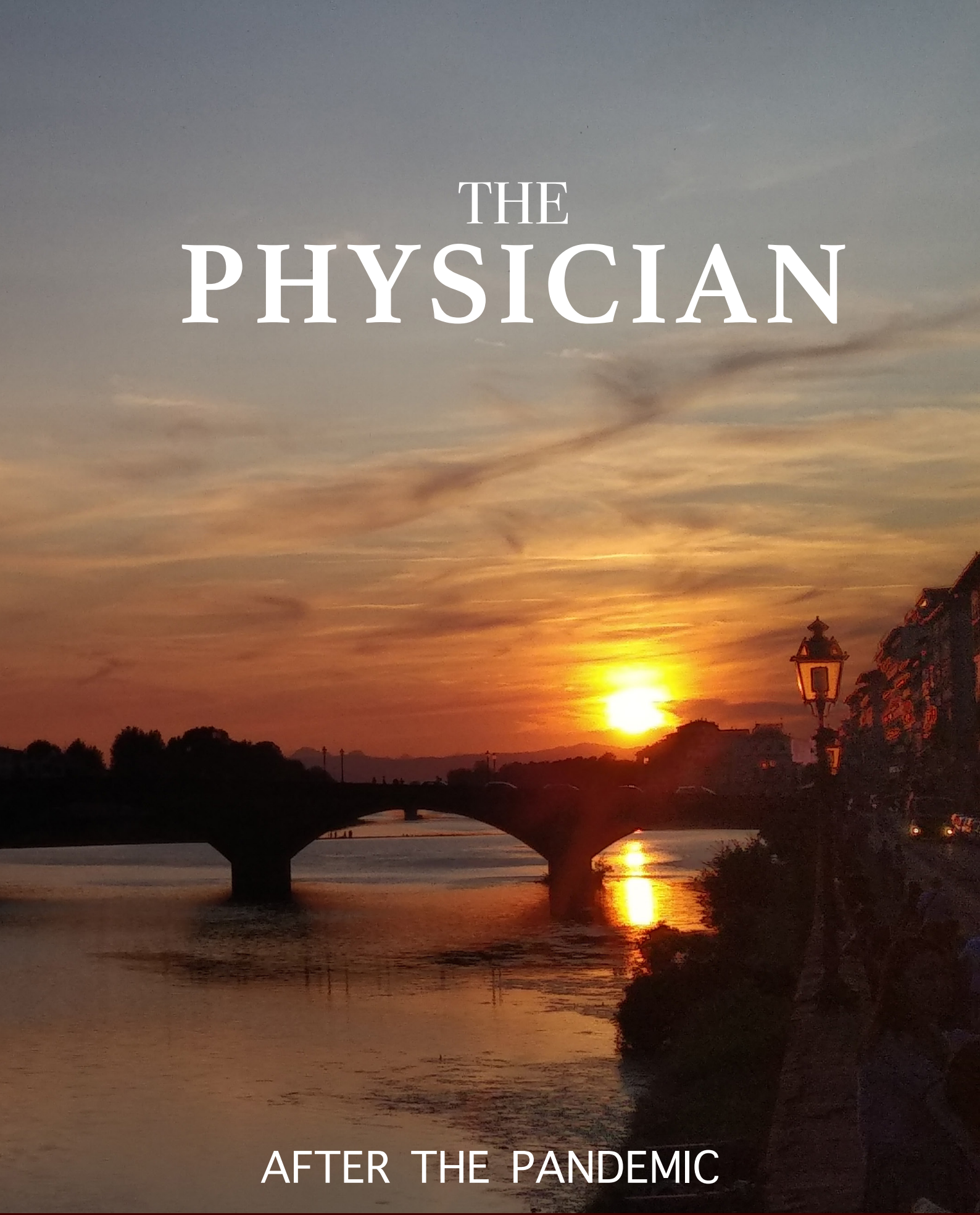

THE PHYSICIAN

AFTER THE PANDEMIC

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IMPACT OF COVID-19

Indranil Chakravorty, Abhay Chopada & Vipin Zamvar

As the world reeling from the surge of COVID-19, prepares to recognise the impact on lives and livelihoods, this editorial explores the sequelae of COVID-19 on patients, people and economies.

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Background

Some parts of the world including the UK, are emerging from the storm of COVID-19. What is presumed to have originated from a market in Wuhan, China back in November 2019, has swiftly spread its devastation across the globe.[1] At the last count in September 2020, there are nearly 900,000 deaths and over 27 million cases.[2] COVID-19 has not only wreaked havoc on lives, health, and livelihoods of humanity but also touched every aspect of civilization, and disrupted every equilibrium that modern society has learned to expect.

Not all such disruption has been destructive, akin to the changes experienced after such catastrophic events as the World Wars, there has been a surge of innovation and progress in many ways. The much-maligned lockdown policies enacted by several governments variably across the world, while brutally separating people from their families and loved ones across continents, has also brought us together. There has never been so much collaboration of scientific, economic, social, and political thinkers across the world. Science and technology, especially digital access has become ubiquitous in every aspect of society. Education and enterprise have been delivered digitally across the internet in almost every country in the world, whether rich or small.

There have been many tragedies, industries such as travel, airlines, and hospitality have folded. Manufacturing that depends on the swift movement of goods or components across the world has halted. Household names have been lost. Even the most 'healthy and resilient' economies have shrunk by almost a third. The effects on employment, therefore livelihoods and lives are huge.

Health is intricately linked to and interdependent on the wealth of economies. So the impact on health even after the COVID-19 pandemic abates (although there are no signs of that yet) will be felt for generations. Yet our survival depends on the indomitable nature of the human spirit. The articles in this issue of The Physician will explore the long view of the impact on health, consider the shoots of recovery, and the nature of innovations and developments which will make the world better equipped to deal with such maladies in the future. As healthcare professionals, we have a duty of care to all our patients and peers.

Impact on Health

There is growing evidence from follow up of patients that the SARS-CoV-2 virus which causes COVID-19 is not restricted in its influence on the pulmonary system but causes a long-lasting impact on multiple systems of the individual. We now know that the virus affects individuals variably dependent on a variety of host factors. The multi-system manifestation of a COVID-19 infection [3,4] is caused by a combination of specific host defense responses with associated inflammatory activity and (micro) vascular involvement with distinct coagulopathy and thromboembolic complications. The hyper-inflammatory tissue response in a proportion of patients leads to multiple organ dysfunction affecting the lungs, heart, kidneys, nerves, muscles, gastrointestinal tract, and brain. In the patients most severely affected, a cytokine "storm" occurs, characterized by very high levels of pro-inflammatory cytokines and Tumour Necrosis Factor (TNF)-α, interleukins, granulocyte-colony stimulating factor, and several chemokines. [5,6] These patients are those at the highest risk of multi-system failure and significant mortality. Males and those with pre-existing hypertension or coronary disease are at higher risk of severe disease, consistent with known correlates of angiotensin-converting enzyme type 2 gene (ACE-2) expression.[7]

Considering the cardiovascular system, cardiac enzyme release can be observed even in the early stages, suggesting myocardial inflammation and damage. [8–10] Acute kidney injury (AKI) and often renal failure are recognized in COVID-19 patients. Although proteinuria, haematuria, and AKI often resolved in such patients, renal complications in COVID-19 are associated with high mortality.[11] Gut and liver dysfunction, manifest by deranged tests of liver function and slow tolerance of enteral feeding, are well recognized. Some patients also report diarrhoea, vomiting, and abdominal pain. SARS-CoV-2 RNA is identified in stool specimens of infected patients, and its viral receptor ACE-2 is found to be highly expressed in gastrointestinal epithelial cells. [12]

Neurologic abnormalities are documented in up to 50% of the most severely ill patients, including impaired consciousness, acute cerebrovascular events, and muscle dysfunction, [13] manifested as headache, nausea, and vomiting. The SARS-CoV has been reported in the brains of both patients and experimental animals, where the brainstem is heavily infected. Furthermore, some coronaviruses have been demonstrated able to spread via a synapse-connected route to the medullary cardiorespiratory center from the mechanoreceptors and chemoreceptors in the lung and lower respiratory airways. [14] Children who are expected to have a low prevalence of disease and manifest only the mildest of symptoms, also are at risk of a multi-system manifestation.[15]

In addition to being male, of greater age and deprivation, diabetes, severe asthma, and various other medical conditions, ethnicity was also found to be a significant determinant of death due to COVID-19. Compared with people of white ethnicity, Black and South Asian people were at higher risk, even after adjustment for other factors. [16]

Once the acute phase is over, there is the issue with a post-viral syndrome which can manifest in long term fatigue, pulmonary, cardiovascular, and renal dysfunction. Post-intensive care syndrome (PICS) patients can have some combination of physical impairment, cognitive impairment, and psychiatric impairment.

In the absence of an established consensus, **Long-COVID** is a term coined and defined and includes, (1) post-acute COVID-19 extending beyond three weeks from the onset of first symptoms and (2) chronic COVID-19 as extending beyond 12 weeks. Since many people were not tested, and that false-negative tests are common, hence a positive diagnosis is not considered essential for consideration in such cases. [17]

Around 10% of patients who have tested positive for SARS-CoV-2 virus remain unwell beyond three weeks, and a smaller proportion for months. A study found that only 65% of people had returned to their previous level of health 14-21 days after a positive test.[18, 19] Recovery after any severe debilitating illness may be prolonged. Survivors of COVID-19 acute respiratory distress syndrome are at risk of long term impairment of lung function. Serious interstitial lung disease seems to be rare in patients who are not hypoxic, though data on long term outcomes are not yet available. Those who have had significant respiratory illness may benefit from pulmonary rehabilitation, which includes, exercise training and behavioural modification

designed to improve the physical and psychological condition. In the context of COVID-19, rehabilitation can be delivered by virtual models. There is much debate and controversy about the role of graded exercise in chronic fatigue generally [20] and in COVID-19 in particular. [21]

Perhaps 20% of patients admitted with COVID-19 have clinically significant cardiac involvement, occult involvement maybe even commoner. Cardiopulmonary complications include myocarditis, pericarditis, myocardial infarction, dysrhythmias, and pulmonary embolus may present several weeks after acute COVID-19. They are commoner in patients with pre-existing cardiovascular disease, [22] but they have also been described in young, previously active patients. [22] In this issue, we present the prevalence data from patients admitted with COVID-19 to a London hospital and the message that up to half of the patients may have persistent cardiac dysfunction needing monitoring. Intense cardiovascular exercise must be avoided for three months in all patients after myocarditis or pericarditis; athletes are advised to take three to six months of complete rest from cardiovascular training followed by specialist follow-up, with the return to sport guided by functional status, biomarkers, absence of dysrhythmias, and evidence of normal left ventricular systolic function

Thromboembolism

COVID-19 is an inflammatory and hypercoagulable state, with an increased risk of thromboembolic events. Many hospitalised patients receive prophylactic anticoagulation. We have reported a case report of a COVID-19 patient returning to the hospital with a major pulmonary embolism. [23] Recommendations for anticoagulation after discharge vary, but higher-risk patients are typically discharged from the hospital with 10 days of extended thromboprophylaxis. It is not known how long patients remain hypercoagulable following acute COVID-19. The case for thrombolysis or management of patients with sub-massive PE remains unclear, as is described from a large case series reported in this issue. [24]

COVID-19 tends to affect older patients more severely. [25] Those who survive are at high risk of muscle wasting, malnutrition, depression, and delirium. Physical symptoms add to the psychosocial impact of disrupted access to health care, personal routines, social interactions.

Most studies report negative psychological effects including post-traumatic stress symptoms, confusion, and anger. Stressors included longer quarantine duration, infection fears, frustration, boredom, inadequate supplies, inadequate information, financial loss, and stigma. Some have suggested long-lasting effects. [26] Most studies on COVID-19 and mental health have emphasised individual reactions to the pandemic such as anxiety, stress, and conditions related to broken routines, loneliness, and social isolation in uninfected individuals; the World Health Organisation has issued guidance on these.[27] Added to the fear of contracting the virus in a pandemic such as COVID-19 are the significant changes to daily lives as movement is restricted, people are faced with new realities of working from home, temporary unemployment, home-schooling of children, and lack of physical contact with others. Both for health workers and patients' wellbeing, mindfulness, social connection, self-care (including diet and hydration) and peer support can mitigate some of the impacts. [28]

This pandemic has exposed many inequalities in society. COVID-19 is more common and has a worse prognosis in the acute phase in people who are poor, elderly, and from certain minority ethnic groups (notably black, south Asian, and Jewish.[29] In a survey with over 1200 responses, the majority (94%) from BAME backgrounds, a quarter of respondents reported inadequate personal protective equipment, 2/3 could not comply with social distancing and a third reported being reprimanded in relation to PPE, or avoidance of risk. [30] It is imperative that employers consolidate risk reduction measures and foster a culture of safety to encourage employees to voice any safety concerns. It is too early to say whether these sociodemographic patterns persist in post-acute COVID-19. Some have experienced family bereavements as well as job losses and consequent financial stress and food poverty. The strain on many carers has been high. For an important few, the lockdown has worsened safeguarding concerns such as the risk of a child or intimate partner abuse.

The direct costs of the COVID-19 pandemic associated with illness and mortality are lower than the indirect losses caused by the crisis. [31] A low impact of COVID-19 in terms of case numbers and deaths does not necessarily translate into a low economic impact. Many countries are experiencing a recession, even though COVID-19 has not had a serious effect on them in terms of health. Even minor public health events can severely affect firms in lower-income countries due to their poor socio-economic conditions (vulnerability) and their weak capacity to respond to crises (resilience). Moreover, in a globalised world, many countries are suffering indirect consequences from value chain disruptions and lower international demand for goods due to widespread recession. The growing COVID-19 crisis threatens to disproportionately hit developing countries, not only as a health crisis in the short term but as a devastating social and economic crisis over the months and years to come. [31] Income losses are expected to exceed $220 billion in developing countries. With an estimated 55 percent of the global population having no access to social protection, these losses will reverberate across societies, impacting education, human rights, and, in the most severe cases, basic food security and nutrition.

Under-resourced hospitals and fragile health systems are likely to be overwhelmed. This may be further exacerbated by a spike in cases, as up to 75 percent of people in the least developed countries lack access to soap and water. Additional social conditions, such as poor urban planning and overpopulation in some cities, weak waste disposal services, and even traffic congestion impeding access to healthcare facilities, may all add to the caseload.[32]

The June 2020 Global Economic Prospects [33] describes both the immediate and near-term outlook for the impact of the pandemic and the long-term damage it has dealt with prospects for growth. The baseline forecast envisions a 5.2 percent contraction in global GDP in 2020, using market exchange rate weights—the deepest global recession in decades, despite the extraordinary efforts of governments to counter the downturn with fiscal and monetary policy support. Over the longer horizon, the deep recessions triggered by the pandemic are expected to leave lasting scars through lower investment, an erosion of human capital through lost work and schooling, and fragmentation of global trade and supply linkages.

Policies to rebuild both in the short and long-term entail strengthening health services and putting in place targeted stimulus measures to help reignite growth,

including support for the private sector and getting money directly to people. During the mitigation period, countries should focus on sustaining economic activity with support for households, firms, and essential services. Global coordination and cooperation—of the measures needed to slow the spread of the pandemic, and of the economic actions needed to alleviate the economic damage, including international support—provide the greatest chance of achieving public health goals and enabling a robust global recovery.[20]

The pandemic has also shifted the expectation matrix away from physical consultation towards virtual consultation this will also spare on more integration of technology and enable universal models of care delivery. Integration across various disciplines including data sciences and clinicians along with electronic engineers hopefully bring about a positive change for future health care delivery models.

We certainly look towards the future of optimism and recognise human resilience as the single most important factor, which should allow us to work through this unpredictable and unfortunate phase of having faced a global pandemic and build a better future.

Bibliography

1. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-273. doi:10.1038/s41586-020-2012-7
2. Coronavirus Update (Live): 27,069,697 Cases and 883,771 Deaths from COVID-19 Virus Pandemic - Worldometer. Accessed September 6, 2020. https://www.worldometers.info/coronavirus/
3. Zheng KI, Feng G, Liu W-Y, Targher G, Byrne CD, Zheng M-H. Extra-pulmonary complications of COVID-19: a multi-system disease? J Med Virol. Published online July 10, 2020. doi:10.1002/jmv.26294
4. Covid-19: a complex multisystem clinical syndrome. The BMJ. Published May 1, 2020. Accessed September 6, 2020. https://blogs.bmj.com/bmj/2020/05/01/covid-19-a-complex-multisystem-clinical-syndrome/
5. Hu B, Huang S, Yin L. The cytokine storm and COVID-19. J Med Virol. Published online June 27, 2020. doi:10.1002/jmv.26232
6. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet. 2020;395(10229):1033-1034. doi:10.1016/S0140-6736(20)30628-0
7. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020;395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3
8. Szekely Yishay, Lichter Yael, Taieb Philippe, et al. Spectrum of Cardiac Manifestations in COVID-19. Circulation. 2020;142(4):342-353. doi:10.1161/CIRCULATIONAHA.120.047971
9. Kang Y, Chen T, Mui D, et al. Cardiovascular manifestations and treatment considerations in COVID-19. Heart. 2020;106(15):1132-1141. doi:10.1136/heartjnl-2020-317056
10. Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. Nature Reviews Cardiology. 2020;17(5):259-260. doi:10.1038/s41569-020-0360-5
11. Pei G, Zhang Z, Peng J, et al. Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia. J Am Soc Nephrol. 2020;31(6):1157-1165. doi:10.1681/ASN.2020030276
12. Wong SH, Lui RN, Sung JJ. Covid-19 and the digestive system. J Gastroenterol Hepatol. 2020;35(5):744-748. doi:10.1111/jgh.15047
13. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. Published online April 10, 2020. doi:10.1001/jamaneurol.2020.1127
14. Li Y-C, Bai W-Z, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. Journal of Medical Virology. 2020;92(6):552-555. doi:10.1002/jmv.25728
15. BAME children are most at risk of developing Multisystem Inflammatory Syndrome-Temporally Associated with COVID-19 | The Physician. Accessed September 6, 2020. https://physicianjnl.net/index.php/phy/article/view/35
16. Collaborative TO, Williamson E, Walker AJ, et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. medRxiv. Published online May 7, 2020:2020.05.06.20092999. doi:10.1101/2020.05.06.20092999
17. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. BMJ. 2020;370. doi:10.1136/bmj.m3026
18. Tenforde MW, Kim SS, Lindsell CJ, et al. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March-June 2020. MMWR Morb Mortal Wkly Rep. 2020;69(30):993-998. doi:10.15585/mmwr.mm6930e1
19. Mahase E. Covid-19: What do we know about "long covid"? BMJ. 2020;370. doi:10.1136/bmj.m2815
20. Larun L, Brurberg KG, Odgaard-Jensen J, Price JR. Exercise therapy for chronic fatigue syndrome. Cochrane Database Syst Rev. 2017;4:CD003200. doi:10.1002/14651858.CD003200.pub7
21. statement.pdf. Accessed September 13, 2020. https://www.nice.org.uk/guidance/gid-ng10091/documents/statement
22. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. Published online March 25, 2020. doi:10.1001/jamacardio.2020.0950
23. Rahimzadeh M, Pooprasert P. Pulmonary Embolism in a Post Covid-19 Patient - A Case Report. phy. 2020;6(1). doi:10.38192/1.6.1.8
24. Asthana A, Konar N, Chakravorty I. Mortality from Pulmonary Embolism by Clinical Severity. phy. 2020;6(2). doi:10.38192/1.6.2.17
25. Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. J Infect. 2020;80(6):639-645. doi:10.1016/j.jinf.2020.03.019
26. Brooks SK, Webster RK, Smith LE, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. The Lancet. 2020;395(10227):912-920. doi:10.1016/S0140-6736(20)30460-8
27. Mental health and COVID-19. Accessed September 6, 2020. https://www.who.int/teams/mental-health-and-substance-use/covid-19
28. Mistry M. Mindfulness for Healthcare Professionals. Sushruta Journal of Health Policy & Opinion. 2019;12(1):33-33. doi:10.38192/12.1.19
29. Disparities in the risk and outcomes of COVID-19. :92.
30. Daga S, Jafferbhoy S, Menon G, et al. Does Gender or Religion Contribute to the Risk of COVID-19 in Hospital Doctors in the UK? Sushruta Journal of Health Policy & Opinion. 2020;13(3):1-11. doi:10.38192/13.3.1
31. Coronavirus: the economic impact – 10 July 2020 | UNIDO. Accessed September 13, 2020. https://www.unido.org/stories/coronavirus-economic-impact-10-july-2020
32. COVID-19: Looming crisis in developing countries threatens to devastate economies and ramp up inequality. UNDP. Accessed September 6, 2020. https://www.undp.org/content/undp/en/home/news-centre/news/2020/COVID19_Crisis_in_developing_countries_threatens_devastate_economies.html
33. The Global Economic Outlook During the COVID-19 Pandemic: A Changed World. World Bank. Accessed September 6, 2020. https://www.worldbank.org/en/news/feature/2020/06/08/the-global-economic-outlook-during-the-covid-19-pandemic-a-changed-world

Perspective

Poor metabolic health is a major issue for increased COVID-19 mortality in BAME groups

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Editorial Note

Type 2 diabetes mellitus and hypertension are the most common co-morbidities in patients with coronavirus infections. Emerging evidence demonstrates an important direct metabolic and endocrine mechanistic link to the viral disease process. Metabolic syndrome (METS) is a common denominator to these co-morbidities and includes insulin resistance, dyslipidaemia, central obesity and hypertension, which are risk factors for the development of type 2 diabetes and cardiovascular diseases. In 2017, it was estimated that METS affected 20% of the North American population, 25% of the European population and approximately 15% of the Chinese population. In this scenario, the relationship between METS and its comorbidities that aggravate the COVID-19 prognosis cannot be ignored. Also, its presence in different ethnicities and continents places METS as an important risk factor for COVID-19. The authors offer their scientific and epidemiological perspective on this emerging association and urge an international awareness of its devastating consequences among certain populations. This article welcomes debate among scientists, policymakers and wider community leaders.

The authors urge clinicians to encourage thorough metabolic control for all patients at risk of COVID-19. (a,b)

The Physician welcomes contributions from interested scientists, policymakers and patient representative organisations to continue this discourse.

Introduction

According to Public Health England those from Black, Asian and Minority Ethnic (BAME) backgrounds are at increased risk of poor outcomes from COVID-19. After accounting for effect of sex, age, deprivation and region Bangladeshi's are twice risk of death compared to white British. Other ethnic groups including Chinese, Indian, Pakistani, other Asian, Caribbean and other black ethnicity had a 10-50% increased mortality risk. However, correcting for "co-morbidities" the risk is greatly reduced if not eliminated. [1] It is a known fact that those from South Asian backgrounds (2 billion of the world's population) have a type 2 diabetes prevalence at least twice as high as Caucasians and develop the condition five to ten years earlier at lower levels of adiposity.[2] Two thirds of type 2 diabetes deaths are due to thrombotic complications and amongst Asian Indians in India 52% of cardiovascular death occurs prematurely, in those under the age of 70. [3] If these premature fatalities trends from heart attack and stroke continue it's estimated that it will cost the Indian economy $2 trillion by 2030.

Why the greater risk amongst BAME?

Obesity and conditions of the metabolic syndrome are associated with impaired innate and adaptive immunity. Underlying chronic inflammation also linked to excess body fat appears to potentiate risk of the cytokine storm of the Acute Respiratory Distress syndrome. [4] Optimal metabolic health is having all five, and the metabolic syndrome (METS) is defined as failing to achieve at least three of the following:

- **Blood Pressure (systolic <120 and diastolic <80mmHg)**
- **HbA1c< 5.7%**
- **Waist Circumference <102cm for a man <88cm for a woman (for south Asians it's <90cm for a man and <85cm for a woman)**
- **Blood Triglycerides <1.7mmol/l (< 150mg/dL)**
- **HDL-C >1mmol/l (>40/50mg/dL for men/women)**

Disturbingly only 1 in 8 American adults are now considered to have optimal metabolic health. [5] Although there are age disparities, the young are also adversely affected with 1 in 4 aged between 20 and 40 having optimum parameters. On a biological level chronic hyperinsulinemia and/or insulin resistance is strongly associated in the pathogenesis and likely causal. [6] But just as racism is endemic in the UK National Health Service (NHS)racial bias exists in the identification and management of patients from BAME backgrounds at high risk. Using Body Mass Index (BMI) as a proxy for "healthy weight" may provide the illusion of protection and will miss a substantial proportion of those fromblack and south Asian ethnic minority groups with METS risk. This is due to an inherent propensity for METS even at lower levels of intra-abdominal adiposity. For example, data from the United States reveals 43.6% of normal BMI south Asians are metabolically unhealthy, compared to 38.5% in Hispanics, 32.2% in Chinese Americans, 31.1% in African Americans, and 21% in whites. Normal BMI metabolically unhealthy have a threefold increased all-cause mortality and or cardiovascular event risk compared to metabolically healthy normal weight over a ten-year period. [7] Unfortunately, the current NHS risk assessment tool doesn't directly measure metabolic health which is a more sensitive method to identify and subsequently manage BAME individuals at high risk.

Identifying and managing the causes of the causes.

Eighty percent of chronic metabolic disease is rooted in lifestyle and environment. Medical literature data is not well publicised on the dietary and lifestyle behaviours of those from BAME backgrounds but what is available paints a concerning picture. In essence an inherent susceptibility to METS is then exacerbated by poor lifestyle behaviours.

Poor Diet

A 2007 study in JAMA revealed low intake of whole fruit and vegetables, as a risk factor for early myocardial infarction, was very common amongst South Asians, living in the US even amongst vegetarians. [8] Furthermore, the average Indian is consuming more than double the ideal maximum limit of sugar recommended as daily intake from the World Health Organisation. [9] A diet high in refined carbohydrates and ultra-processed foods is likely to be a causative factor in driving metabolic syndrome in South Asians.

Inadequate physical activity

A cross sectional study revealed that South Asians may require 233 minutes a week of moderate activity a week to have the same cardiometabolic benefits of white Europeans carrying out 150 minutes. South Asians, in part due to lower muscle mass, may have a genetic predisposition to lower cardiorespiratory fitness than Caucasians. [10] Amongst all BAME groups in the UK average levels of physical activity are also considerably lower that white British. The latest data from sport England reveals 62% of adults in England meet the Chief Medical Officer's physical activity guidelines compared to just 56% of Black people and 55.1% of Asians.

Low Vitamin D status

Vitamin D plays an essential role in innate and adaptive immunity. Severe Vitamin D deficiency which has been strongly correlated with adverse outcomes from COVID-19 also has a high prevalence amongst BAME groups in the UK. The majority of those from South Asian of Black backgrounds are either deficient or severely deficient. [11]

It's imperative that those from BAME backgrounds know their Vitamin D status but it's not currently routinely measured in primary care. In those who are deficient measures should be taken to correct it. More sun exposure is required to generate adequate levels compared to those of lighter skin colour. If it is not possible to obtain adequate levels through increased sun exposure or through diet then supplementation should be offered. The most important food sources of Vitamin D are fatty fish, cod liver oil, eggs and mushrooms.

Health inequalities require a broader approach

Numerous dietary intervention studies reveal rapid benefits in improving metabolic risk factors. [12] It is plausible that this would also simultaneously reduce risk of severity of COVID-19 complications. For example, better glucose control on hospital admission in type 2 diabetes patients has revealed a ten-fold difference in COVID-19 mortality risk between those with the worst control. [13] A recent small randomised trial revealed reversal of METS in over half of participants within 28 days of a dietary changes in obese adults. This was independent of weight loss. [14]

More research and publicity on diet and lifestyle interventions in metabolically unhealthy BAME groups including those with a normal BMI who are at highest risk is also urgently required. We also cannot ignore the bigger picture issue. All the biological risk factors (as well as increased psychological stress) in ethnic minority groups will be fueledby socio-economic factors. The disproportionate impact of COVID-19 on BAME communities has also highlighted racial and social injustices. The power of modern medicine is dwarfed by the power of prevention and the wider determinants of health.

In our view the medical profession and policy makers have an ethical and moral duty to be advocates for policy change to reduce health inequalities. [15] This would have a far greater impact on population health than downstream individually tailored behaviour change. As pioneering German Physician Rudolf Virchow said, *"for medicine to fulfil her greatest task she must also enter the political and social life".* But the evidence is clear, time for action on metabolic health is long overdue. Otherwise there will be even more misery and devastation when the next pandemic comes round.

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References

a. Bornstein, S.R., Dalan, R., Hopkins, D.et al.Endocrine and metabolic link to coronavirus infection.Nat Rev Endocrinol16,297–298 (2020). https://doi.org/10.1038/s41574-020-0353-9

b. Costa, F.F., Rosário, W.R., Farias, A.C.R., de Souza, R.G., Gondim, R.S.D., Barroso,W.A. Metabolic syndrome and COVID-19: An update on the associated comorbidities and proposed therapies. Diabetes & Metabolic Syndrome: Clinical Research & Reviews,202014(5),809-814, https://doi.org/10.1016/j.dsx.2020.06.0161.

1. Harrison, E., Docherty, A., Semple, C. (2020) Investigating associations between ethnicity and outcome from COVID-19 UK Gov CO-CINePub 25/04/2020(accessed 7.7.2020) https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/886433/s0238-co-cin-report-ethnicity-outcomes-250420-sage29.pdf

2. Unnikrishnan, R., Anjana, R.M., Mohan, V. (2014) Diabetes in South Asians: Is the Phenotype Different?Diabetes63(1)53-55;DOI:10.2337/db13-1592

3. Chauhan, S., Tamber Aeri, B. (2013) Prevalence of cardiovascular disease in India and its economic impact-A review. Int J Scien ResPubl, 3(10)http://www.ijsrp.org/research-paper-1013/ijsrp-p2234.pdf(accessed 7.7.20)

4. Andersen CJ, Murphy KE, Fernandez ML. (2016) Impact of Obesity and Metabolic Syndrome on Immunity.Adv Nutr. 7(1):66-75. doi:10.3945/an.115.0102075.

5. Arau jo, J.,Cai,J., Stevens,J.(2019) Prevalence of Optimal Metabolic Health in American Adults: National Health and Nutrition Examination Survey 2009–2016. Metabolic syndrome and related disorders. 17(1) Mary Ann Liebert, Inc. Pp. 46–52 DOI: 10.1089/met.2018.0105

15.Berwick DM. The Moral Determinants of Health.JAMA.Published online June 12, 2020. doi:10.1001/jama.2020.11129

6. Kelly, C.T., Mansoor,J.,Dohm, G.L.,Chapman III, W.H.H., Pender IV,J.R., Pories,W.J.(2014) Hyperinsulinemic syndrome: The metabolic syndrome is broader than you think.Surgery 156 (2); 405-411https://doi.org/10.1016/j.surg.2014.04.028

7. Stefan, N., Schick, F., UlrichHaring, H. (2017) Causes, Characteristics, and Consequences of Metabolically Unhealthy Normal Weight in Humans. Cell Metabolism26 (2) 292-300https://doi.org/10.1016/j.cmet.2017.07.008

8. Joshi P, Islam S, Pais P, et al. Risk Factors for Early Myocardial Infarction in South Asians Compared With Individuals in Other Countries.JAMA.2007;297(3):286–294. doi:10.1001/jama.297.3.286

9. Dasgupta R, Pillai R, Kumar R, Arora NK. Sugar, salt, fat, and chronic disease epidemic in India: is there need for policy interventions?.Indian J Community Med. 2015;40(2):71-74. doi:10.4103/0970-0218.153858

10. Iliodromiti S, Ghouri N, Celis-Morales CA, Sattar N, Lumsden MA, Gill JM. Should Physical Activity Recommendations for South Asian Adults Be Ethnicity-Specific? Evidence from a Cross-Sectional Study of South Asian and White European Men and Women. PLoS One. 2016;11(8):doi:10.1371/journal.pone.0160024 doi:10.1172/jci.insight.128308

11.Patel, J.V., Chackathayil, J., Hughes, E.A., Webster, C., Lip, G.Y.H., Gill, P.S. (2012) Vitamin D deficiency amongst minority ethnic groups in the UK: a cross sectional study. Int J Cardiol 167 (5) 2172-2176 https://doi.org/10.1016/j.ijcard.2012.05.081

12. Hu T, Mills KT, Yao L, et al. (2012) Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: a meta-analysis of randomized controlled clinical trials.Am J Epidemiol. 176(Suppl 7):S44-S54doi:10.1093/aje/kws264

13. Zhu L, She ZG, Cheng X, et al. (2020) Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes.Cell Metab. 31(6):1068-1077.e3. doi:10.1016/j.cmet.2020.04.021

14. Hyde PN, Sapper TN, Crabtree CD, et al. (2019) Dietary carbohydrate restriction improves metabolic syndrome independent of weight loss.JCI Insight. 4(12):

A History of pandemics over the ages and the human cost

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Abstract

The present CoVid-19 pandemic has occupied our imagination and has affected our lives like never before. There had been pandemics before from ancient times that had profoundly affected and influenced human civilisation in every aspect known.

Dynamics of pandemics have evolved as civilisation progressed and pandemics were often facilitated by technological advances. However, pandemics also were stark reminders of inequalities that have always existed in human society. Pandemics demand social distancing and social isolation for containment as they are spread by contagion and thus threaten human existence driven by a delicate social fabric.

This article traces the history of pandemics from the Roman times to the present day and presents an overview of these pandemics and their human cost.

Introduction

We are living in unprecedented times with the CoVid-19 pandemic, times that occur once in generations. Apart from the human cost in lives and disease, a pandemic affects governments, infrastructure of countries, economy and most of all the very social fabric of civilisation that includes our values. The toll is widespread and affects the whole human race in all aspects of their existence. Pandemics repeat themselves forcing us to learn from our past and shape our present and future accordinglyPandemic can be defined in epidemiological terms as "an epidemic occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people"[1,2].

A pandemic or an epidemic is theaffliction of the human race by invading microorganisms that infect humans leading to disease and in many instances death. The hallmark of an epidemic or a pandemic is its spread by contagion that is determined by the virulence of the organism concerned and by complex social, economic and political dynamics. This implies that the speed of spread can outstrip the efforts to contain it. Marcus Aurelius, the philosopher emperor of Rome, who following the Antonine Plague in the Roman empire in in 166 CE wrote: , "To bear in mind constantly that all of this has happened before and will happen again—the same plot from beginning to end, the identical staging."[3] This observation resonates to this day.This article traces the history of pandemics affecting the human race from the ancient world to present times and discusses the effect they had on our civilisation. We have selected only those where the estimated death toll was in excess of 100,000 and where the outbreak was a true pandemic crossing geopolitical boundaries or those pandemics that fit the WHO definition of 'the worldwide spread of a new disease'. Therefore we have not included either the small pox epidemic in the New World during the Spanish conquest or the Great Plague of London as although they had a huge toll in human lives, were still confined to geopolitical boundaries making them epidemics rather than pandemics.

We have similarly left out small pox in 15th-19th century Europe as this was endemic rather than pandemic and had been identified since the times of Galen. We have further excluded HIV/AIDS that has killed an estimated 35 million people worldwide as the WHO considers it as a global epidemic rather than a pandemic.

Table 1 illustrates the different epidemics and pandemics since ancient times to the present day.

The pandemics[1].

The Antonine plague circa 165 –180 AD

The Roman empire was at its height during the reign of Marcus Aurelius Antoninus who lodged successful campaigns in Dacia, Armenia and Parthia. The victorious Roman army returned with an infection that ravaged not only Rome but the empire and its vassals in Eastern and Western Europe and left 5 million people dead in its wake. The direct fallout was an increased persecution of the Christians in the false belief that they started the pestilence and a severe curtailment of the mighty Roman army. In fact Commodus who succeeded Marcus Aurelius can be considered as the first emperor of the declining Roman Empire and the end of Pax Romana [4].

It also significantly affected Roman trade, especially with China, leading to a substantial drop in revenue and adding to the weakening of the empire. However, from the medical perspective, the association of Claudius Galenus, the court physician of Marcus Aurelius with the plague deserves special mention. His writings chronicling the symptoms and signs of the disease is a treatise de force on systematic study of medicine and from his descriptions, it appears that the disease could have been small pox rather than plague [5].

2. The plague of Justinian, the first plague pandemic circa 541-542 AD

This plague was the classical Yersinia pestis bacterium transmitted through rodents. Justinian was one of the greatest of Roman emperors in Byzantium in eastern Europe and Asia with Constantinople as his capital at the height of his power. The organism was very likely imported from eastern Asia through Egyptian ports like Pelusium near present day Port Said as described by Procopius the historian 6and then spread east. It devastated much of Europe and western Asia including the Sassanid empire in Persia.

It decimated up to 40% of Constantinople's population and about 50% of the Eurasian population in three waves that continued until the 8th century[7]–an estimated 30-50 million people. This pandemic dealt a severe blow to Justinian's flourishing empire. There were hardly sufficient people to till the land, so agricultural output dropped dramatically. There was little land revenue coming in. The army was significantly weakened. The plague led to widespread revolts across the empire and heralded in 2 world orders –the rise of the Franks in western Europe and the rise of Islam in the middle east [8].

Procopius wrote, "All work slackened; craftsmen abandoned all their crafts and every task which any man had in hand."[6]. After 1.5 millennia, during the current CoVid-19 pandemic, this is a striking similarity.

3. The Black Death, the second plague pandemic 1345 –1353

The plague that hit Justinian times did not extinguish completely but simmered. As with other pathogens the organism mutated and assumed a more virulent form9. It spread through the silk route in the medieval world from Mongoliaand before sweeping across Asia, Europe and North Africa from 1345 leaving nearly 200 million dead and whole regions devastated. Boccacio's Decameron graphically merged passion and plague in 14th century Florence [10]. Guy de Chaulliac, the eminent contemporary French surgeon wrote in 1363: "the father no longer visited the son or the son his father. Charity was dead and hope abandoned." [9]. de Chaulliac's stark observation about suffering relationships rings a strange bell in 2020. Fear was all pervasive. The main sting of the second pandemic was over in 8 years but it regularly made its appearance as late as the early part of the 19th century throughout defined countries in Europe and Asia.

The effect of the Black Death was profound affecting every aspect of society. Governments raised taxes from the survivors. The poll tax or a charge on services was introduced that continue to this day in UK as the council tax. Agriculture ceased leading to a severe deficit in food stuff as the landed gentry could not employ labourers from the rural communities due to the sheer number of dead. The feudal world and serfdom took a significant back seat 11 as common folk exercised more choices as to who they would work for influencing the dynamics of labour. Minority persecution was at its peak. However, it also led to a development of public health services with improved sanitation and quarantine methods that eventually paid dividends in later outbreaks.

4. The cholera pandemics 1817 –present day

There have been six pandemics of cholera caused by the bacterium Vibrio cholerae spread by the fecal-oral route and the seventh one is still continuing. Cholera pandemic is a prime example as to how science and public health measures can control the spread of infection and with each pandemic, there were new discoveries as to the causation and more importantly how to contain it. As a result, death rates have dropped dramatically.

The first pandemic (1817-1823) originated in British India in the Gangetic basin and was exported from Calcutta in 1817, when the British East India Company had conquered much of India and life was relatively peaceful with no fresh new war looming. There was an influx of British personnel including military who came to India after the Anglo-Mysore War in 1799 and to southeast Asia to maintain trading colonies. It struck these regions before making its way to the Mediterranean coast.

The second pandemic (1829-1849) travelled to Russia and thence to Europe and finally through Irish immigrants to the Americas[12]. The third pandemic (1846 –1862), the most devastating of all, ravaged all continents. There was a reason for it. As Snowden [13] eloquently described, "the Industrial Revolution and its pathologies created favouring conditions. Cholera thrived on such features of early industrial development as chaotic and unplanned urbanization, rapid demographic growth, crowded slums with inadequate and insecure water supplies, substandard housing, an inadequate diet, ubiquitous filth, and the absence of sewers. When the vibrio disembarked in the port cities of Marseille, Hamburg, Valencia, and Naples, it found ideal conditions awaiting it." London was the melting pot of the colonies and here it was particularly virulent decimating nearly 23,000 lives in 1854.The fourth pandemic (1865 –1875) spread through Muslim Haj pilgrims and hit Mecca first before spreading to Europe. The fifth pandemic (1881 –1896) took its toll in Asia, South America and parts of Europe and Germany but spared USA and Britain due to improved sanitation and identification of the source with quarantine methods in force. By this time the organism had been identified by Robert Koch. The sixth pandemic (1899 –1923) affected parts of North Africa, the middle east, Europe and most of all India. The current pandemic that started in 1961 originated in Indonesia and is still claiming lives albeit much less compared to before[15].

Cholera differs from other disease pandemics in three broad aspects. Firstly it was a 'class conscious' affliction and did not affect the well to do middle class or the rich. It was a disease exclusively confined to the lower middle class and the poor due to unhygienic living conditions. Secondly, its spread was facilitated by improved transport and the intense political turmoil ongoing in Europe at the time. Thirdly it generated more fear than plague in people as nearing death the human form adopted what can be called a 'death grimace' due to dehydration and the symptoms were often dramatic.

Again in Snowden's words13, this terror ledto "mass flight, riot, social hysteria, scapegoating, and economic disruption". Cholera claimed a death tally of nearly 1 million and it is a great credit to the ingenuity of science that the death toll was not as high as plague.

John Snow in London in 1854 correctly identified a water pump in Soho as the sourceof cholera and then quarantined the area leading to a drastic fall in deaths. William Brooke O'Shaughnessy, professor of chemistry in the nascent Calcutta Medical College propounded the theory of replacing dehydration by saline therapy in 1831. This was followed up by Thomas Latta in 1832 who physically performed the experiment and published it but died of the disease[14]. The science of epidemiology blossomed and with it sanitation methods. The sewers of Paris and Naples to exclude human efflux were refurbished and rebuilt setting examples.Plague, syphilis, tuberculosis and small pox have led to creativity and were depicted in arts in several ways as they involved allclasses (Figure 1). Cholera was a filth that originated from the gutters and sewers in the lowest of human class and did not evoke much artistic movement. In Gabriel Garcia Marquez's Love in the Times of Cholera, cholera was only in the background[13].

Compare this to Boccacio's Decameron where the central theme of his novel was the plague and how people reacted to it. Luchino Visconti in adapting Thomas Mann's 'Death in Venice' (1971) as a film kept cholera hovering in the background as an unwanted pest whereas Ingmar Bergman's 'The Seventh Seal' (1957) romanticised death from plague in a human form playing chess with a knight (Figure 2)[5].

The third plague (1855 –1912)

The third plague incorporated both the pneumonic and the bubonic variety of Yersinia pestis. It originated in China in 1855, made its way to Hong Kong and finally erupted in 1894.

A Figure 1: Artistic depiction of plague -Saint Sebastian pleads with Jesus for the life of a gravedigger afflicted by plague during the Plague of Justinian. Josse Lieferinxe, c. 1497–1499, Walters Art Museum. (This work is in the public domain https://commons.wikimedia.org/wiki/File:Plaguet03.jpg)

A number of factors were responsible for its spread. Ease of transport, increased maritime trade in the colonies and increased demand for migrant labour facilitated its spread like wildfire in the east. Coupled with this were the stark poverty, lack of hygiene and sanitation that the populace in these parts faced.When it reached Europe through the ports, the devastation was limited to these cities by the sea or river estuaries. In fact Europe was largely spared of much mortality or spread due to better sanitation, general health and stricter control of public health.

It reached London in 1896 carried by two Indian sailors and within a few months, a conference on plague epidemiology concurred on public health measures to control the outbreak. Besides, the third plague like the cholera pandemics was mainly limited to only the poor classes [15].

In India it was different. The pestilence hit India in 1896 and swept across the country from the ports especially Bombay. It was given much fuel by an emaciated and starving population already devastated by a famine due to prolonged draught in 1897 that decimated part of the population. It must be remembered that sanitation and sewerage disposal in big colonial metropolis like Bombay and Calcutta were literally non-existent. Dedicated underground sewerage work in the cities started in the 1870s but were limited to the affluent parts and not in the slums. In addition, this teeming mass of humanity engaged in every trade imaginable requiring godowns for storage which bred the rats. Rodent density flourished and with it the fleas and the plague bacillus [13]. Imbibed with the fruits of western industrial revolution, the wealthy had a vastly improved quality of life but the condition of the poor remained as they had been for centuries. Out of a total 12 million dead globally, India accounted for as much as 90%.

This plague had a profound political impact in India. The British government enforced draconian sanitation measures and propagated a racial disharmony. The ruling class and the wealthy were not affected by the plague unlike the Justinian or the Black Death which led to the idea that the disease spared the white race by divinity. Further, these measures hurt traditional Indian religious sentiments. There was a violent back lash.

The first political assassination in India in colonial times post 1857 Sepoy Rebellion took place in Pune in 1897 when three Chapekar brothers shot dead Rand, the Indian Civil Service plague inspector and Ayerst, his deputy. The brothers' execution inspired the armed struggle against British rule that continued until the 1930s and finally culminated in the 1940s with the formation of the Indian National Army of Subhash Chandra Bose who contributed significantly to India's freedom. A similar political fallout during the third plague was in South Africa where segregation wasstrictly enforced in quarantine camps that probably led to Apartheid being adopted officially.

The plague also saw breakthroughs in medicine. The bacillus was discovered during this time by Yersin and Kitasato in 1894 and for the very first time vector transmission of disease was identified9. The first systemic studies in immunology commenced and W Haffkine, a Ukrainian living in India developed a plague vaccine. Sanitation techniques were refined and there were 'rat hunting campaigns'. The disease smouldered and was finally extinguished in 1940. It however still remains in patches especially in Africa.

6. The Flus 1889 –2010

For the purposes of this article and for brevity, flu and influenza will be used interchangeably.There had been several flu pandemics with evolving strains of the influenza virus over the last two centuries. The Russian flu pandemic in 1889 –1890 started in Asia Minor and was imported to Russia especially St Petersburg via Constantinople. It then reached Paris in two months and engulfed the whole of Europe. The death toll was 1 million. This was a pandemic that was most rapidly spread as a result of increased world population and the massive transport revolution brought about by the railways. In addition, this was the first pandemic that was systemically covered with accurate epidemiological data in the press[16].The most well-known and intense flu pandemic from the number of dead point of view was the Spanish flu, so named as it was most reported in Spain who had been neutral duringthe first world war and was not subjected to wartime censorship[2]. Astonishingly the flu only lasted for 1 year from 1918 to 1919, yet it killed nearly 40 million people worldwide. The vast majority of mortality was in young adults. The death toll was attributed to secondary bacterial infections [17] and possibly a cytokine storm much like what is happening in the COVID-19 pandemic.The Spanish flu can be deemed as a collateral of the first world war. War obligated massive troop movements by enhanced transport and the set-up of military camps all over Europe. It probably originated in a military base hospital for British troops in France in 1918, a camp that not only processed war casualties who may have been exposed to gas attacks, but also was regularly stocked by poultry and piggery to feed the troops18. The virus now identified as the H1N1 virus was later identified as spreading from human to swine to human[17].

The Spanish flu pandemic is often known as the 'forgotten pandemic' as it came and went like a cyclone and at a time in war ravaged Europe leaving no indelible memories or a fallout in different aspects. Research was rekindled in the 2000s leading up to the resurgence in 2009.

The next two flu pandemics involved the H2N2strain of the influenza virusand were dubbed as the Asian flu of 1957-58 and the Hong Kong flu of 1968-1970. They each claimed about 1 million people but they occurred in flourishing virology, bacteriology and epidemiological advances in science. Vaccination became a reality and it was likely that herd immunity had already developed by then.

These two pandemics much like today's CoVid-19 affected individuals with pre-existing lung disorders in the majority.

Our last discussion is about the very recent and contemporary swine flu outbreak of 2009-2010 that claimed an estimated 200,000 lives. Most of the readership of this article has probably lived through this pandemic. This was caused by the H1NI influenza virus. A difficulty in writing about contemporary history is that the readership would have formulated their own opinions by first-hand experience rather than the historian pondering through voluminous past evidence to present a historical account. The flu originated probably in Asia or Mexico in pigs and then travelled through humans[19]. By this time science has several methods in its armamentarium to fight a pandemic and the death toll was kept at a minimum.

That brings us to the CoVid-19 pandemic. It is curious and fascinating to note as we have seen from the previous pandemics in this discourse, that CoVid-19 can be called a mixture of all pandemics from ancient times to the present day in terms of its effects on human civilisation and natural history of disease.

Pandemic dynamics, in our view has reached its culmination. There will be future infectious disease pandemics but we believe that the epidemiological pattern will be similar. Unless of course, there is one strain of an organism unleashed in the future that will wipe out the human civilisation like a zombie apocalypse which is highly unlikely.

The Human Cost

Whilst infections of living organisms by another can be deemed as a natural phenomenon, yet pandemics are as a result of a paradox. They occur by the virtues and vices of human civilisation. They spread by technological advances in mobility and by inequality existing in mankind partly generated by the wealth that is a direct result of technology.

Factors responsible for spread of pandemic include disease movement, novel mutations in the infectious organism, the virulence of the organism to which innate immunity has not developed due to its novel mutations and the difficulties in containment[20]. Like all natural disasters, pandemics cull the human population and probably maintain the eco balance in this fragile planet.

Pandemics will affect the health, the economy and the very delicate and sensitive social fabric of human society and lead to political redefinitions. Human social fabric is built around interacting with each other at close proximity to each other. A pandemic challenges that.

As Dr Erin Myers in Steven Soderbergh's futuristic film 'Contagion' (2011) said, "The average person touches their face two or three thousand times a day...three to five times every minute. In between that we're touching doorknobs, water fountains, and each other –don't touch anyone"-that threatens our very existence as a race.

A new after effect of pandemics is the threat of bioterrorism. Technology has made possible the frightening thought that the organisms responsible for pandemics can be mutated artificially for a more virulent strain that can wreak havoc when unleashed. Whether human sense and sensibility has evolved with progression of civilisation is a complex topic to ponder and we can only hope that human ingenuity, intelligence and resilience to survive will overcome the devastating effects of any pandemic.

Conclusions

Throughout history, pandemics are integral parts of human civilisation regardless of how much we progress to beat them. The more we adapt to fight these, the more they adapt and evolve. Societies change, mind sets change, science is enriched and politics changes. **What does not change is our will to survive as a race.**

Figure 2: Artistic depiction of plague –Ingmar Bergman's The Seventh Seal(1957) where silhouettes in cinematic imagery were successfully used for the first time with plague appearing as a character in the film. Plague is the only pandemic that has found the most artistic expression. (Talia Felix has released this "Seventh Seal" image under Public Domain license, CCO Public Domain https://publicdomainpictures.net/pictures/50000/velka/seventh-seal.jpg

References

1. Harris, SS. A Dictionary of Epidemiology, Fourth Edition. 2000; Oxford University Press, New York
2. Morens, DM et al. What is a pandemic? J Infect Dis. 2009; 200: 1018-1021. doi: 10.1086/644537)
3. Marcus Aurelius. Meditations. Full text available at athttp://classics.mit.edu/Antoninus/meditations.mb.txt accessed 19.05.2020 at 20.47pm
4. Edward Gibbon. Decline and Fall of the Roman Empire. 1988. Wordsworth Classics
5. Littman RJ, Littman LM.Galen and the Antonine Plague. The American Journal of Philology. 1973. 94: 243-255
6. Procopius. History of the Wars, Secret History, and Buildings. 1967. Trans. and ed. Averil Cameron New York: Washington Square Press Inc
7. Lotfy WM. Plague in Egypt: Disease biology, history and contemporary analysis: A mini review.Journal of Advanced Research. 2015;6: 549-554
8. Joshua North, "The Death Toll of Justinian's Plague and Its Effect on the Byzantine Empire," Armstrong Undergraduate Journal of History. 2013; 3
9. Wong TW and Fung KP. The Plague Pandemics and the Discovery of the Plague Bacillus. Asia-Pacific Journal of Public Health1988 -Vol2 No. 2
10. Levenstein J. Out of Bounds. Passion and the Plague in Boccaccio's Decameron. Italica. 1996; 73: 313-335
11. James T. Black Death: The lasting impact. 2011. http://www.bbc.co.uk/history/british/middle_ages/black_impact_01.shtml accessed 18.5.2020 at 10.32am
12. https://www.cbc.ca/news/technology/cholera-s-seven-pandemics-1.758504
13.Snowden FM. Epidemics and Society. Chapters 1,2,7 and 8. Yale University Press. 2019; https://www.jstor.org/stable/j.ctvqc6gg5.18
14. Latta T. The First Use of Intravenous Saline for the Treatment of Disease. International Journal of Epidemiology. 2013; 42: 387–390 https://doi.org/10.1093/ije/dyt045 15. Brabanti B , Dean KR et al. The Third Plague Pandemic in Europe. Proc. R. Soc. B. 286: 20182429. http://dx.doi.org/10.1098/rspb.2018.2429.
16. Kempińska-Mirosławska B., Woźniak-KosekA. The influenza epidemic of 1889–90 in selected European cities –a picture based on the reports of two Poznańdaily newspapers from the second half of the nineteenth centu ry. Med Sci Monit, 2013; 19: 1131-1141; DOI: 10.12659/MSM.889469
17. Kilbourne ED. Influenza Pandemics of the 20th Century. Emerging Infectious Diseases. www.cdc.gov/eid • Vol. 12, No. 1, January 2006
18. Oxford JS et al. "A hypothesis: the conjunction of soldiers, gas, pigs, ducks, geese and horses in northern France during the Great War provided the conditions for the emergence of the "Spanish" influenza pandemic of 1918-1919" (PDF). Vaccine. 2005; 23 (7): 940–45. doi:10.1016/j.vaccine.2004.06.035. PMID 15603896
19. Jilani T et al. H1N1 Influenza (Swine Flu). https://www.ncbi.nlm.nih.gov/books/NBK513241/
20. Qiu W et al. The Pandemic and its Impacts. Health, Culture and Society. 2016-17; 9–10; DOI 10.5195/hcs.2017.221

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Quest of a COVID-19 Vaccine: A Race Against Time

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Abstract

Covid-19 or Coronavirus disease-2019, caused by the novel Coronavirus (SARS CoV-2), continues to be a major global public health crisis. There is no specific drug for its treatment and no immunity against the virus. Allowing herd immunity to develop naturally would add to the already high morbidity and mortality and it may take many years. But, the speed with which the virus is spreading leaves us with no choice but to have a vaccine, or at least an emergency-use vaccine ready for use, at the earliest. There are frantic efforts across the world to develop a vaccine. Different approaches such as inactivated and attenuated vaccines, viral vector-based vaccines and DNA- and RNA-based vaccines are being studied. Many vaccines have shown promise in preclinical studies; many have completed or are in phase 1 trials. A safe and effective vaccine against Covid-19 is eagerly awaited. But, even when a vaccine is available, public health measures such as personal hygiene, social distancing, will be equally important to reduce disease transmission. In this article, we give a brief overview of the types of vaccines and the various vaccine initiatives around the world.

Introduction

The world is eagerly awaiting a vaccine for Coronavirus disease(Covid-2019) to control a pandemic, which is showing no signs of stopping and continues to spread around the world. Covid-19 has caused considerable morbidity and taken a heavy toll of lives. The economic fallout of the disease too has been enormous. Globally, more than 5 million people have been affected and more than 3 lakh people have died due to Covid-19, as per the Worldometers website on 21st May.[1]According to data available from the Ministry of Health & Family Welfare, Govt. of India website on 21stMay, 2020, India has 63624 active cases; 45299 have been cured / discharged; there have been 3435 deaths. Covid-19 is an infectious disease caused by a novel corona virus (nCoV), officially named as SARS-CoV-2. It is a rapidly evolving disease, caused by a highly infectious and contagious virus.

Although we are nearly five months into the outbreak (at the time of writing this), we do not know much about it. We are still learning about the disease. There is no specific proven antiviral drug for its treatment. Treatment is mainly directed towards managing symptoms of the patient and preventing development of complications.[2] Potential therapies are being explored. Existing medicines (hydroxychloroquine, azithromycin, lopinavir, ritonavir) are being repurposed.

COVID-19 is a new virus; hence, the population has no immunity against thevirus. In such a situation, vaccines become the option.The need of the vaccine also arises when there are a large number of asymptomatic persons in the community. We now know this to be true for Covid-19.

Asymptomatic transmission is playing a major rolein the spread of the disease and has been described as the "Achilles' heel" of present approaches to control the infection.[3] The spread of any outbreak slows down when the population to develop natural "herd" immunity in due course of time. Young children, the elderly, pregnant women, immunocompromised individuals, people who lack access to immunization or those who do not opt for immunization, benefit from herd immunity.[4]

There are many ways to describe herd immunity. One, it is the percentage of individuals in a population, who have immunity against the infection. Secondly, it is the threshold specific percentage of individuals with immunity, which reduce the infection.

Herd immunity is also referred to as the pattern of immunity that should protect a population from a new infection.[5] Smith in 1970 and Dietz in 1975 put forth the term "Herd Immunity Threshold" (HIT), which means that if immunity (i.e., successful vaccination) were delivered at random and if members of a population mixed at random, such that on average each individual contacted R_0 individuals in a manner sufficient to transmit the infection, then incidence of the infection would decline if the proportion immune exceeded

$(R_0 -1)/R_0$, or $1 - 1/ R_{0.5}$

Here, R_0 (R naught) is the reproduction number andmeasures the contagiousness or transmissibility of the pathogen i.e. the number of persons infected by one infected person. The R_0 for Covid-19 it is 3-4.

- Low R0 values are associated with lower HITs, while higher R0 values lead to higher HITs.5
- If R0 is 1, then 10% of population would need to get infected to develop herd immunity.
- If R0 is 1.5, then 29% of population would need to get infected to develop herd immunity.
- If R0 is 3, then 66% of population would need to get infected to develop herd immunity.

But, allowing natural immunity to develop through infection would result in high rate of serious illness and death, which would leave the health systems unable to cope. The more infectious a disease, the greater the population immunity needed to ensure herd immunity.[6]

Herd immunity can be developed faster through vaccines.It may take at least 3 years or more to build up herd immunity of any substance for Covid-19. But, we still do not know if Covid-19 infection provides immunity to the affected individual.

The WHO has also said that there is currently no evidence that people who have recovered from Covid-19 and have antibodies are protected from a second infection.[7] However, two studies in macaque monkeys, published May 20, 2020 in Science, have shown protective immunity against re-exposure to the Covid-19 virus acquired either due to natural infection or through vaccine.[8,9]

Types of vaccines

Live attenuated vaccine

Live attenuated vaccine is an established standard method, which uses a weakened (or attenuated) form of the disease-causingpathogens (virus or bacteria). Unlike the killed vaccines, they can emulate the infection and produce a strong and long-lasting immune response after only a single immunization.[10] Live attenuated vaccines provide long-term protection without the need for a booster dose.[11]

To date, live attenuated vaccines for Covid-19 virus have not been evaluated. Systems have been developed to generate complementary DNAs (cDNAs)encoding the genomes of CoVs, including SARS-CoV. The panel of cDNAs spanning the entire CoV genome can be systematically and directionally assembled by in vitro ligation into a genome-length cDNA from which recombinant virus can be rescued. This system has been used for genetic analysis of SARS-CoV protein functions and will enable researchers to engineer specific attenuating mutations or modifications into the genome of the virus to develop live attenuated vaccines.[12] The Covid-19 virus has been isolated from the foeces of Covid-19 patients.[13] This has raised concerns that a live attenuated SARS-CoV vaccine strain may also be shed in faeces and be a potential source of infection to unimmunized persons.[12]

There is alsoa concern that reassortants may sometimes be produced. The live attenuated strain combines with the circulating strain (wild-type CoV) and a new reassortant virus emerges, which either dies naturally or may establish itself. This has happened in HIV and polio. Killed inactivated vaccinesInactivated vaccines are prepared by treating the agent with a chemical (e.g. formalin) to denature the toxin or to kill the agent.10Inactivated whole-cell vaccines are safe as they do not contain live components. But,require several doses to produce adequate immune response.[14]

The presence of contaminants in the culture filtrate may generate reactogenicity in some inactivated vaccines.[10] However, the development of inactivated vaccines requires the propagation ofhigh titers of infectious virus, which in the case of SARS-CoV requires biosafety level 3-enhanced precautions and is a safety concern for production. Additionally, incomplete inactivation of the vaccine virus presents a potential public health threat. Production workers are at risk for infection during handling of concentrated live SARS-CoV, incomplete virus inactivation may cause SARS outbreaks among the vaccinated populations,and some viral proteins may induce harmful immune or inflammatory responses, evencausing SARS-like diseases.[12]

Genetically engineered vaccines

These vaccines use genetically engineeredRNA or DNA that has instructions for making copies of the S protein, which produce an immune response to the virus. There is no handling of handling of infectious virus in these vaccines.[15]

DNA vaccines

DNA vaccines encoding the S, N, M, and E proteins of SARS-CoVhave been evaluated in mice. These vaccines induce a strong immune response against the virus in animal models, mice in particular. But there is limited clinical data in humans. Both humoral and cellular immune responses are seen with DNA vaccines encoding for S-, M-, and N-proteins.[12]

Vector-based vaccines

In viral vector-based vaccines, an unrelated, modified virus is used as a vector (tool) to deliver the viral antigen (protein) in the host, in whom antigens are expressed and an immune response is produced against the target pathogen when delivered. Replicating (but often attenuated) or non-replicating viruses are used as vectors.[16]

Some of the viruses used as vectors are adenoviruses, paramyxoviruses (measles virus, Newcastle disease virus or human parainfluenza virus), parvoviruses (adeno-associated viruses, AAV), rhabdoviruses (vesicular stomatitis virus, VSV), and poxviruses (Modified vaccinia Ankara, MVA).[16]

Chimeric parainfluenza virus, MVA, rabies virus, VSV and adenoviruses have been used as vectors for SARS-CoV proteins. Studies with vector-based vaccines further demonstrate that induction of S protein specific neutralizing antibodies is enough to confer protection.[12]

Dengvaxia, a recombinant Dengue vaccine based on the yellow fever attenuated strain 17D, is the only viral vector based vaccine licensed for use in humans.[16]

Combination vaccines against Coronavirus

Combination vaccines have been evaluated for their ability to augment immune responses to SARS-CoV. Administration of two doses of a DNA vaccine encoding the S protein, followed by immunization with inactivated whole virus, was shown to be more immunogenic in mice than either vaccine type alone. The combination vaccine induced both high humoral and cell-mediated immune responses. High neutralizing antibody (Nab) titers were also observed in mice vaccinated with a combination of S DNA vaccines and S peptide generated in Escherichia coli. Combination vaccines may enhance the efficacy of DNA vaccine candidates.[12]

The SARS-CoV vaccine strategies reported to date demonstrate that S protein-specific NAbs alone are enough to provide protection against viral challenge. While SARS-CoV has not yet re-emerged, its unknown reservoir leaves open the possibility that it, or a related virus, will again infect the human population. The development of vaccines targeting this virus will help, in the event of its re-emergence, to potentially stop its spread before it wreaks the social and economic havoc caused by the previous outbreak.

Furthermore, lessons learned from the generation of these vaccines may aid in the development of future vaccines against known and newly identified coronaviruses.[12]

Monoclonal antibodies

Monoclonal antibodies (mAbs) against the infectious pathogenstarget the virus surface proteins and prevent the entry of the virus in the cells. Palivizumab approved for prevention of respiratory syncytial virus (RSV) infection is a monoclonal antibody against the RSV fusion (F) glycoprotein. Antiviral mAbs targeting the conserved hemagglutinin A stem of Haemophilus influenzae is undergoing investigation.[17] Some mAbs against bacteria can be both therapeutic and prophylactic, for example, by targeting the protective antigen domain of Bacillus anthracis or a Clostridioides difficile toxin).[17] The high costs and requirement for parenteral administration preclude the routine use of mAbs.

The high costs and requirement for parenteral administration preclude the routine use of mAbs. But, they may be helpful for certain emerging infectious diseases, where treatment of active disease and/or targeted prophylaxis might be especially important in persons who have not been vaccinated against a pathogen, but need immediate protection.[17]

Vaccine initiatives around the world

Institutes and pharmaceuticals across the world are engaged in efforts to develop a vaccine to prevent the infection. Inactivated and attenuated vaccines, viral vector-based vaccines and DNA-and RNA-based vaccines are some of the types of vaccine being studied.[18] Of the four major structural proteins of the Covid-19 virus, it is the S protein, which induces an immune response in the host, neutralizing antibodies and/or protective immunity against the infection.Vaccine developed from the S protein could produce antibodies, which may block the binding and fusion of the virus or neutralize the infection.[19]

Hence, most vaccines are being developed using either the pre-fusion or full-length spike (S) protein. Here is brief review of the some of the vaccines being developed against Covid-19.

Moderna vaccine

The most promising vaccine is the LPN-RNA vaccine being developed by Moderna Therapeutics, a US-based biopharmaceutical company. The vaccine was developed using a genetic platform called mRNA (messenger RNA). It has completed Phase 1 trial of its two-dose vaccine mRNA-1273, with the help of Emory, and has started recruiting for Phase 2. The phase I clinical trial (6 weeks) was conducted in 45 healthy individuals aged 18–55 years. It was led by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH) and started on 16th March.

Three different doses (25, 100, 250 μg) were used in phase 1. Study participants were administered two doses of the vaccine via intramuscular route in the upper arm at a gap of 28 days.In the second phase, Moderna will enroll 600 healthy volunteers, half of whom are 18-55 years old and the rest over 55 years old. On May 18, 2020, Moderna published interim clinical data from the phase 1 study, which are encouraging. The vaccine was generally safe and well tolerated.[20]

- Dose dependent increases in immunogenicity were seen across the three dose levels, and between prime and boost within the 25 μg and 100 μg dose levels.
- All participants ages 18-55 (n=15 per cohort) across all three dose levels seroconverted by day 15 after a single dose.
- At day 43, two weeks following the second dose, at the 25 μg dose level (n=15), levels of binding antibodies were at the levels seen in convalescent sera tested in the same assay.
- At day 43, at the 100 μg dose level (n=10), levels of binding antibodies significantly exceeded the levels seen in convalescent sera.

Novavax vaccine

The vaccine from Novavax is NVX-CoV2373; it is a stable, prefusion protein made using Novavax' proprietary nanoparticle technology. The vaccine has demonstrated high immunogenicity and stimulated high levels of neutralizing antibodies in animal models. High levels of spike protein-specific antibodies with ACE-2 human receptor binding domain blocking activity and SARS-CoV-2 wild-type virus neutralizing antibodies were observed after a single immunization.[21]

It is also undergoing Phase-I trial in the United States (US) and Australia. The Phase 1 trial is a placebo-controlled observer blinded study of around 130 healthy adults. Besides safety and immunogenicity, the trial will also evaluate the dosage and number of vaccinations. The preliminary immunogenicity and safety results of the phase 1 clinical trial are expected to be available in July.[21] In partnership with Cadila Pharmaceuticals inIndia, the US-based Novavax is using the virus-like particles (VLP) platform, which has been previously used for the papilloma virus vaccine. Using this platform, the company has marketed seasonal influenza, H1N1 and rabies vaccines in India.

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Oxford vaccine

Oxford University is using a chimp-adenovirus platform, infused with the genetic material of SARS-CoV-2 spike proteinto develop a vaccine candidate "ChAdOx1 nCoV-19". Data available May 13, 2020 on the preprint serverbioRxiv from vaccine efficacy testing on the macaques at NIAID's Rocky Mountain Laboratories (RML) in Hamilton, Montana show that a single dose of ChAdOx16

nCoV-19 vaccine reduced replication of the virus in the lungs of rhesus macaques and protected them from COVID-19 pneumonia.22These findings are not yet peer-reviewed.The vaccine is in the Phase 1 trial stageto study safety and efficacy in healthy volunteers aged 18 to 55 years, across five trial centers in Southern England. It will be manufactured by AstraZeneca in Europe and Serum Institute in India.

Coronavirus vaccine: A quick review

• Coronaviruses:Virus, spike protein; envelope, membrane, RNA, nucleocapsid

• Difficulties/ limitations: Virus causes immune inflammatory reaction, causes cytokine storm, causes thrombo-inflammatory reaction, brings down immunity (we do not know the exact method of
protection that the vaccine will afford and there is a fear of autoimmune reaction); Covid-19 also has latency like HIV (we do not know if the current vaccines under development will be able to tackle the virus within the cell); another challenge is that men and women respond differently to the infection as do children and the elderly.

• Immunity: Several unanswered questions -Short term or long term; multiple doses, booster doses, immunity lasting one year,•Herd immunity threshold:R-1/R, protecting older people, disabled people, immunocompromised people.

• Long development time: Pre clinical studies 3 months, small phase I study for safety, medium size phase 2 study, formulation, dose, safety immunogenicity and reactogenicity, large phase 3 efficacy

• People have no immunity to COVID-19. Therefore, it is likely that two shots will be needed, 3 to 4 weeks apart. People would likely start to achieve immunity to COVID-19 one week after the first vaccination and a large boost after the second dose.

There are 120 vaccine initiatives around the world.

•Virus vaccines (Live attenuated or inactivated): At least seven teams are developing vaccines using the virus itself, in a weakened or inactivated form. Sinovac Biotech in Beijing has started to test an inactivated version of SARS-CoV-2 in humans. The inactivated version will also be developed in the Serum Institute.

•Viral-vector vaccines(Replicating or non-replicating):The following platforms are being used: Measles, Chimp adenovirus, Adenovirus 26, Pox virus vectors etc.

•Nucleic-acid vaccines: (in the form of DNA or RNA) for a coronavirus protein that prompts an immune response. The nucleic acid is inserted into human cells, which then churn out copies of the virus protein; most of these vaccines encode the spike protein of the virus.

•Protein-based vaccines:Many researchers want to inject coronavirus proteins directly into the body. Fragments of proteins or protein shells with adjuvants that mimic the outer coat of the coronavirus can also be used (virus subunit or virus like particle)

INOVIO vaccine

INOVIO Pharmaceuticals has developed a DNA vaccine candidate "INO-4800", which has gone into Phase 1 open-label trial in the US in 40 healthy volunteers to investigate safety, tolerability and immunogenicity. The preliminary results are expected in June 2020. The vaccine may enter Phase 2/3 efficacy trials in the summer after regulatory approval. The two dose vaccine will be administered intradermally followed by electroporation. INO-4800 is also in phase 1 trial in South Korea.

Johnson & Johnson vaccine

The Johnson & Johnson vaccine is using Adeno-26 platform and pre-fusion spike protein, which has been successfully used by them in Ebola and RSV vaccine trials. This platform is not being used by any company in India. Adeno-26 is a rare adenovirus and is not present in the population, it does not have oncogenicity.

In India,

• Gennova Pharmaceuticalshas developed and patented a messenger RNA vaccine that is used with a carrier lipid iron oxide (LION) and an adjuvant known as GLA-SE. Experiments in convalescent serum and mouse and monkey challenge studies have obtained very high neutralizing antibody titers.

• Aurobindo has bought a small start-up from Pfizer in the US and is using a vesicular stomatitis virus platform for vaccine development, which is likely to be manufactured in their unit in Hyderabad.

• The other projects moving fast in India are the CSIR-funded CCMB-Bharat Biotechpartnership using a killed-vaccine for which the strain was obtained from the National Institute of Virol ogy, Pune.

• Zydus-Cadilain India is also in the fray with a measles virus platform.

•The Serum Institute of Indiahas collaborated with Codagenix, an US biotech company to develop a live attenuated vaccine in which viral sequences have been changed by swapping its optimized codons with non-optimized ones to weaken the virus. Johnson and Johnson (New Brunswick, NJ, USA) and Altimmune Inc. (Gaithersburg, MD, USA) are developing intranasal, recombinant adenovirus-based vaccines to stimulate the immune system.[18]

Immunoglobulins

Immunoglobulins against specific epitopes of Covid-19 antigens will come before vaccines only 1 is available from Israel and a cocktail of 3 are available in United States and are undergoing trials (These provide passive vaccination).

Conclusion

Pandemics are striking with greater frequency primarily because of deforestation, environmental degradation, rapid urbanisation, overpopulation, migration and growing animal and human conflict. There is no herd or population immunity against new pathogens such as the Sars-Cov-2 that causes the coronavirus disease (Covid-19), and till herd or population immunity crosses 70%, it will continue to spread.

In these circumstances, public health interventions in combination with an effective vaccine may mitigate the situation.The speed with which the Covid-19 pandemic is progressing leaves the world with no choice but to have an emergency-use vaccine ready within six to eight months. We cannot afford to wait for years.

In the past, the Ebola vaccine has been rapidly made available. The world already has some experience with coronavirus vaccines against viruses that cause Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS). The platforms and proven adjuncts being used for vaccines development are established and have been used to deliver other vaccines. Since we are not starting from scratch, an early vaccine is possible.

There are 110-plus vaccine projects going on at the moment, with unprecedented approaches being adopted by developers. Emergency use of the vaccine is given as soon as they finish Phase-II and move to Phase-III, and mass manufacturing begins taking up the risk of failure in Phase-III. Countries in which they are situated often fund for risk reduction and provide market commitments. This has never happened before.

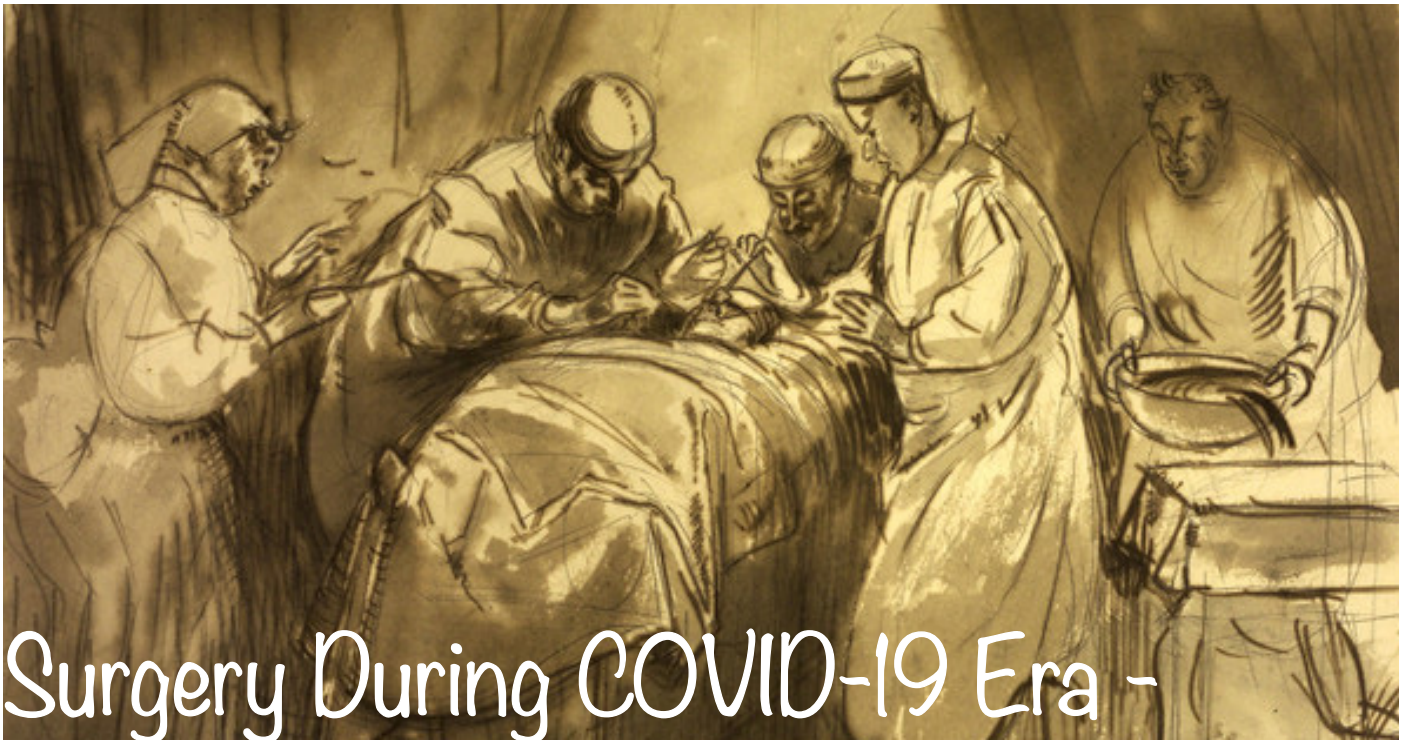
One of the challenges will be to determine who gets vaccinated first. There are several scenarios; one of them is to vaccinate frontline workers, doctors, health care, sanitation and delivery workers. Dentists and anesthetists are the most vulnerable population among the doctors.

The second scenario is to give them to children, people with underlying comorbidities and old people with comorbiditie sand the last is to conduct ring vaccination around the hotspots to immunize all the contacts and the asymptomatics. The World Health Organization (WHO) will provide guidance in this matter.

Even when we have a vaccine, public health measures will be equally important, including avoiding risky behavior, keeping social distancing, working on nutrition and access to poor populations and creating a mechanism to avoid animal and human transmission.If trials fail and a vaccine is not available in time globally, the world will have to live with this disease for a very long time.

References

1. Covid-19 coronavirus pandemic. Available at: https://www.worldometers.info/coronavirus/#countries, Accessed May 21, 2020.
2. Paudel S, Dangal G, Chalise A, et al. The Coronavirus pandemic: what does the evidence show? J Nepal Health Res Counc. 2020;18(1):1-9.
3. Gandhi M, Yokoe DS, Havlir DV. Asymptomatic transmission, the Achilles' heel of current strategies to control Covid-19. N Engl J Med. 2020 Apr 24. [Epub ahead of print]
4. Meissner HC. Why is herd immunity so important? AAP News May 2015;36(5):14.
5. Fine P, Eames K, Heymann DL. "Herd immunity": a rough guide. Clin Infect Dis. 2011;52(7):911-6.
6. Herd immunity. Available at: https://www.gavi.org/vaccineswork/what-herd-immunity, Accessed May 15, 2020.
7. "Immunity passports" in the context of COVID-19 Scientific Brief, 24 April 2020. Available at: https://www.who.int/news-room/commentaries/detail/immunity-passports-in-the-context-of-covid-19, Accessed May 17, 2020.
8. Chandrashekar A, Liu J, Martinot AJ, et al. SARS-CoV-2 infection protects against rechallenge in rhesus macaques. Science. 20 May 2020.
9. Yu J, Tostanoski LH, Peter L. DNA vaccine protection against SARS-CoV-2 in rhesus macaques. Science20 May 2020.
10. Dertzbauch MT. Genetically engineered vaccines: An overview. Plasmid.1998;39(2):100-13.
11. Tahamtan A, Charostad J, Hoseini Shokouh SJ, et al. An overview of history, evolution, and manufacturing of various generations of vaccines. J Arch Mil Med. 2017; 5(3):e12315.
12. Coronavirus vaccine. Available at: https://www.sinobiological.com/research/virus/coronavirus-vaccine.
13. Chen Y, Chen L, Deng Q, et al. The presence of SARS-CoV-2 RNA in the feces of COVID-19 patients. J Med Virol. 2020 Apr 3.
14. Vaccine safety basics e-learning course, WHO. Available at: https://vaccine-safety-training.org/inactivated-whole-cell-vaccines.html, Accessed May 17, 2020.
15. COVID-19 (coronavirus) vaccine: Get the facts. Available at: https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/coronavirus-vaccine/art-20484859, Accessed May 17, 2020.
16. Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol. 2018;9:196.
17. Manis JP. Overview of therapeutic monoclonal antibodies. Available at: https://www.uptodate.com/contents/overview-of-therapeutic-monoclonal-antibodies.
18. Uddin M, Mustafa F, RizviTA, et al. SARS-CoV-2/COVID-19: Viral genomics, epidemiology, vaccines, and therapeutic interventions. Viruses. 2020 May 10;12(5).
19. Du L, He Y, Zhou Y, et al. The spike protein of SARS-CoV--a target for vaccine and therapeutic development. Nat Rev Microbiol. 2009;7(3):226-36.
20. Moderna announces positive interim phase 1 data for its mRNA vaccine (mRNA-1273) against novel coronavirus, May 18, 2020. Available at: https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-positive-interim-phase-1-data-its-mrna-vaccine.
21. Novavax identifies coronavirus vaccine candidate; accelerates initiation of first-in-human trial to mid-May. April 08, 2020. Available at: https://ir.novavax.com/news-releases/news-release-details/novavax-identifies-coronavirus-vaccine-candidate-accelerates.
22. Doremalen NV, Lambe T, Spencer A, et al. Single dose ChAdOx1 nCoV-19 vaccination reduces SARS-CoV-2 replication and prevents pneumonia in rhesus macaques. bioRxiv. May 13, 2020.



Surgery During COVID-19 Era - An Overview

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Abstract
COVID-19 pandemic has affected more than 215 countries worldwide. Patient management has seen a tremendous change in the current pandemic with many specialities adopting measures to contain human to human transmission of the virus and to make judicious use of resources available. Surgical practices have changed globally with the use of virtual consultation, prioritisation of all elective and non-emergency services, COVID swab testing, chest imaging for all patients undergoing surgery and use of PPE to ensure staff safety. A major impact of COVID-19 has been on emergency surgery services and on surgical training. This article highlights the impact of COVID-19 on the safe delivery of surgical services and emphasizes on the use of webinars, online teaching and simulation as a meaningful tool to deliver surgical training in COVID era.

Keywords; COVID-19, surgery, impact, PPE, training
Pic- Hunterian museum, Royal College of Surgeons

Introduction:

COVID-19 pandemic has affected more than 215 countries globally. It was declared a Global Public Health Emergency by World Health Organisation (WHO) on January 30th 2020 [1]. According to the official World Health Organisation site, as of 29th May 2020, there are 5,704,736 infected cases worldwide, resulting in 357,736 deaths. United Kingdom is amongst the top 5 worst affected countries at the time of writing this review [2]. To combat the effects of corona pandemic, meticulous use of available resources is crucial. In order to minimize resource exhaustion, the use of surgical appliances and staff must be well contemplated and balanced [3]. Surgical practices have changed in U.K. and worldwide, which includes prioritisation of all elective and non-emergency surgeries, use of virtual consultation wherever possible, reduction in face to face consultations, suspension of endoscopy services, etc. However, acute surgical emergencies are inevitable and should be managed in a timely manner in order to avoid patient morbidity and mortality.

COVID-19 is a newly emerged zoonotic coronavirus which causes an acute respiratory disease. It is a single stranded enveloped RNA virus, which was isolated from a patient suffering with pneumonia in Wuhan where it originally began. Genetic analysis revealed that COVID-19 is closely

related to Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and has been named as SARS-CoV-2, it belongs to the genus Beta coronavirus, subgenus Sarbecovirus. The transmission of the virus occurs from human to human via droplets and by touching the droplet-contaminated surfaces or objects [4]. COVID-19 pandemic has had an immense impact on the management of surgical emergencies. In order to limit the exposure of healthcare personnel to COVID and suspected COVID patients, the four Royal College of Surgeons (RCS), Association of Coloproctology of Great Britain and Ireland (ACPGBI), Association of Surgeons of Great Britain and Ireland(ASGBI) and Association of Upper Gastrointestinal Surgery ofGreat Britain and Ireland (AUGIS) proposed guidelines in March 2020, for triage of patients with acute surgical emergencies [5,6]. Before the COVID-19 pandemic, the standard of treatment for acute appendicitis and acute cholecystitis was surgery either through laparoscopy or open method [7,8] but since the outbreak of COVID-19, it has been suggested that for uncomplicated acute appendicitis, acute cholecystitis, uncomplicated acute diverticulitis conservative and inpatient or outpatient management with antibiotics should be attempted first wherever applicable. Also, in cases where appendicitis is secondary to a faecolith, a judicious use of Computed Tomography (CT) scan has been advocated and in presence of any unfavourable features, we should consider semi-urgent or emergency surgery. However, many surgeons have argued against these guidelines, as with conservative approach patients may take longer to recover, requiring longer hospital stay and further increasing the risk of hospital acquired infections including COVID infection, which in turn would increase the morbidity of the patients and would incur additional burden on hospitals
9. Changes to emergency surgery:
Patients who require an emergency surgery in COVID era, triple assessment has been recommended with use of proper history, COVID-19 test and recent CT chest (last 24h) or failing that, a Chest X-ray[9]. COVID-19 test is a real time reverse transcription polymerase chain reaction (RT-PCR) test which qualitatively detects nucleic acid from SARS-CoV-2 in upper and lower respiratory tract specimen like nasopharyngeal/oropharyngeal swab or bronchoalveolar lavage, collected from patients who are suspected of COVID-19 infection [10]. The sensitivity of COVID-19 test has been reported to be 71-98%[11]. For patients who needed CT abdomen and pelvis for evaluation of acute abdomen, CT chest is mandatory. These recommendations are based considering the high false negative rate of 2-29% of COVID-19 testing. It has also been recommended to factor in, the increased risk of adverse outcomes following surgery pertaining to higher risk of acquiring and developing post-operative complication due to COVID-19 infection as inpatient, into planning and consent [12]. Consideration is to be given to stoma formation rather than primary anastomosis in order to reduce the probability of unplanned post-operative critical care for complications.

Staff Protection:
The guidelines also recommend the use of Personal Protective Equipment (PPE) by all theatre personnel during all operations under general anaesthesia, and infection control practices to be followed based on national and local protocols which advises on level of PPE to be used based on risk from proximity to potential viral load. Droplet transmission increases with aerosol generating procedures (AGP) like endotracheal intubation, bag and mask ventilation, tracheostomy, gastrointestinal endoscopy, naso-gastric tube insertion and while reducing pneumoperitoneum in laparoscopic surgeries and suction of body fluids. AGPs are high risk, hence full PPE is needed while performing them. PPE recommended when dealing with positive or suspected patients includes double layer of disposable gloves and gowns, eye protection/visor and Filtering Face Piece 3 (FFP) mask. It is imperative to practise sterile donning and doffing of PPE in advance. Negative pressure operating rooms (ORs) wherever available should be used for performing the procedures in COVID suspected or confirmed patients. All staffs should have their specific role allocated prior to the procedure to minimise the

theatre traffic. It is recommended that high risk patients be intubated and extubated in theatre, and staff immediately present should be at a minimum. Surgeons and scrub staff should wait outside the OR until 10 minutes after induction and intubation [5,6,9,13]. Even though there is no current evidence on virus transmission during abdominal surgeries, early information from Italy, China and previous Severe Acute Respiratory Syndrome (SARS) experience suggest that care should be taken during open procedures also as the smoke plume from coagulating instruments may portray some risk hence adequate arrangement should be made for smoke evacuation from diathermy/other energy devices.

The choice of approach (open vs laparoscopy) has been a subject of debate among surgeons. The consensus among surgeons is to prefer open procedure. In a statement published recently, the Association of Laparoscopic Surgeons of Great Britain and Ireland (ALSGBI) found that there is no evidence to suggest increased risk of COVID-19 in laparoscopy as compared to open procedure especially in elective settings. Although literature suggests a theoretical risk of COVID-19 transmission during laparoscopy through the chimney effect, it can be considered in selected individuals where the benefit outweighs the risk of viral transmission [5,6,9,14,15.] If Laparoscopy is used, it is imperative to check the proper functioning of suction system, use of trocars with balloon and suitable size holes to prevent any air leak. It is recommended that the procedure be performed by senior well trained surgeon in order to minimise the operative time and risk of aerosolization, to maintain lowest abdominal insufflation pressure for safe progress (12 mmHg or less), use of vacuum suction device to extract the surgical smoke during procedure and pneumoperitoneum at the end of procedure before removing the specimen and trocars [14,15].

COVID-19 may itself present as an early post-operative complication and adequate measures should be taken to prevent its occurrence. An international, multicentric, observational cohort study done by the COVIDSurg Collaborative, recently published in the Lancet, demonstrated that the outcomes of patients with SARS-CoV-2 were considerably worse than in pre-pandemic era. The study showed an overall 30-day mortality of 24% and a morbidity of 51%, mainly from post-operative pulmonary complications which included pneumonia, Acute respiratory distress syndrome (ARDS) and unexpected post-op ventilation [12].

Staff management and leadership:

An important limiting factor during the management of patients during COVID-19 era is shortage of the staff [9]. The major factor for staff shortage is significant exposure to COVID patients and staffs contracting COVID-19 infection which necessitates some health care staff to self-isolate themselves. Public Health England (PHE) released guidelines on staff testing and return to work for health and social care staff according to which testing should be organised for staff suspected of COVID-19 and should be done within 72 hours of symptom onset as the sensitivity of COVID-19 test reduces thereafter. Staff who tested positive should remain in isolation for 7 days and should only return to work if the symptoms have improved and there is no fever for 48 hours [16]. The situation has been constantly changing and demands every surgeon to take up leadership roles in the hospitals. To facilitate this, surgical review committees have been formed which comprises of surgeons, anaesthetists and nursing staffs who work in an integrated manner and have review meetings at regular intervals to address the changes that need to be implemented for safety of both patients and health care personnel. Surgeons should also take initiative to develop preparedness for potential redeployment into areas of the frontline in ICUs or medical wards that are outside of their regular practice patterns.

Education and Training:

COVID-19 pandemic also had a great impact on medical/surgical education and training.Trainees and trainers have therefore needed to device an alternate method of meeting their needs of adequate training. Because of the need for cross-specialty cover and redeployment, there is an additional demand for COVID-19 specific training. Various training and simulation courses have been organised in the hospitals to educate and train surgeons in basic management of ICU and critically ill patients. Social distancing, an important element of curbing the spread of corona virus, necessitates developmentof innovative ways to deliver teaching required for training. One such innovation has been the evolution of seminars into webinars which has become an indispensable tool for imparting education in COVID-19 era. Webinars provides the advantage of interaction between trainee and trainers and hence, facilitates deep and meaningful learning [17]. Online teaching materials, virtual/e-learning, videoconferencing, webinars are being organized RCS and various educational institutes worldwide and will play an important part towards trainee education and progression even after COVID-19 era. These modalities can also serve to extend health care services to remote areas which do not have access to adequate healthcare facility especially in low-and middle-income countries.

Conclusion:

These are uncertain times and the numbers of affected patients seem to be rising daily. A second wave of corona is being foreseen by scientists across the world, hence, it is crucial to consider few aspects before resumption of services. First and foremost, we should be able to see a sustained decline in the number of new COVID-19 patients for a period. We also need to ensure the adequate availability of necessary staff and associated facilities like intensive care units, availability of diagnostic testing and clear policies for frequency of testing of staffs and patients, adequate PPE and surgical supplies for the type of procedures performed. Essential perioperative services like diagnostic imaging, anaesthesia, critical care, sterile processing should be adequately accounted for before resumption of elective services.

Innovation flourishes during times of crisis. The education of surgical trainees is of paramount importance and should be maintained, even during the difficult times we currently face. While operative skills will be difficult to develop, the use of technology can allow for the remote delivery of expert teaching to a large number of trainees worldwide.

REFRENCES:
1. Coronavirus Disease (COVID-19) -events as they happen [Internet]. Who.int. 2020 [cited 29 May 2020]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen
2. COVID-19 situation reports [Internet]. Who.int. 2020 [cited 29 May 2020]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports
3. Wong J, Goh Q, Tan Z, Lie S, Tay Y, Ng S et al. Preparing for a COVID-19 pandemic: a review of operating room outbreak response measures in a large tertiary hospital in Singapore. Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 2020;67(6):732-745.
4. [Internet]. Ecdc.europa.eu. 2020 [cited 8 June 2020]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-supply-substances-human-origin.pdf
5. Intercollegiate General Surgery Guidance on COVID-19 UPDATE | The Royal College of Surgeons of Edinburgh [Internet]. The Royal College of Surgeons of Edinburgh. 2020 [cited 3 June 2020]. Available from: https://www.rcsed.ac.uk/news-public-affairs/news/2020/march/intercollegiate-general-surgery-guidance-on-covid-19-update
6. Updated General Surgery Guidance on COVID-19, 2nd Revision, 7th April 2020 | The Royal College of Surgeons of Edinburgh [Internet]. The Royal College of Surgeons of Edinburgh. 2020 [cited 3 June 2020]. Available from: https://www.rcsed.ac.uk/news-public-affairs/news/2020/april/updated-general-surgery-guidance-on-covid-19-2nd-revision-7th-april-2020
7. Gorter RR, Eker HH, Gorter-Stam MAW,et al.Diagnosis and management of acute appendicitis. EAES consensus development conference 2015.Surgical Endoscopy.2020;30:4668–4690. Available from: https://doi.org/10.1007/s00464-016-5245-7.
8. Ansaloni L, Pisano M, Coccolini F,et al.2016 WSES guidelines on acute calculous cholecystitis.World J Emerg Surg. 2016;11:25. Available from: https://doi.org/10.1186/s13017-016-0082-5.
9. Cheeyandira A. The effects of COVID-19 pandemic on the provision of urgent surgery: a perspective from the USA. Journal of Surgical Case Reports. 2020; 4:1-2.
10. [Internet]. Files.labcorp.com. 2020 [cited 8 June 2020]. Available from: https://files.labcorp.com/labcorp-d8/2020-04/LabCorp-COVID-EUAsum3.pdf
11. Watson J, Whiting PF, Brush JE. Interpreting a COVID-19 test result. BMJ.2020;369:m1808.doi: 10.1136/bmj.m1808
12. Nepogodiev D, Glasbey JC, Li E, Omar OM, Simoes JF, Abbott TE, et al. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. The Lancet. 2020. Available from: https://doi.org/10.1016/S0140-6736(20)31182-X
13. [Internet]. Scts.org. 2020 [cited 3 June 2020]. Available from: https://scts.org/wp-content/uploads/2020/03/SCTS-ACTACC-SCPS-Theatre-COVID-pathway-Final.pdf
14. Schwarz L, Tuech JJ. Is the use of laparoscopy in a COVID-19 epidemic free of risk? British Journal of Surgery. 2020;107(7).
15. Laparoscopy in The Covid-19 Environment -ALSGBI Position ... [Internet]. [cited 2020Jun8]. Available from: https://www.alsgbi.org/2020/04/22/laparoscopy-in-the-covid-19-environment-alsgbi-position-statement/
16. Public Health. COVID-19: management of staff and exposed patients and residents in health and social care settings [Internet]. GOV.UK. GOV.UK; 2020 [cited 2020Jun8]. Available from: https://www.gov.uk/government/publications/covid-19-management-of-exposed-healthcare-workers-and-patients-in-hospital-settings.
17. Ali SR, Dobbs TD, Whitaker IS. Webinars in plastic and reconstructive surgery training -a review of the current landscape during the COVID-19 pandemic. Journal of Plastic, Reconstructive & Aesthetic Surgery. 2020. Available from: https://doi.org/10.1016/j.bjps.2020.05.038

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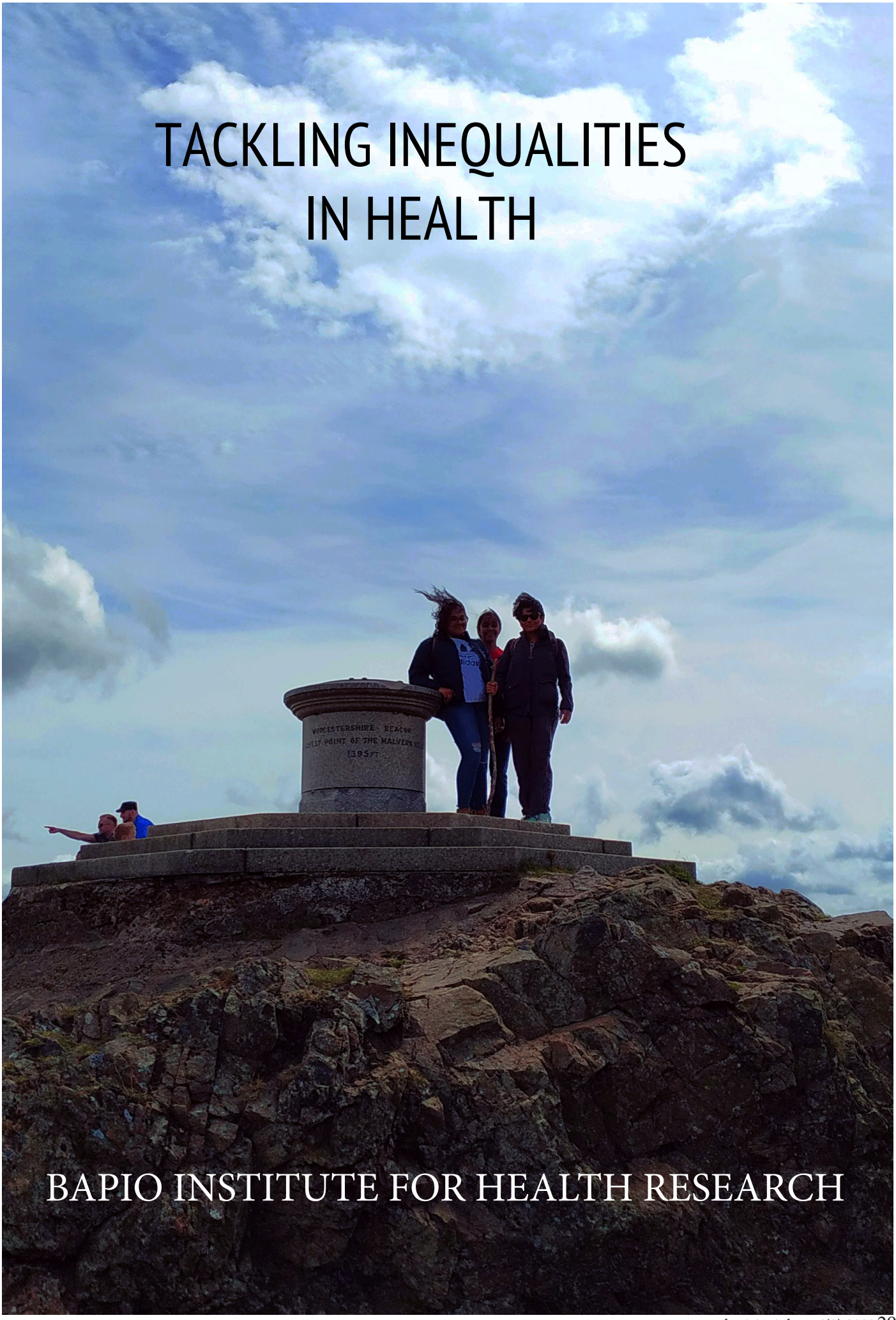
TACKLING INEQUALITIES IN HEALTH



BAPIO INSTITUTE FOR HEALTH RESEARCH

Abstract
Ethnicity was found to be an independent risk factor in COVID-19 outcomes in the UK and the USA during the pandemic surge. London, being in the epicentre and having one of the most ethnically diverse population in the UK, was likely to have experienced a much higher intensity of this phenomenon. Black Asian and Minority ethnic groups were more likely to be admitted, more likely to require admission to intensive care, and more likely to die from COVID-19.

We undertook an analysis of a case series to explore the impact of ethnicity in hospitalised patients with confirmed COVID-19 during the 3 months of the pandemic. Our results demonstrated that although the proportion of Asian and Black patients were representative of the local population distribution, they were much younger. The prevalence of comorbidities was similar but logistic regression analysis showed that male sex (OR 1.4, 95% CI 1.1-1.9; p=0.02), age (OR 1.03, 95% CI 1.02 - 1.04, p<0.001), those in the 'Other' [Odds ratio 1.7 (1.1-2.6) p = 0.01] and 'Asian'[Odds ratio 1.8 (1.1-2.7) p=0.01], category were at higher risk of death in this cohort.

Our results, therefore, are consistent with the overall data from the UK and USA indicating that ethnicity remains a significant additional risk and hence our clinical services must ensure that adequate provision is made to cater to this risk and research must be designed to understand the causes.

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Exploring *ethnicity* in Hospital Patients with COVID-19 in South London

Background

At the beginning of the COVID-19 pandemic in China, predictors of worse disease related outcomes were male sex, advanced age and cardiovascular comorbidities. However, the global progression of the SARS-CoV-2 virus resulted in emerging data on the impact of ethnicity across the United Kingdom (UK) and United States of America. [1] During the surge in UK cases, local centres saw a high incidence of intensive care unit (ITU) admissions and mortality rates in Black, Asian and Minority (BAME) ethnic backgrounds; this identified a need for further research. [1, 2]

A comprehensive analysis of National Health Service (NHS) Digital databases which included approximately 80,000 patients, showed that individuals from a BAME background were more likely to be diagnosed with COVID-19, more likely to be admitted to hospital and intensive care, and more likely to die in comparison to general population. [3] BAME background emerged as an independent risk factor for the pandemic, in particularly South Asian ethnicity. [2, 4] Although BAME patients affected by COVID-19 were younger and with significantly lower median ages (Asian 51, Mixed/Other 57, Black 57 years old) than white patients (69 years old), the total burden of comorbidities was similar across all ethnicities. Additionally, respiratory diseases were more prevalent in White patients whilst cardiovascular and endocrine diseases were more prevalent in BAME patients. Increased prevalence of COVID-19 amongst individuals from a BAME background may be explained by the geographical distribution of the virus in the UK, in addition to deprivation and occupational exposure.

The UK is a country with a large ethnically diverse population, and analysis can therefore contribute to our understanding of the disease's effects in various ethnic groups; the ethnic minority population of the UK was around 13% at the time of the last census in 2011.[5] Greater London and the South East have the highest number of people who were born outside of the UK, out of which almost a third speak a language other than English as their first language. Furthermore, London's ethnically diverse population includes 18.5% Asian, 13.3% Black, 5% Mixed, 3.4% Other and 44.9% White ethnic groups. [6] Thus, the impact of ethnicity on COVID-19 outcomes in Greater London is likely to be more apparent than the UK as a whole. Being at the epicentre of the pandemic in the UK, our Hospital experienced the early surge of patients affected by COVID-19 with a total number of 855 cases between March and May. This report aims to explore the impact of ethnicity on COVID-19 outcomes in order to improve current clinical practice.

Aim

To explore the relationship between ethnicity and health related outcomes in patients with COVID-19.

Design & Methods

A retrospective review of patient case notes of those with a polymerase chain reaction (PCR) confirmed SARS-CoV-2 infection, diagnosed March-May 2020 in St George's Hospital, London. The data collection was registered as an institutional audit (registration number: 10051). Patients were included if they were admitted overnight. Exclusion criteria were age below 16 years old and being employed by our Trust. Data collection included: demographics, ethnicity, length of stay, history of co-morbidities. The primary outcome was death or discharge.

Ethnicity was defined as per UK census definition and from NHS records as 0 = not known, 1 = Asian, 2 = Black, 3= Mixed, 4 = Other ethnicity and 5 = White. Age on admission was classified into categories; 1= <40 years, 2 = 40-49, 3 = 50-59, 4 = 60-69 and 5 = >70 years. The data were collected from hospital electronic records, anonymised and analysed using SPSS statistical software (SPSS v26, IBM Inc, USA). Data analysis included descriptive statistics and binary logistic regression modelling.

Results

Data collection identified confirmed 1966 SARS-CoV-2 cases between March and May 2020. Inclusion and exclusion criteria were applied, narrowing this to 1016 cases. 161 patients were admitted more than once, thus the final data analysis included 855 patients.

This cohort consisted of 470 (55%) men and 385 (45%) women. 419 (49%) patients were from Asian, Black, Mixed and Other backgrounds, whilst 513 (59.8%) were white. For 141 (16.4%) patients ethnicity was unknown (table 1). The mean age of male patients in our sample was 67.1 (SD=16.4) years whilst the mean age of women was 67.7 (SD=18.8) years.

Figure 1 shows the distribution of age in each of the ethnic groups with Asian (mean 60.8, SD 17.8 years for men and mean 61.9, SD 19.8 years for women) and Black women (mean 63.8, SD 19.1 years) being younger in this cohort compared to White ethnic group (mean 70.1, SD 15.5 years for men and mean 71.2, SD 18.2 years for women).

In total, 295 patients died whilst 560 survived to discharge (Figure 3). The length of stay in hospital was 12.2 (SD =11.3) days for men and 11.9 (SD =10.9) days for women (table1). Figure 2 shows the proportion of patients in each age group with co-morbidities. There was a rising trend for the presence of comorbidities with increasing age band.

Binary logistic regression analysis showed that male sex (OR 1.4, 95% CI 1.1-1.9; p=0.02), age (OR 1.03, 95% CI 1.02 - 1.04, p<0.001), those in the 'Other' [Odds ratio 1.7 (1.1-2.6) p = 0.01] and 'Asian'[Odds ratio 1.8 (1.1-2.7) p=0.01], category were independent predictors of death in this cohort.

Discussion

Analysis of data from the UK has demonstrated that ethnicity is an independent risk factor for poor outcomes in patients with COVID-19 (1). The causes are likely to be multi-factorial. London has a higher proportion of ethnic diversity in the local population, thus we conducted this analysis to explore the proportions of each ethnic group represented among the patients admitted to hospital during the COVID-19 surge in the UK.

Our results show that Black and Asian ethnic groups admitted to the hospital with COVID-19 were represented proportionally in relation to local population. In contrast, white patients were under-represented indicating that out of the local population groups, fewer patients from white backgrounds had a diagnosis of COVID-19. Our catchment area has a widely variable population demographic, age distribution, ethnic diversity and social deprivation. Representation of Black ethnic groups vary from 25.9% in Lam-

beth to 4.9% in Sutton, while the Asian ethnic groups make up 6.9% of the Lambeth population and 16.3% in Kingston. Hence, for the comparison we have used the Greater London population estimates. [6] However, these results mirror those reported by the analysis of UK NHS digital and ITU data. Patients from BAME backgrounds appear to have a higher rate of hospital admissions, severe disease and death.

Our logistic regression indicates that male sex, age and Asian ethnicity is associated with a higher risk of death from COVID-19. The other key finding is the age distribution, where Asian men and Black women were significantly younger than other groups.

This analysis is limited to patients admitted to hospital, rather than in the whole population. The majority of the COVID-19 cases were community based and did not require testing or hospital stay between March-June, and therefore our report includes patients with higher disease burden. The group of patients classified as 'other-not known' is also a sizeable cohort and seem to sit in the middle of the risk profile. Further exploration of this group and reclassification would help to strengthen our conclusions.

This analysis does not explore the potential causes of the deaths seen in this cohort of patients. UK and international data shows that genetic predisposition, cardiovascular comorbidities as well as socio-economic and racial disparities are likely to play a role (7). The COVID-19 pandemic certainly has highlighted the need for increased awareness of the impact of ethnicity on disease, and has highlighted that there remains significant inequalities within the NHS, an organisation where care is aspired to be universal. It is the responsibility of all individuals and organisations within and outside of the NHS to be cognisant of this disparity, and to monitor and adopt measures that will help to balance this injustice.

Category	Ethnic-not known (%)	Ethnic -Asian	Ethnic –Black	Ethnic –Mixed	Ethnic –Other	Ethnic-White
London Population	na	18.5	13.3	5	3.4	59.8
Proportion (%)	16.4	16.4	14.1	2.2	16.4	34.2
Men (%)	60	60.5	48.2	50	56.3	51.9
Age (SD) years	66.7 (16.7)	61.2 (18.5)	67.1 (17.9)	62 (18.7)	68.5 (16.6)	70.7 (16.8)
LoS (SD) days	13.2 (11.9)	10.6 (10.9)	12.9 (12.3)	8.6 (7.6)	12.9 (11.3)	11.8 (10.4)
Comorbidities (%)	51.8	50	68.6	73.3	61.6	53.4
Death (%)	33.7	31.1	29.6	36.4	31.3	24.6
OR for death	1.7 (1.1-2.6)	1.8 (1.1-2.7)	NS	NS	NS	NS

Table 1 shows the proportions in each ethnic group for gender, comorbidities and death

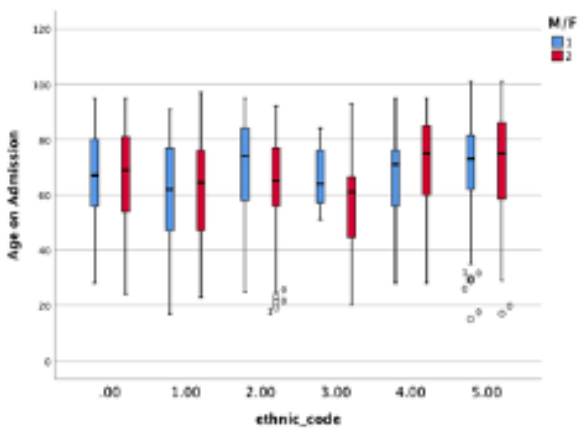


Figure 1: Box plots showing distribution of age in each ethnic group by gender.

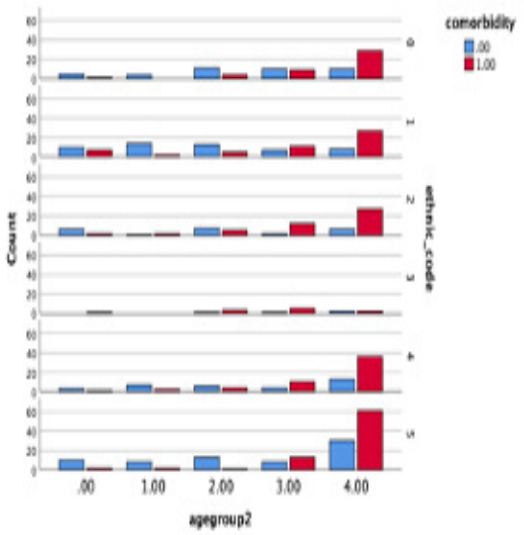


Figure 2: Bar chart depicting the proportions of patients with comorbidities in each age-group

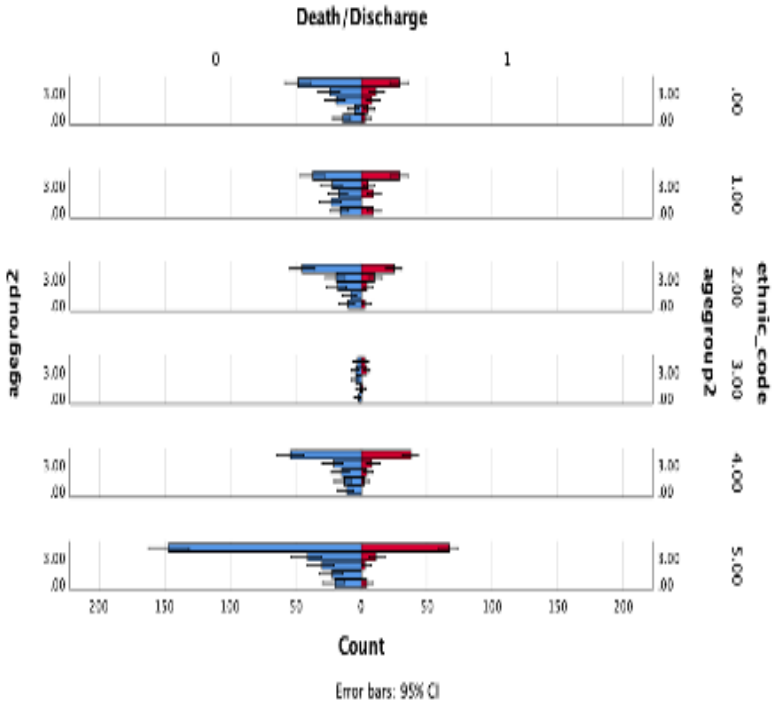
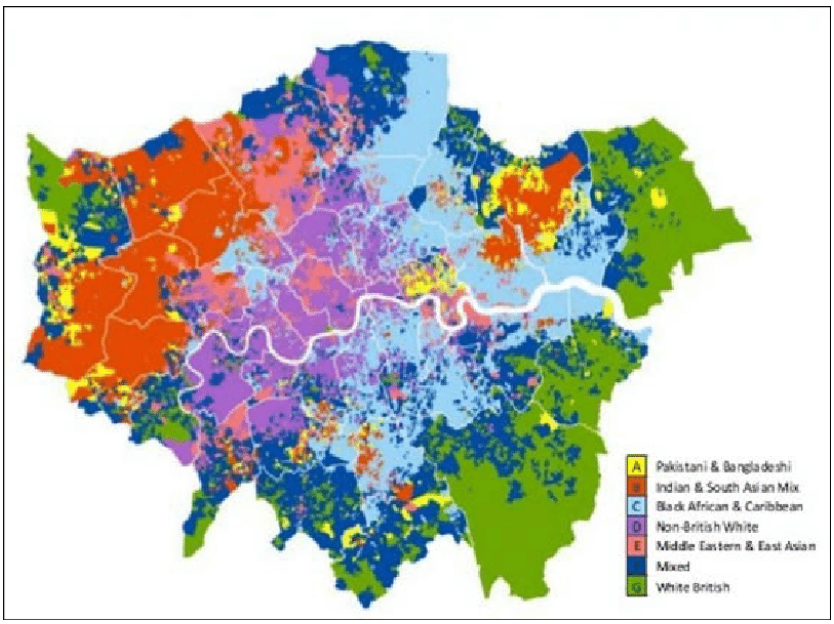
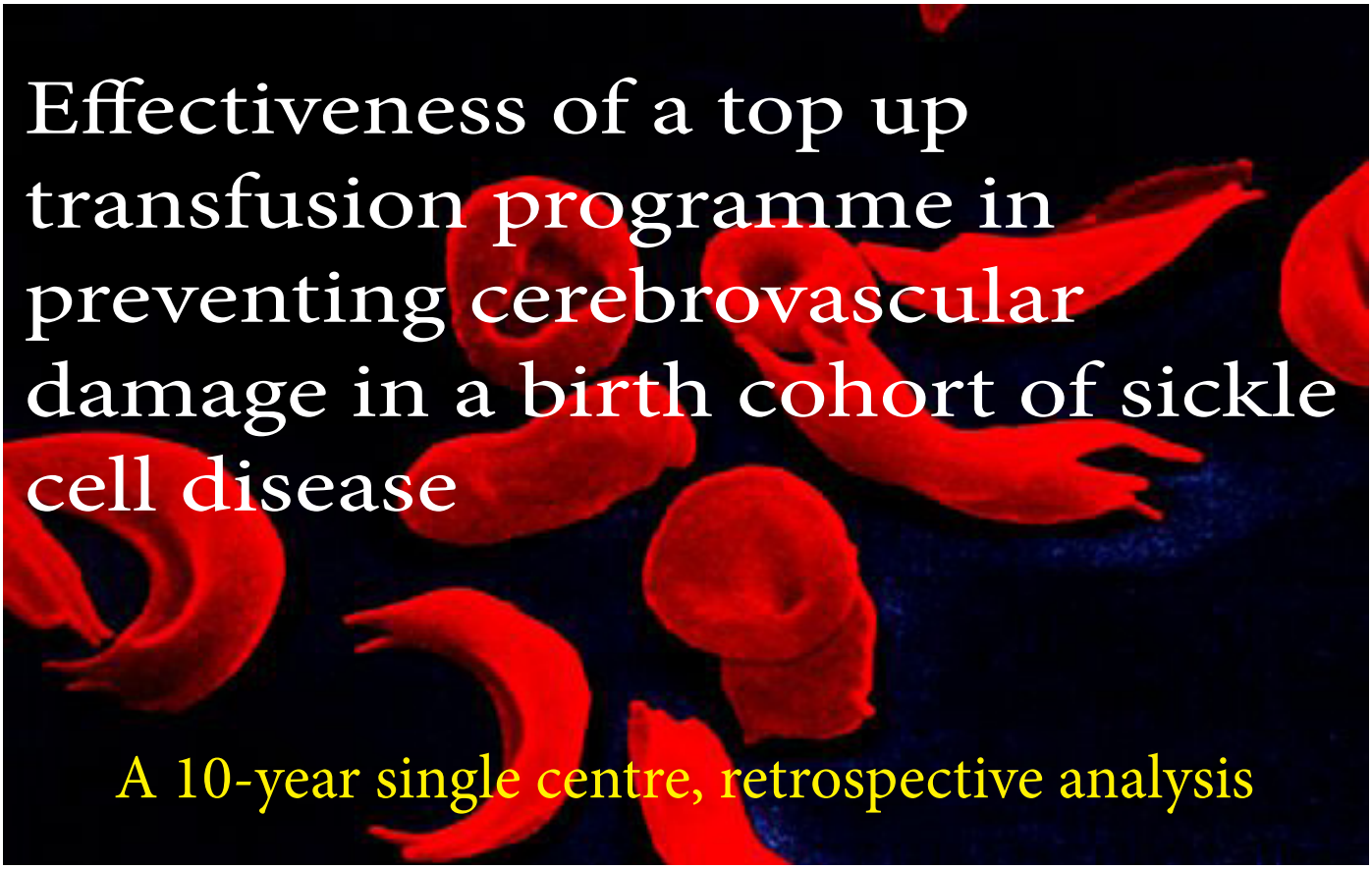


Figure 3 indicates the proportion of patients who died or were discharged in each ethnic group based on their age-group.

References

1. Collaborative TO, Williamson E, Walker AJ, Bhaskaran KJ, Bacon S, Bates C, et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. medRxiv. 2020 May 7;2020.05.06.20092999.
2. Pan D, Sze S, Minhas JS, Bangash MN, Pareek N, Divall P, et al. The impact of ethnicity on clinical outcomes in COVID-19: A systematic review. EClinicalMedicine [Internet]. 2020 Jun 1 [cited 2020 Aug 16];23. Available from: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30148-6/abstract
3. Ethnicity and outcomes of coronavirus(COVID-19) patients in England [Internet]. NHS Digital. [cited 2020 Aug 14]. Available from: https://digital.nhs.uk/coronavirus/coronavirus-data-services-updates/ethnicity-and-outcomes-of-covid-19-patients-in-england
4. Pareek M, Bangash MN, Pareek N, Pan D, Sze S, Minhas JS, et al. Ethnicity and COVID-19: an urgent public health research priority. The Lancet. 2020 May 2;395(10234):1421–2.
5. Regional ethnic diversity [Internet]. [cited 2020 Aug 14]. Available from: https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/regional-ethnic-diversity/latest#ethnic-groups-by-area
6. London Population 2020 (Demographics, Maps, Graphs) [Internet]. [cited 2020 Aug 15]. Available from: https://worldpopulationreview.com/world-cities/london-population
7. Khunti K, Singh AK, Pareek M, Hanif W. Is ethnicity linked to incidence or outcomes of covid-19? BMJ [Internet]. 2020 Apr 20 [cited 2020 Aug 14];369. Available from: https://www.bmj.com/content/369/bmj.m1548





Effectiveness of a top up transfusion programme in preventing cerebrovascular damage in a birth cohort of sickle cell disease

A 10-year single centre, retrospective analysis

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Abstract

Regular transfusions are effective in managing strokes in paediatric sickle cell patients. However, there are associated risks, including alloimmunisation and iron overload. This study evaluated the efficacy of top-up transfusions in primary and secondary stroke prevention in a single tertiary paediatric centre in Central London.

Forty-seven children with sickle cell disease who received transfusions in the last decade were included. No patient on a primary stroke prevention transfusion programme had a cerebrovascular event during the study period but 9.5% on secondary stroke prevention programme did. Twenty-one per cent of patients in this cohort converted to exchange transfusions following transfer to adult services, of which 11% had subsequent strokes. Targeted pre-transfusion haemoglobin S % was not always met; 43% of HbS% readings in a 12- month period were above the set target of 30% and 37% were above the set target of 50%. About a third of patients had evidence of severe hepatic iron overload, but no significant cardiac iron. 25% of patients became alloimmunised, but not severe enough to warrant discontinuation of the transfusion programme.

Although transfusions are effective for primary stroke prevention, iron overload remains a significant burden.

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Introduction

In the United Kingdom, sickle cell disease (SCD) is one the most common genetic disorders, affecting 1 in 2000 births [1]. The risk of stroke in SCD is highest in the first decade of life [2] and can present overtly or as silent cerebral infarcts (SCIs). SCIs are more prevalent, affecting 17-35% of children, compared to 11% presenting with overt strokes [3,4]. Within five years of having a SCI, there is a 14-fold increased risk of having an overt stroke. [5] Without management, strokes recur in 67% of children.

One of the most effective ways for prevention is transfusion therapy. In patients with a past history of stroke, maintaining a Hb_S concentration of less than 30% transfusions can reduce the risk of stroke recurrence to 13% [6,7]. It is unknown for how long transfusions must be maintained before it can safely be stopped without the risk of stroke recurrence, with one study showing the risk of stroke returning after 12 years of treatment [8].

Regular transfusions for primary prophylaxis reduce the risk by 92% [9].Although transfusion therapy is effective at reducing the risk of stroke, it has its disadvantages. Alloimmunisation rates are high mainly due to antigenic differences between blood donors and patients, as well as due to the chronic inflammatory state of SCD [10]. Additionally, excess iron from transfusions is deposited in organs leading to organ failure [11].

Iron chelation can help prevent this but is associated with high costs and problems with adherence to therapy. Consequently, alternatives to transfusion therapy have been explored such as hydroxycarbamide [12,13.] Transfusions can be given as an additive (top-up) or via red cell exchange. Exchange transfusions can assist in reducing iron burden by removing patients' own blood at the same time as transfusing healthy red cells [14,15].

The aim of this study is to evaluate the effectiveness of the paediatric top-up transfusion programme for stroke prevention in SCD and the extent of iron overload in the cohort.

Materials and Methods

Study Population

Paediatric SCD patients receiving two to six-weekly top-up blood transfusions for a minimum of six months in a London tertiary centre from January 2009 to February 2018 were included in this study. All patients were homozygous for haemoglobin S (HbSS).

Indication for regular transfusion therapy were abnormal transcranial dopplers (TCDs), unresponsiveness to hydroxycarbamide, history of transient ischaemic attacks (TIAs) and strokes. Some patients further went on to receive exchange transfusions upon reaching adulthood. At the time of this study, automated exchange transfusions were not available for children in this centre.

Transfusion data

The total amount of blood each patient received over the course of the study and in their last year of top-up transfusions were collected. The frequency and duration of transfusion therapy were noted, as well as the HbS percentage in their last year of treatment. Alloimmunisation rates were collected.

Neuroimaging TCD readings from the distal internal carotid, the middle cerebral and the bifurcation of the internal carotid artery were analysed; categorised as normal (<170cm/s), conditional (between 170cm/s and 200cm/s) and abnormal (>200cm/s), as defined by the STOP trial [9]. Magnetic resonance imaging/magnetic resonance angiography (MRI/MRA) were used to look for cerebral damage and vascular stenosis and categorised as normal, abnormality in the parenchyma or abnormality in the vessels [16].

Measuring Iron Overload

Liver iron concentration (LIC) was measured using R2 MRI (Ferriscan) imaging and quantified as mg Fe/g dry tissue and cardiac iron was measured by T2* MRI imaging. Severe liver iron overload was defined as LIC >15 mg Fe/g dry tissue and cardiac iron overload was defined as below 20 msec as per published guidelines. The type and dose /kg body weight of chelation therapy each patient received during transfusions were recorded. The proportion of normal, abnormal, and condition al TCDs were measured to determine the effectiveness of the programme for primary prophylaxis. The rate of developing new strokes in children receiving transfusions for secondary stroke prevention was compared to published data.

Statistical Analysis

Microsoft Excel 2016 and SPSS version 24.0 (IBM Statistics, Armonk, New York, USA) were used to collect and analyse the data. A Mann-Whitney U test was conducted to compare alloimmunisation rates with the total volume of blood transfused for each patient, with a p-value of 0.05 to determine significance.

Ethical approval

The study constituted a clinical audit. No patient identifiable material was used in this study and no formal ethical approval was required for this study.

Results

Study Population

Data from 47 children were analysed. The demographics of the patient population is described in Table 1.
The total patient follow-up time is 341 patient years. At the time of this study, 20 patients were still being transfused on the paediatric top-up programme. Most of the population were male (75%). The most common indication was high TCDs (32%). More than half of patients started transfusions under the age of 5 years (51%). Thirty-eight percent (n=18) patients received regular transfusions for 5-9 years. 57% of patients used deferasirox film coated tablets (Exjade FCT©) for chelation and about a fifth were additionally taking hydroxycarbamide (19%, n=9). Three patients (6%) underwent bone marrow transplant.

The total volume of blood transfused during the study period, the duration of top-up transfusions and the annualised blood volume transfused per kg body weight can be seen in Figure 1. Six patients (13%) received more blood than 200ml/kg per year. The HbS percentage varied throughout the course of the top-up transfusion programme.

Table 1 Demographic data of the transfused patients

Parameter	n = 47	Percentage (%)
Sex	Male = 35	75
	Female = 12	25
Indication		
High TCD	15	32
Stroke	12	26
SCI	9	19
Vasculopathy	4	9
Symptom control	7	15
Age starting transfusion		
1-5	24	51
6-10	12	26
11-15	9	19
16-19	2	4
Duration of Transfusion	Years	
0.5 - 4	15	32
5 - 9	18	38
10 - 14	10	21
15 - 19	4	9
Chelation during Top up transfusion		
Desferasirox	15	32
Exjade FCT	27	57
None	5	11
Hydroxycarbamide		
Yes	9	19
No	38	81
Bone Marrow Transplant		
Yes	3	6
No	44	94

Figure 2 shows the target HbS% in their last year of top-up transfusions. Pre-transfusion HbS% targets were not met in 43% of tests for those with a target of 30%. For those with a pre-transfusion HbS % target of 50%, 37% of tests did not meet the target.

Primary Stroke Prophylaxis

Twenty-six patients (55%) had no history of stroke or SCI before starting transfusions. Of those, 23 (89%) had TCDs annually after starting the programme. The proportion of normal, conditional, and abnormal readings in the middle cerebral artery (MCA), bifurcation of the internal carotid artery and the distal internal carotid artery (dICA) are seen in Table 2. The MCA had the highest proportion of conditional readings (9.3%) and the dICA had the highest proportion of abnormal readings (n = 12; 4.8%).

Secondary Stroke Prophylaxis

Twenty-one patients in the cohort (45%) patients had a history of stroke or SCIs. Of these, two (9.5%) had further strokes after starting transfusion programme.

Alloimmunisation Rate

Twelve patients (26%) became alloimmunised whilst receiving top-up transfusions. No significant difference was noted between the rate of alloimmunisation and the volume of blood transfused. The different antibodies that the alloimmunised patients developed can be seen in Table 3, with anti-C being the most common. None of these were severe enough to warrant withdrawal from the transfusion programme.

Iron Overload

MRI-based organ iron overload monitoring results were available in 35 (75%) patients. Of these, 12 patients (34%) had MRI estimate of liver iron concentrations above 15mg/g of dry tissue, with the highest concentration being 39.9 mg/g of dry tissue, indicating severe iron overload. In contrast, none of the patients had evidence of clinically significant cardiac iron deposition (Figure 2)

Exchange transfusions

Following the transfer of clinical care from paediatric to adult services within the same institution, 10 patients in the study went on to receive regular exchange transfusions. Of these, nine patients had a past history of strokes. Subsequent to the commencement of exchange transfusion, one patient with a past history of stroke developed a subsequent stroke. MRI assessment of organ iron overload was available for analysis in six out of 10 patients and demonstrated severe liver iron overload in three patients but no significant cardiac iron deposition.

Discussion

Regular transfusions can prevent strokes in SCD, as both primary and secondary prevention. Consequently, many services have adopted regular transfusions as a part of their stroke management programme.

This study aimed to look at the effectiveness of a top-up programme in one paediatric haemoglobinopathy tertiary centre. The rate of stroke recurrence in the secondary prophylaxis group was 9.5%, similar to rates seen previously [17]. No patient on transfusions for primary prevention developed an ischaemic stroke during this study.

The HbS percentage of the patients varied, and the pre-transfusion target was not always maintained. In this study, 43% HbS

Table 2 showing the total number of normal, conditional, and abnormal TCD readings for the middle cerebral artery (MCA), bifurcation of internal carotid artery and the distal internal carotid artery (distal ICA) in children on transfusions for primary stroke prevention.

	Normal n (%)	Conditional n (%)	Abnormal n (%)	Total
MCA	222 (86.7)	24 (9.3)	10 (3.9)	256
Bifurcation	230 (93.1)	14 (5.7)	3 (1.2)	247
Distal ICA	225 (90.7)	11 (4.4)	12 (4.8)	248

Table 3 Number of patients who became alloimmunised during the study period and details of antibodies developed

Alloimmunised	n (%)
No	35 (74.5)
Yes	12 (25.5)
Type of Antibody	
C	8 (67)
Cw	1 (8)
e	1 (8)
Kp (a)	5 (42)
Lu (a)	2 (17)

readings were above the set target of 30% and 37% were above the set target of 50%.

More than a third of patients in this study had evidence of severe iron overload and a significant proportion of patients who converted to exchange transfusions remained severely iron overloaded. Adherence to chelation therapy was significant problem in the cohort and persisted beyond childhood.

Over a quarter of the cohort became alloimmunised, similar to previous studies [18,19]. The most common alloantibodies were for the Rh and Kell systems, despite the presence of routine matching for ABO, Rh and Kell systems. This apparent disparity may be due to the presence of genotypic differences in blood groups due to the ethnic mismatch between blood donors and recipients in the UK [20].

In contrast to previous studies, the rate of alloimmunisation was not associated the total amount of blood transfused [21].

This may be due to the majority of patients starting transfusions under the age of 5 years which can affect alloimmunisation rates [18].

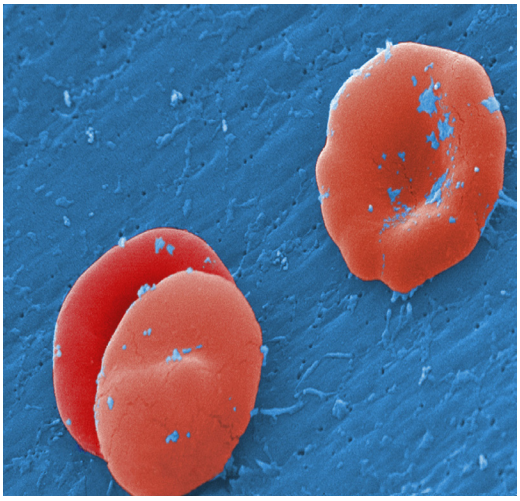
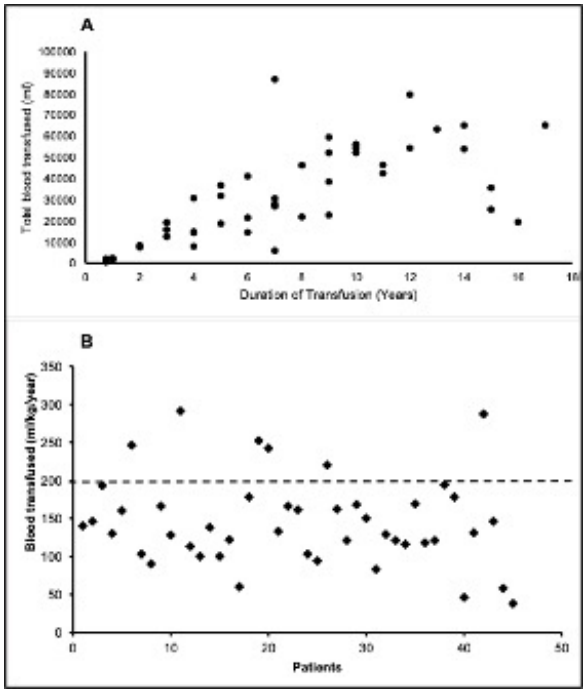


Figure 1. Comparison of the total amount the blood transfused and the duration of transfusion therapy in years (A) and the total amount transfused per kilo in the last year of the patients' top-up transfusion (B).



In conclusion, this study provides real world evidence of the efficacy of top-up transfusions in primary stroke prevention for SCD in a 10-year retrospective analysis of a single tertiary centre in the UK.

Iron overload is still a significant disadvantage for both top-up and exchange transfusions despite regular chelation.

Acknowledgments
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There are no relevant conflicts of interests to declare.

References
1. Streetly A, Latinovic R, Henthorn J. Positive screening and carrier results for the England-wide universal newborn sickle cell screening programme by ethnicity and area for 2005-07. Journal of clinical pathology 2010;63:626-9.
2. Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood 1998;91:288-94.
3. Belisario AR, Silva CM, Velloso-Rodrigues C, Viana MB. Genetic, laboratory and clinical risk factors in the development of overt ischemic stroke in children with sickle cell disease. Hematol Transfus Cell Ther 2018;40:166-81.
4. Switzer JA, Hess DC, Nichols FT, Adams RJ. Pathophysiology and treatment of stroke in sickle-cell disease: present and future. Lancet Neurol 2006;5:501-12.
5. DeBaun MR, Armstrong FD, McKinstry RC, Ware RE, Vichinsky E, Kirkham FJ. Silent cerebral infarcts: a review on a prevalent and progressive cause of neurologic injury in sickle cell anemia. Blood 2012;119:4587-96.

Figure 2. Target HbS% in the last 12 months of top-up transfusions in the study. 43% of the total number of HbS% readings were above the 30% target (2A) and 36.6% of HbS% readings were

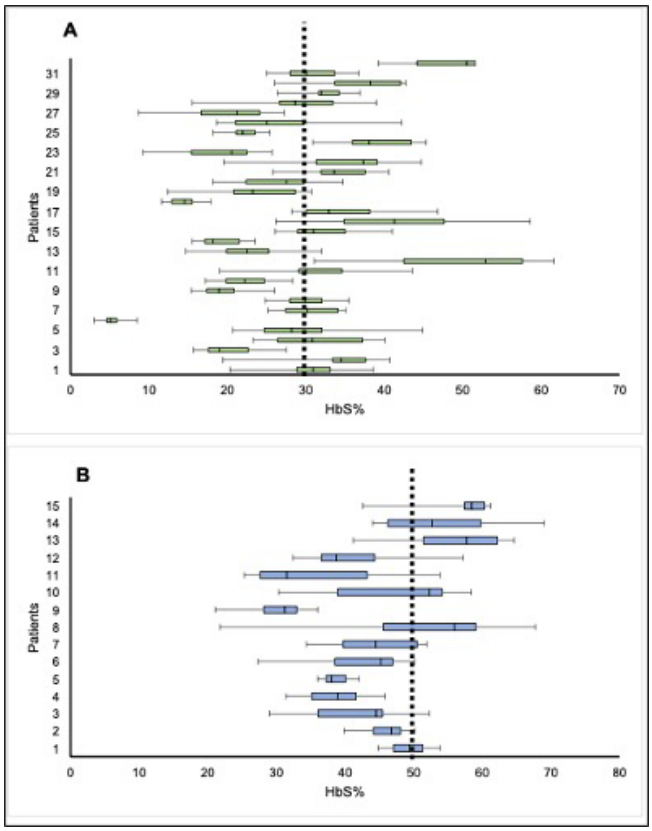
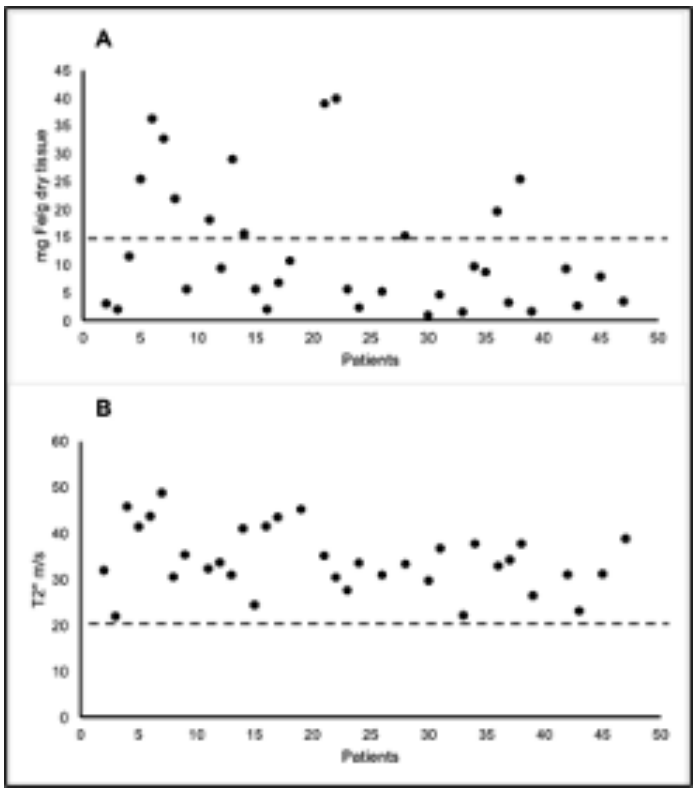
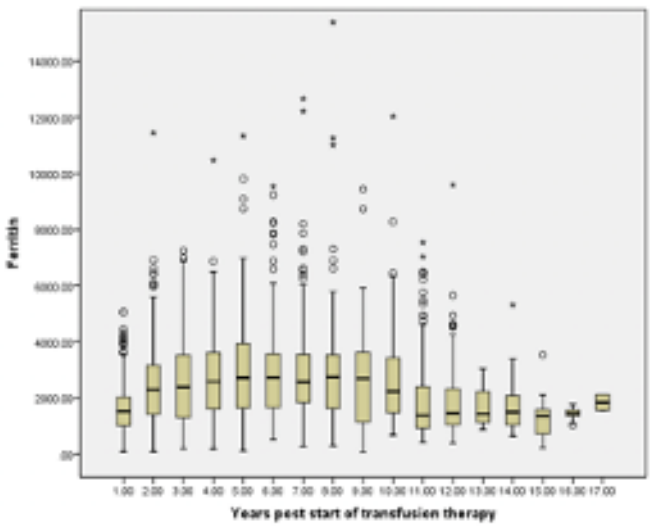


Figure 3 Liver iron concentration (A) and cardiac iron concentration (B) during the top-up transfusion programme. Ferritin levels of the patients during the transfusion programme are displayed in Figure 3C.



6. Pegelow CH, Adams RJ, McKie V, et al. Risk of recurrent stroke in patients with sickle cell disease treated with erythrocyte transfusions. J Pediatr 1995;126:896-9.
7. DeBaun MR, Gordon M, McKinstry RC, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. N Engl J Med 2014;371:699-710.
8. Wang WC, Kovnar EH, Tonkin IL, et al. High risk of recurrent stroke after discontinuance of five to twelve years of transfusion therapy in patients with sickle cell disease. J Pediatr 1991;118:377-82.
9. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 1998;339:5-11.
10. Fasano RM, Booth GS, Miles M, et al. Red blood cell alloimmunization is influenced by recipient inflammatory state at time of transfusion in patients with sickle cell disease. Br J Haematol 2015;168:291-300.
11. Olivieri NF. Progression of iron overload in sickle cell disease. Seminars in Hematology 2001;38:57-62.
12. Ware RE, Helms RW, Investigators SW. Stroke With Transfusions Changing to Hydroxyurea (SWiTCH). Blood 2012;119:3925-32.
13. Ware RE, Davis BR, Schultz WH, et al. Hydroxycarbamide versus chronic transfusion for maintenance of transcranial doppler flow velocities in children with sickle cell anaemia-TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicentre, open-label, phase 3, non-inferiority trial. Lancet 2016;387:661-70.
14. Swerdlow PS. Red cell exchange in sickle cell disease. Hematology Am Soc Hematol Educ Program 2006:48-53.
15. Kim HC, Dugan NP, Silber JH, et al. Erythrocytapheresis therapy to reduce iron overload in chronically transfused patients with sickle cell disease. Blood 1994;83:1136-42.
16. Naffaa LN, Tandon YK, Irani N. Transcranial Doppler screening in sickle cell disease: The implications of using peak systolic criteria. World J Radiol 2015;7:52-6.
17. Russell MO, Goldberg HI, Hodson A, et al. Effect of transfusion therapy on arteriographic abnormalities and on recurrence of stroke in sickle cell disease. Blood 1984;63:162-9.
18. Campbell-Lee SA, Kittles RA. Red blood cell alloimmunization in sickle cell disease: listen to your ancestors. Transfus Med Hemother 2014;41:431-5.
19. Alkindi S, AlMahrooqi S, AlHinai S, et al. Alloimmunization in Patients with Sickle Cell Disease and Thalassemia: Experience of a Single Centre in Oman. Mediterranean journal of hematology and infectious diseases 2017;9:e2017013.
20. Yazdanbakhsh K, Ware RE, Noizat-Pirenne F. Red blood cell alloimmunization in sickle cell disease: pathophysiology, risk factors, and transfusion management. Blood 2012;120:528-37.
21. Rosse WF, Gallagher D, Kinney TR, et al. Transfusion and alloimmunization in sickle cell disease. The Cooperative Study of Sickle Cell Disease. Blood 1990;76:1431-7.



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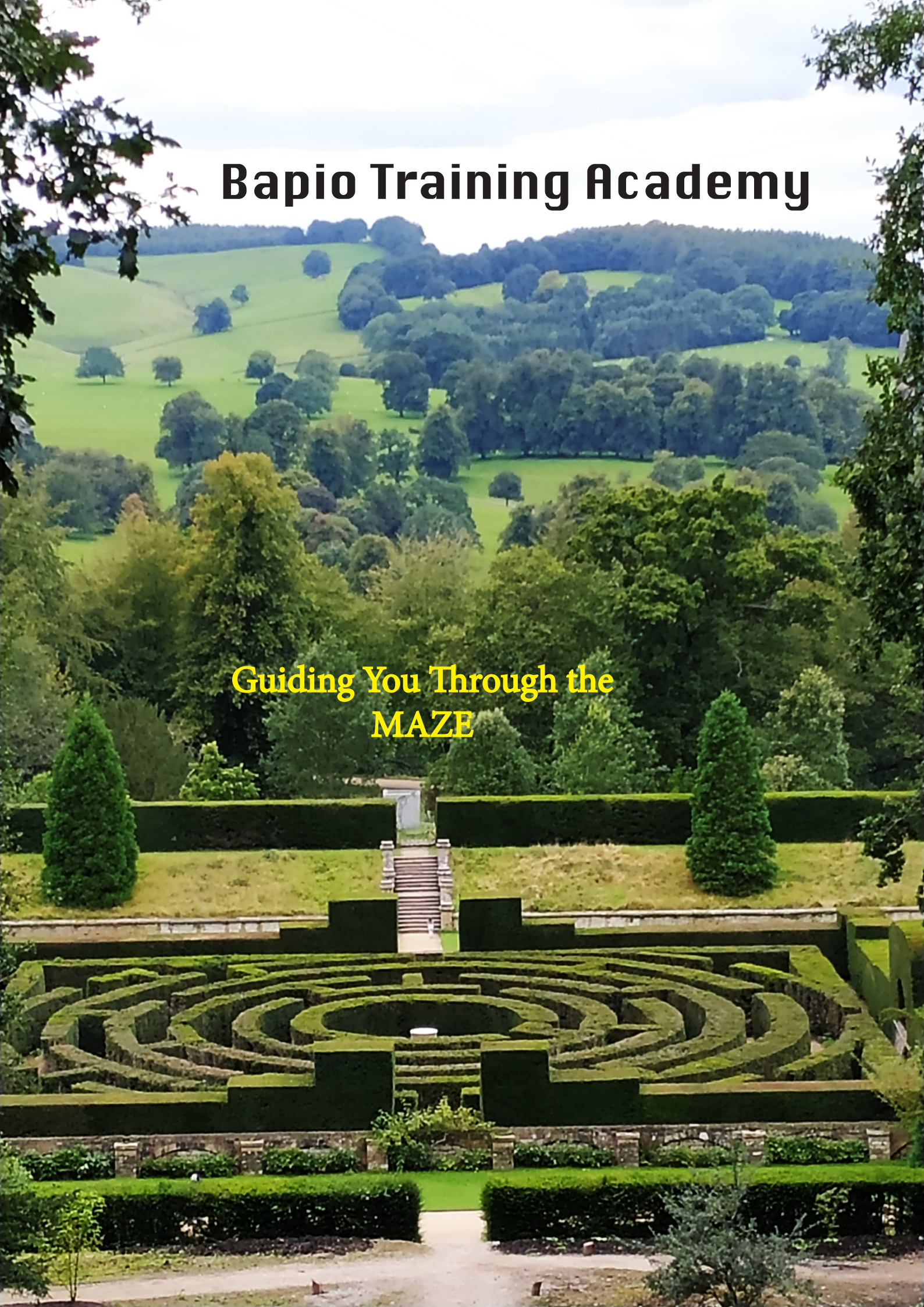

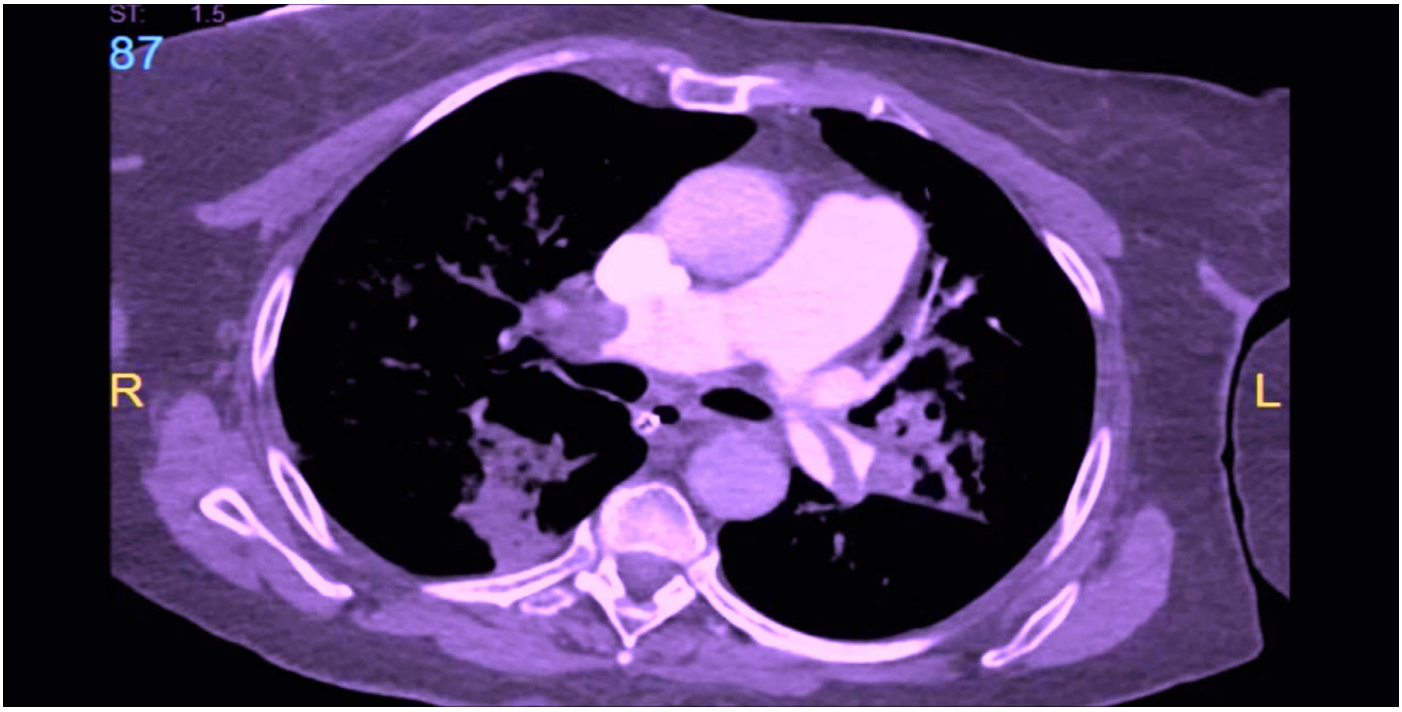

Mortality from Pulmonary Embolism by Clinical Severity

Aim:
To report all-cause and PE related short term mortality by clinical severity of PE and to identify any missed opportunities for thrombolysis.
Background:
Mortality related to pulmonary embolism varies widely in the reported literature even for the same clinical severity category of PE.
Method:
Electronic medical records of all patients presenting to a large tertiary care teaching hospital in London, between October 1, 2018, and January 16, 2020, who had a discharge diagnosis of acute pulmonary embolism were reviewed retrospectively.
Results:
There was no PE related mortality in the low-risk PE group. There was one PE related death in the submassive PE group (1.47% mortality on day 14 and day 30).
Conclusion:
Massive PE was associated with a 29.4% PE related mortality short-term mortality.

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Background

Mortality related to pulmonary embolism (PE) has varied considerably in published literature over the years. [1,2,3,4,5] Wide differences exist even for the same clinical severity of PE, among clinical-trial data and data from registries. [2,3,6] In a study of the RIETE database, a multinational registry of patients with PE, 34,390 patients were included and 3.5% had haemodynamic instability. All cause 30-day mortality was 14% for those with haemodynamic instability compared to 5.4% for those without.[2] In the PEITHO trial of patients with moderate-risk PE, 2.4% of those thrombolysed and 3.2% of those treated with anticoagulation alone, died by day 30.[7] The MOPETT [8] and SEATTLE II [9] clinical trials also reported much lower mortality with moderate-risk PE. Mortality from acute massive PE in registry data has been as high as 52%.[10]

The main aim of our research was to provide contemporary, real world data on mortality from pulmonary embolism by its clinical severity at a large tertiary care teaching hospital in London, where treatment was expected to be largely based on the current management guidelines.

The terms massive, submassive (alternatively called intermediate-or moderate-risk) and low-risk PE are classifications of clinical severity and not of the radiologic burden of the thrombus, which has not been shown to be a predictor ofmortality.[11] As current descriptions stand, massive PE refers to acute PE that results in haemodynamiccompromise, defined in most guidelines as a systolic blood pressure of less than 90 and in some guidelines additionally, as a drop in systolic blood pressure by 40 mm of Hg or more, compared to the initial or baseline systolic blood pressure.[12]

Submassive PE, also referred to as moderate-risk or intermediate-risk PE, refers to PE not associated with a low blood pressure but associated with evidence of right heart strain, either on imaging (CT scan or echocardiogram) or in the form of raised troponin or brain natriuretic peptide (BNP) levels. Troponin rise in the context of PE represents right ventricular microinfarction as a result of right ventricular strain from the burden of thrombus. [13]

The American Heart Association (AHA) classifies all other PE as low risk.[14] Existing PE severity scoring systems, such as the Pulmonary Embolism Severity Index (PESI) and Geneva scores are often used to guide decision-making about outpatient versus inpatient management.[15,16] The broader clinically distinct categories of PE used in our paper, have implications on the choice of initial treatment, specifically, whether or not thrombolysis is appropriate. The National Institute of Clinical Excellence (NICE) and European Society of Cardiology (ESC) 2019 guidelines recommend thrombolytic therapy only when PE is massive, that is, it results in a low blood pressure.

Currently, majority of guidelines advice against thrombolysis for submassive PE.[17, 18] There is evidence to show that thrombolysis in submassive PE results in improved pulmonary arterial pressures and decreased incidence of right ventricular failure.[9] However, a mortality benefit to thrombolysis in submassive PE has not yet been demonstrated. [19] The risk of major bleeding, including intracranial bleeding from thrombolysis has also been reported variably in published literature and has been as high as 9.2% in a meta-analysis.[20, 21]

In the face of relatively low, albeit variably, reported mortality rates in submassive PE, the benefits of thrombolysis are not felt to outweigh the associated risk of major bleeding. Due to the much higher mortality with massive PE, the consensus swings in favour of thrombolysis, with the bleeding risk being outweighed by the afforded mortality benefit.It should also be noted that clinical trials done so far have been inadequately powered to detect a mortality benefit in either low-dose or full-dose thrombolysis in submassive PE.[22] Exceeding large sample sizes would be needed to adequately power such a study, at the given mortality rates.

A secondary goal of our paper was to identify the mortality associated with the clinical severity categories of PE in contemporary practice and add to the existing but variable literature on PE associated mortality. We also reviewed records of all deaths individually to audit whether there had been any potential opportunities for thrombolysis.

Methods:

Institutional audit was registered. Electronic medical records of all patients presenting to a large tertiary care teaching hospital in London, between October 1, 2018 and January 16, 2020, who had a discharge diagnosis of acute pulmonary embolism were reviewed retrospectively. Haemodynamic instability was defined by a systolic blood pressure of less than 90 mm of Hg or by a drop in systolic blood pressure by 40 mm of Hg or more. Right heart strain was identified by either a diagnosis of the same on a CT pulmonary angiogram (CTPA) or echocardiogram or by an elevated level of cardiac biomarkers (troponin or nt-pro Brain Natriuretic Peptide (BNP).PE associated with haemodynamic instability was classified as massive, while PE without haemodynamic instability, but with right heart strain, was classified as submassive. All other PE were classified as low risk.

Major bleeding was defined as [23]
(1) fatal bleeding and/or
(2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or
(3) bleeding causing a fall in Haemoglobin level of 2 g/dL or more or requiring a transfusion of two or more units of whole blood or red cells.

Mortality data was reviewed on electronic medical records. For in-hospital deaths, the date of death was updated on records by the hospital staff; for out-of-hospital deaths, records were updated by the GP. Records of all patients who died were reviewed for PE related 14 day and 30-day mortality. Mortality attributable to a cause other than PE was not considered PE related mortality but was reported in all-cause mortality. Records were also reviewed to identify patients that would be deemed to have a high-risk of bleeding.[24]

This data was used when auditing individual deaths as it would have bearings on decisions surrounding thrombolysis.

Results

There were 229 presentations to our hospital between October 1, 2018 and January 16, 2020 where the discharge diagnosis was "acute pulmonary embolism". Attendances that recurred for the same instance of acute pulmonary embolism and attendances where the diagnosis was subsequently disproven on scan were excluded. Also excluded was a patient in whom PE was diagnosed at another hospital two weeks ago and a patient in whom mortality data was unavailable.

There were 171 patients, who had a confirmed discharge diagnosis of acute PE between October 1, 2018 and January 16, 2020. Approximately half of the them were male, thirty percent had a history of cancer and in about 8%, the PE was a recurrence. (Table 1)

Table 1. Characteristics of patients with confirmed acute pulmonary embolism *

Variable	Total 171
Male: Number (%)	86 (50.3%)
Age in years: Mean (SD)	62.4 (17.1)
History of cancer: Number (%)	52 (30.6%)
Recurrent PE: Number (%)	14 (8.2%)
Identified as high-risk for bleeding: Number (%)	19 (11.1%)

Table 2. Mortality by PE risk-category

PE Risk Category	n	Mortality - All causes n (%)	Mortality - PE related n (%)
Massive	17	6 (35.3%)	5 (29.4%)
Submassive	68	2 (2.9%)	1 (1.5%)
Low	83	2 (2.4%)	0
Unclassified	3	0	0

All-cause mortality was 4.1 % at day 14 and 5.8 % at day 30. PE related mortality at day 14 and 30 was 2.9 % and 3.5 % respectively. Of the 171 patients, 83 had low-risk PE, 68 had submassive PE, 17 had massive PE and for 3 patients there was not enough data to accurately categorize the PE. There was no PE related mortality recorded in the low-risk PE group. There was one PE related death in the submassive PE group (1.5% mortality at day 14 and day 30). Massive PE was associated with a 29.4% PE related mortality short-term mortality.

Major bleeding occurred in 4 patients (2.3%), three of whom had received thrombolytic therapy. A total of 22 patients were thrombolysed. Ten of these had massive PE and 12 had submassive PE. Most of the seven patients with massive PE who were not thrombolysed had relative contraindications to thrombolysis.

Discussion

Though our sample size was smaller than most registry data, records of each patient were independently reviewed to ensure accuracy of diagnosis and all other data obtained. This is not necessarily the case with registries. For example, the International Cooperative Pulmonary Embolism Registry, ICOPER, accepted without independent review diagnoses provided by participating centres.6 Mortality rates from PE at our institute were comparable to those reported in the more recent studies and lower than those reported in some registries.

Of the 10 patients who died by day 30 of admission, three had had an out of hospital cardiac arrest with subsequent return of circulation and eventual cardiac arrest again. Of these three, two received thrombolysis.

The CT pulmonary angiogram of the patient who had an out-of-hospital cardiac arrest and did not receive thrombolysis reported "subtle bilateral pulmonary emboli with evidence of right heart strain". The cardio-pulmonary resuscitation (CPR) downtime for this patient was 40 minutes with evidence of ischemic hepatitis and an International normalized ratio (INR) of 3.8. The decision to not offer thrombolysis was documented.

Of the 10 patients who died by day 30 of admission, six had massive PE, two had submassive PE and two had low-risk PE. Both patients with low-risk PE had non-PE related mortality.

Of the two who died with submassive PE, one had sickle cell disease with acute kidney injury on a background of chronic kidney disease and severe pulmonary hypertension. A CT pulmonary angiogram had shown segmental pulmonary emboli within the right upper lobe; the cardiac arrest itself was from hyperkalaemia with a serum potassium of 9.1 mmol /L. Thrombolysis, along with anti-hyperkalaemia treatment were instituted at the pointof cardiac arrest, with subsequent return of circulation and eventual further deterioration and death the next day in intensive care.

The other patient with submassive PE who died had a sudden cardiac arrest at the point of discharge from the hospital, two days after admission. A CTPA had reported "...major massive central pulmonary embolism with a saddle embolus present across the bifurcation of the main pulmonary artery with associated right ventricular strain". This patient was treated initially with low-molecular weight heparin and an interim plan was made to offer thrombolysis should the systolic blood pressure dip to less than 100 mm of mercury or should any oxygen requirement develop. This patient remained haemodynamically stable and without supplemental oxygen, until a sudden cardiac arrest, at which point thrombolysis was instituted. There was a brief return of circulation, but death occurred shortly after. This was this patient's third PE and there was a background of breast cancer under surveillance.

Three patients with massive PE had in-hospital deaths. One had bilateral pulmonary emboli with right heart strain and was treated with low-molecular weight heparin. This patient also had evidence of major haemorrhage at the time of admission evidenced as a new drop in haemoglobin from 99 to 69 g/L and necessitating >2 units of packed red cells to be transfused. Subsequent upper GI endoscopy had shown no stigmata of recent bleeding and this patient was awaiting a CT colonogram. Thrombolysis was offered at the point of cardiac arrest. Whilst no

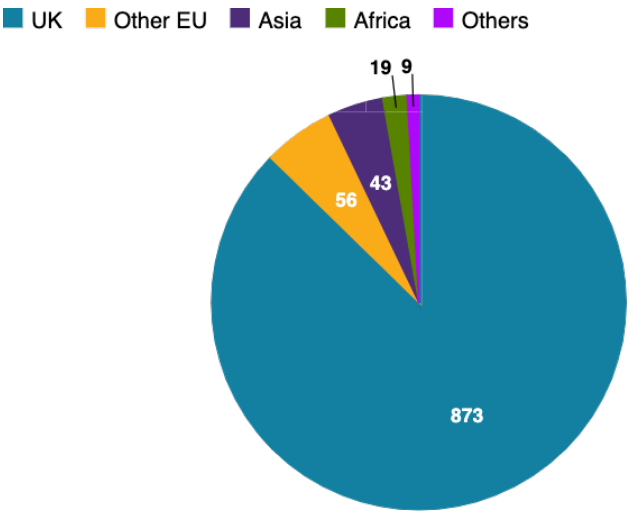
blood pressure reading was recorded as less than 90 mm of mercury, the drop in systolic blood pressure from her best baseline readings was > 40 mm of Hg. Further, this patient had rapidly progressive hypoxia. This was this patient's third PE and mortality was directly PE related. Both of the other two patients with massive PE and in-hospital deathhad been offered thrombolysis. Notably, individualised 'case-by-case basis thrombolysis'for submassive PE was practiced at our institute. Twelve of the 68 patients with submassive PE were thrombolysed. None of these twelve patients suffered major bleeding and all but one survived. The single death in this group was not PE related.Our data reaffirms that mortality from submassive and low-risk PE is low. There was no major bleeding observed in our selection of patients with submassive PE who received thrombolysis. Mortality from massive PE continues to approach 30% even today.

References

1. Horlander KT, Mannino DM, Leeper KV. Pulmonary Embolism Mortality in the United States, 1979-1998: An Analysis Using Multiple-Cause Mortality Data. Arch Intern Med.2003;163(14):1711–1717. doi:10.1001/archinte.163.14.1711
2. Jimenez D, et al.forthe RIETE investigators. Epidemiology, patterns of care and mortality for patients with hemodynamically unstable acute symptomatic pulmonary embolism. International Journal of Cardiology. Vol 269, p327-333,Oct 15, 2018. doi: https://doi.org/10.1016/j.ijcard.2018.07.059
3. Lilienfeld, David E. Decreasing mortality from pulmonary embolism in the UnitedStates, 1979–1996. InternationalJournalofEpidemiology, Vol 29, Issue 3, June 2000, Pages 465–469, https://doi.org/10.1093/ije/29.3.465
4. Alpert, Joseph S., et al. Mortality in Patients Treated for Pulmonary Embolism. JAMA.1976;236(13):1477-1480. doi:10.1001/jama.1976.03270140029017
5. Lehnert P., et al. Acute Pulmonary Embolism in a National Danish Cohort: Increasing Incidence and Decreasing Mortality. Thromb Haemost 2018; 118(03): 539-546 DOI: 10.1160/TH17-08-0531
6. Goldhaber, Samuel Z., et al. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry(ICOPER). The Lancet; Vol 353, Issue 9162,24 April 1999, Pages 1386-1389. Doi: https://doi.org/10.1016/S0140-6736(98)07534-5
7. Meyer,G.,etal.forthePEITHOinvestigators.FibrinolysisforPatientswithIntermediate-RiskPulmonaryEmbolism.N Engl J Med 2014; 370:1402-1411DOI: 10.1056/NEJMoa1302097
8. Sharifi, M., et al. Moderate Pulmonary Embolism Treated With Thrombolysis (from the "MOPETT" Trial). The American Journal of Cardiology. vol 111, issue 2,P273-277, Jan 15, 2013. Doi: https://doi.org/10.1016/j.amjcard.2012.09.027
9. Piazza, G., et al for the SEATTLE II investigators. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism. J A C C : Cardiovascular Interventions. vol . 8 , no. 10 , 2 0 1 5. doi: . h t t p : / / d x . d o i . o r g / 1 0 . 1 0 1 6 / j . j c i n . 2 0 1 5 . 0 4 . 0 2 0
10. Kucher, N., et al. Massive Pulmonary Embolism. Circulation. 2006;113:577–582. Doi: https://doi.org/10.1161/CirculationAHA.105.592592
11. Morris, Micheal F., et al. CT Findings and Long-Term Mortality After Pulmonary Embolism. AJR 2012; 198:1346–1352. Doi: DOI:10.2214/AJR.11.6801
12. Bernal, Alejandra G., et al. Management of PE. Expert Opinion. American College of Cardiology. Jan 27, 2020.
13. Kucher, N. & Goldhaber, Samuel Z. Cardiac Biomarkers for Risk Stratification of Patients With Acute Pulmonary Embolism. Circulation. 2003;108:2191–2194. https://doi.org/10.1161/01.CIR.0000100687.99687.CE
14. Jaff, Michael R., et al. Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension. A Scientific Statement from the American Heart Association. Circulation. 2011;123:1788–1830. Doi: https://doi.org/10.1161/CIR.0b013e318214914f
15. Zhou, X., Ben, S., Chen, H.et al.The prognostic value of pulmonary embolism severity index in acute pulmonary embolism: a meta-analysis.Respir Res13,111 (2012). https://doi.org/10.1186/1465-9921-13-111
16.Wicki J, Perneger TV, Junod AF, BounameauxH, Perrier A. Assessing Clinical Probability of Pulmonary Embolism in the Emergency Ward:A Simple Score.Arch Intern Med.2001;161(1):92–97. doi:10.1001/archinte.161.1.92
17. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. NICE guideline [NG158]Published date:26 March 2020
18. Konstantinides, Savros V., et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). EuropeanRespiratoryJournal2019;DOI:10.1183/13993003.01647-2019
19. Marti, C., et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis, EuropeanHeartJournal, Volume 36, Issue 10, 7 March 2015, Pages 605–614,https://doi.org/10.1093/eurheartj/ehu218
20. Daley, M. J., Murthy, M. S., & Peterson, E. J. (2015). Bleeding risk with systemic thrombolytic therapy for pulmonary embolism: scope of the problem.Therapeutic Advances in Drug Safety, 57–66.https://doi.org/10.1177/2042098615572333
21. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding, and Intracranial Hemorrhage:A Meta-analysis. JAMA.2014;311(23):2414–2421. doi:10.1001/jama.2014.5990
22. Kucher, N., et al. Randomized, Controlled Trial of Ultrasound-Assisted Catheter-Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism. Circulation. 2014;129:479–486. https://doi.org/10.1161/CirculationAHA.113.005544
23. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S, for the Subcommittee on Control of Anticoagulation. Definitionof clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 2015; 13: 2119–26.
24. Fugate JE, Rabinstein AA. Absolute and Relative Contraindications to IV rt-PA for Acute Ischemic Stroke. Neurohospitalist. 2015;5(3):110-121. doi:10.1177/1941874415578532

Supporting International Medical Graduates in the NHS

Experiences from the pre-COVID & COVID environment



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Abstract

International Medical Graduates represent a significant part of the UK medical workforce. Often highly qualified in their home countries, they arrive in the NHS without the experience of either system or culture. Their chance of success is determined by the orientation program and governance structures are in place to support them. In this report, we describe two structures we designed independently to support IMGs from recruitment through to their transition into working in the NHS. We describe the Epsom St Helier Academy and King's College Orientation Programs in the pre-COVID and COVID19 era. Our programs offer a blueprint for other healthcare organisations looking to improve the integration and experience of IMGs in the NHS.

Keywords
international medical graduates, COVID-19, Induction, UK Practice

Illustration shows the composition of UK healthcare workforce proportion per 1000 from UK Parliament report 2018

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Introduction

Like many hospital Trusts in the United Kingdom (UK), King's College Hospital and Epsom & St Helier Hospital regularly recruit doctors from outside the UK in a wide range of specialties. International Medical Graduates (IMGs) are now the second largest group of doctors employed by the National Health Service (NHS) and constitute 30-40% of the junior doctor workforce. [1, 2] According to the General Medical Council (GMC), 36% of doctors in the UK obtained their primary medical qualification overseas and in 2018 there was a 50% increase in the number of IMGs coming to the UK and taking the Medical licensing examinations.[3] Recruitment of these additional doctors into the NHS is a short-to-medium-term solution to the current workforce crisis.

IMGs are often highly qualified in their home country but struggle with the challenges of adjusting to a different healthcare system and culture. IMGs face multiple challenges while adapting to an unfamiliar training system, medico-legal framework, expectations of roles and responsibilities, and skills. [4] They face hurdles with career progression [5], differences in working practices [6], social (building support networks), communication and common usage or linguistic context.[7] These challenges can hinder performance, progression and significantly impact on wellbeing. Many IMGs find themselves unprepared as they are expected to work without supervision and often without clinical orientation or comprehensive induction to local healthcare systems. For the individual IMG, these challenging experiences can put them off working in the UK, and for the employing organisations, it can lead to unsuccessful recruitment and medico-legal challenges with patient safety or underperformance. It can be a burden to teams often left supporting them. It is clearly apparent that IMGs have learning and pastoral needs that are not met with traditional generic training programs. [4] Hence a robust orientation programme designed to anticipate and mitigate such challenges and facilitate a smooth transition into working in the NHS, is essential.

In order to address this need, we developed the 'King's Overseas Doctors' Development Program' (ODDP) in 2013 and the Epsom St Helier 'IMG Academy Program' in 2017. This article explores facets of the program of support and development available to this group of doctors. In addition the COVID-19 pandemic has readjusted almost all of the working practices of the NHS and we discuss our responses to this crisis with particular focus on IMGs as part of the black and minority ethnic (BAME) group of doctors that appear to have been affected more significantly.

The Epsom & St Helier IMG Academy Experience

At Epsom St Helier Hospital, a standard orientation program for IMGs working in Department of Medicine was developed using principles of quality improvement intervention through each of the processes of recruitment, support, orientation, training, assessment and integration. Doctors were recruited at Core Medical Trainee (Senior House Officer) and Specialist Trainee (Specialist Registrar) level based on their prior clinical experience. They had GMC registration after success in the Professional Linguistic Assessment Board (PLAB) UK medical licensing examination and obtained a certificate of sponsorship (Tier 2). Alternatively, doctors with more extensive non-UK postgraduate medical experience at Senior House Officer (SHO) or Registrar level were recruited through the Medical Training Initiative (MTI) sponsored by the Royal College of Physicians of London. These doctors had a certificate of sponsorship (Tier 5) via the Academy of Medical Royal Colleges.

We invited prospective candidates via social media and personal contacts, arranged telephone screening interviews (conducted by a consultant) and successful candidates were advised to apply online to nationally advertised vacancies. Formal interviews were based on the UK national recruitment model via videoconference and consisted of curriculum vitae (CV) review, clinical case scenarios and ethical scenarios.

All newly recruited IMGs underwent a structured Clinical Orientation Program (COP) 6 weeks duration for SHO and 12 weeks for registrars. During this period IMGs were supernumerary, received close clinical supervision, mentoring, pastoral support, and underwent multiple clinical assessments. At the end of the COP, after completion of specified targets, the doctors were assessed as competent to work in independent roles as junior doctors by their educational supervisor. Training was provided under an umbrella named "The Academy", with an appointed Training Programme Director and a committee consisting of representatives from Division of Medicine, Human Resources, postgraduate medical education, consultant physicians and the Trust's Responsible Officer. Other stakeholders included the clinical and educational supervisors.

Figure 1 : Key Needs for International Medical Graduates

- Communication and culturally tailored language skills (understanding and being understood by patients and colleagues)
- Understanding of systems and pathways (NHS structure, clinical governance, quality improvement and the role of multi-professional workforce)
- Living in the UK: bridging the cultural gap (practicalities of living/working in a new place)
- Career development (job applications and interviews, career pathways)
- Mentorship (Difficulties faced in UK system, worry about making mistakes, feeling alone, difficulty with exams)
- Managing health and wellbeing (access to confidential support from occupational health, practitioner health programmes, professional support unit)
- Ethics and UK Legal framework

Almost 96% of IMGs (n=21) recruited to our Trust in 2019-2020, successfully completed the COP and the support provided facilitated their development and contributed to their clinical exposure, learning opportunities comparable to training provided to UK-trainee doctors. Many continue to remain in the employment of the Trust. The resources needed to support this programme was provided by the Trust and were viewed as an effective utilisation for successful recruitment and ensuring safe delivery of clinical care.

International Medical Graduates: The King's Overseas Doctors Development Program

The King's Program consists of regular teaching days (every 4-6 weeks), freely available to all IMGs including Staff and Associate Specialist Grade (SASG) and trainees. The first session is a focus group discussion with the IMGs, to help identify their learning and development needs specific to their UK medical practice. This diagnostic approach is repeated in brief at the beginning of every session. This has resulted in an iteratively derived list of learning needs (Figure 1).

The program is distinct from the usual UK training days as we aim to provide a safe space for the IMGs to be completely open and honest about their challenges and difficulties. Each study day consists of a variety of teaching activities (Figure 2). A key tenet is to align the IMGs' existing values and beliefs alongside those expected in the NHS.

The enlisted faculty consists of an ethnically diverse group of consultants and medical education fellows, many of whom are IMGs who have had to overcome similar challenges. Faculty members are provided with formal training in the principles of coaching and mentoring and they provide IMGs with on-going coaching support in between contact days. Participants are able to attend sessions as long as needed, until they feel comfortably settled into their UK practice. There is no formal assessment.

The King's Program feedback has been positive, with 100% of participants rating the program 'good' to 'excellent'. Candidates describe feeling supported and valued. Candidates particularly value career guidance and support.

''This was my third overseas programme session, I have attended and they honestly get better every time. As an Foundation year 1, dealing with clinical emergencies was relevant and made this the best session so far"

''It was very helpful. Not only for the information but also for having the possibility to share some feelings with others who feel the same"

"I attended all the modules of the overseas doctors' development programme ‍ and I must confess the programmes has made my journey through the NHS less stressful."

Being flexible to their needs and utilising the skills and personal experiences of the faculty leads to a more enriching experience that leaves them feeling valued and supported. Extra time is factored into each session as learning is negotiated throughout the day and the candidates may be at very different levels of seniority.

We found simulation to be a powerful tool for stimulating reflection on some of the key issues facing IMGs, such as: end-of-life care, assertiveness and communication. For example in some cultures "strong words" (e.g. dying) are avoided and in the NHS this can lead to ambiguity and confusion. This became apparent in a simulated exercise where the candidate had to explain a 'Do Not Attempt Resuscitation' order to a relative. Often IMGs are not familiar with simulation-based learning techniques and for some candidates, suspending disbelief can be challenging to begin with.
The flexible and bespoke nature of the programme requires commitment and leadership from the faculty and postgraduate medical education.

Figure 2: King's College Program: Teaching and learning activities

- Leadership and NHS structure
- Discussion and role-play around ethical dilemmas
- Hi-fidelity Simulation (debriefing including human factors)
- Communication skills training, e.g. making a referral, value of feedback etc.
- Career discussions- interview practice
- Using clinical scenarios for clinical and generic skills
- Case presentations
- Face to face mentoring

International Medical Graduates and COVID-19

The COVID-19 pandemic has changed working practices in the NHS and has had a significant effect on IMGs. Reports that people from ethnic minority backgrounds constitute 14% of the population but account for 34 per cent of critically ill Covid-19 patients and a similar percentage of all Covid-19 cases are of considerable concern. [8]

Moreover, of the initial 119 NHS staff known to have died in the pandemic, 64% were from an ethnic minority background, yet only 20% of NHS staff are from an ethnic minority background. [9-11] The COVID-19 pandemic represents a challenging situation for all our doctors but in particular our IMGs. Firstly there is the emerging data that BAME staff appear to have higher risk from COVID-19; secondly, IMGs have a reduced level of social support networks

and more difficult contact with family members and thirdly they are working in a healthcare system under extreme stress in which they may find accessing information and support more difficult.

Supporting IMG doctors through COVID-19

For each of the interventions that were implemented in our organisation, we considered the impact and applicability to our IMG doctors. We considered that three important facets to underpin our response; (i) honest and timely communication, (ii) fostering team working and cohesion and (iii) access to psychological and well-being resources.

Communication:

Clear lines of communication between the teams that can effect rapid change on the shop floor, is essential. We had regular briefing sessions with the Chief Registrar who was able to report back to the Trust Silver command on frontline issues affecting junior doctors. In addition, walkabouts on the wards were undertaken regularly by senior staff. These walk-abouts enabled us to reach staff including IMGs and to gain from them, invaluable direct feedback in a situation which was changing rapidly.

The IMG doctors reported feelings of vulnerability much like other staff. Whilst the hospital communicated with daily e-briefings (sent out via email) we were concerned that many staff, especially IMGs were not accessing these briefings. We instituted a policy of displaying it in the doctors' mess in each of our hospital sites. The mess acted as a sanctuary, away from the clinical environment, where doctors could relax, find peer support and refreshment.

Psychological Support and Wellbeing:
We were offered support from the South West London and St George's Trust psychotherapy services. A psychologist supported staff deployed to our Intensive therapy unit (ITU). The junior medical staff were often reluctant to discuss emotional issues in front of their supervisors and preferred to speak with someone neutral. Hence, we set up wellbeing support for junior doctors with facilitated (virtual) talking groups (as drop-in), or individual sessions. We also sign-posted staff to the virtual Wellbeing Hub established by the Professional Support Unit of Health Education England.

Personal Safety:

Personal protective equipment (PPE) was a major concern for the entire workforce, but with media reports about the lack of availability, even on COVID-19 wards, staff were understandably anxious. Often this resulted from difficulties in communication and from conflicting guidance received from Public Health England or professional bodies such as the Resuscitation Council (UK), particularly with reference to aerosol generating procedures. The anxiety among staff was further exacerbated by the very high sickness rates, especially in the early part of April 2020. There was the added complication of challenges in obtaining COVID-19 testing for staff much of which was organised on a remote "drive in" site that was not simple for IMGs to access.

At the beginning of the pandemic, the Trust rolled out a Medical Staff Skills Survey to assist in redeployment and working with occupational health department to identify those with underlying health problems who would require shielding. Many of these were consultant staff from BAME groups and they were re-deployed to home or non-patient facing work, in co-ordinating research and working the bereavement office.

Library and Information Services:

We utilised the library and information services to roll out use of video conferencing and also make available on-line educational resources. In addition, the libraries in each of our hospital sites became a hub for drop-in groups and support sessions. The Director of Medical Education (DME) led the re-deployment of over 50 medical staff working with Human resources and medical rostering teams. The close liaison between clinical and educational leadership teams was important to ensure that redeployment was based on strengths and recognised potential vulnerabilities of staff.

Conclusions

In order to address the perpetual NHS medical workforce challenge, we have developed innovative strategies to improve overseas recruitment and retention of junior doctors to our Trusts. The success of our strategy depended on developing a structured program for new IMGs (naive to the NHS) leading to a safe, culturally sensitive, supported transition into the workplace facilitated by an ethnically diverse faculty and appropriate investment of resources.

This group of doctors commonly report feeling unsupported and under-valued and our programs improved their experience, helped them settle into their UK jobs quickly and provided them with a strong foundation for a successful career.

In our view, Trusts should make effective support and development of IMGs an important goal of their 'People' Strategy; for the benefit of patients, IMGs and their colleagues.

The arrival of COVID-19 placed additional pressures on IMGs and a co-ordinated approach supporting the welfare and well-being of these doctors is an important part of any organisational response.

References

1. Kehoe A, McLachlan J, Metcalf J, Forrest S, Carter M, Illing J. Supporting international medical graduates' transition to their host-country: realist synthesis. Med Educ. 2016 Oct;50(10):1015–32.
2. Valero-Sanchez I, McKimm J, Green R. A helping hand for international medical graduates. BMJ [Internet]. 2017 Nov 24 [cited 2020 Jul 8];359. Available from: https://www.bmj.com/content/359/bmj.j5230
3. General Medical Council (Great Britain). The state of medical education and practice in the UK, 2014. [Internet]. 2014 [cited 2020 Aug 1]. Available from: http://www.gmc-uk.org/SOMEP_2014_FINAL.pdf_58751753.pdf
4. Bhat M, Ajaz A, Zaman N. Difficulties for international medical graduates working in the NHS. BMJ [Internet]. 2014 May 12 [cited 2020 Aug 1];348. Available from: https://www.bmj.com/content/348/bmj.g3120
5. Huijskens EGW, Hooshiaran A, Scherpbier A, van der Horst F. Barriers and facilitating factors in the professional careers of international medical graduates. Med Educ. 2010 Aug;44(8):795–804.
6. Morrow G, Rothwell C, Burford B, Illing J. Cultural dimensions in the transition of overseas medical graduates to the UK workplace. Medical Teacher. 2013 Oct 1;35(10):e1537–45.
7. Baker D, Robson J. Communication training for international graduates. The Clinical Teacher. 2012;9(5):325–9.
8. Why are more black and minority ethnic people dying from Covid-19 in hospital? – Race Equality Foundation [Internet]. [cited 2020 Aug 1]. Available from: https://raceequalityfoundation.org.uk/health-care/why-are-more-black-and-minority-ethnic-people-dying-from-covid-19-in-hospital/
9. Cook T, Kursumovic E, April 2020 SL. Exclusive: deaths of NHS staff from covid-19 analysed [Internet]. Health Service Journal. [cited 2020 May 23]. Available from: https://www.hsj.co.uk/exclusive-deaths-of-nhs-staff-from-covid-19-analysed/7027471.article
10. Rimmer A. Covid-19: Two thirds of healthcare workers who have died were from ethnic minorities. BMJ [Internet]. 2020 Apr 23 [cited 2020 May 24];369. Available from: https://www.bmj.com/content/369/bmj.m1621
11. Who's at higher risk from coronavirus (COVID-19) [Internet]. nhs.uk. 2020 [cited 2020 Aug 1]. Available from: https://www.nhs.uk/conditions/coronavirus-covid-19/people-at-higher-risk/whos-at-higher-risk-from-coronavirus/

Author contributions
RB and TJ conceived and wrote the manuscript. All authors equally contributed to the program design, delivery, evaluation and manuscript editing.

Conflict of Interest
None declared

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ABSTRACTS

BAPIO Annual Conference, London 2019

CONFERENCE ABSTRACTS
BAPIOAC19-P11

Introducing Emergency Simulation Training in Paediatrics:

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Keywords: paediatric emergencies, simulation based training

Aim
To introduce regular paediatric emergency simulation sessions for paediatric trainees at QEH, Woolwich and to evaluate early attitudes toward its role in training.
Background
Direct repeated experience is necessary for trainees to gain confidence and competence in management of time critical, life threatening scenarios. The relative infrequency of paediatric arrest and peri-arrest situations means opportunity to gain vital experience can be limited. Simulation offers an effective educational tool to bridge the gap between theoretical knowledge and real life implementation. Multiple studies have shown that simulation in Paediatrics correlate with better health outcomes for patients ranging from an improvement in cardiopulmonary arrest survival rates, earlier identification of a sick child and reduced serious safety incidents in A&E.
Method
We started off by surveying junior doctor attitudes towards simulation in training. My sample population included junior paediatric SHOs, GP trainees and ED SHOs. Though my sample size was small it showed strong support for paediatric simulation. We conducted the sessions in the paediatric resuscitation bay in A&E to make the situation as realisticas possible. This has the added benefit of making sure when in a real emergency, trainees know where to find necessary equipment. Scenarios have been run by experienced registrars for small groups of trainees. Scenarios have been run by experienced registrars for small groups of trainees.
Results
We initially surveyed 10 SHO grade doctors and of these, 7 reported that they felt "very unconfident" in managing paediatric emergencies. Evaluation forms from our simulation session on managing life threatening asthma showed that 7 out of 8 doctors who attended said that they felt more confident to manage the situation after having had simulation in it.
Conclusions
These results show the effectiveness of simulation on trainee confidence in managingemergencies by experiential learning. Good facilitators are crucial to run the simulation. Without reflection, the learning process is greatly diminished.

BAPIOAC19-P02

Cost utility of unnecessary post-operative blood tests: *After trauma and elective orthopaedic surgery at two Manchester Hospitals*

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Published 2020-07-20

Background:
Despite being one of the most efficient healthcare systems in the world, the NHS remains under constant financial pressures in view of ever-increasing health care demands. Clinicians therefore have an important duty to identify areas where efficacy savings can be achieved to ensure that funds are utilised in an effective manner.
Aim:
To identify savings that can be achieved by eliminating unnecessary post-operative blood tests for patients undergoing trauma and elective orthopaedic surgery.
Setting: Manchester Royal Infirmary & Trafford General Hospital, University of Manchester NHS Foundation Trust, UK
Methods:
A retrospective service evaluation study was conducted to assess the cost of unnecessary post-operative blood tests for 50 patients who underwent trauma or elective orthopaedic surgery at 2 different hospital sites. The patients' notes were examined with 3 aims: 1)Identify the operations that were undertaken 2)Identify blood tests done up to 5 days post-operatively 3)Whether there was any clinical indication for the blood tests.
Results:
A cumulative of over 150 unnecessary blood tests were identified. The most common inappropriately ordered tests were CRP, Liver Function Tests, Bone profile and Coagulation screen. The total cost of these tests exceeded £750, a significant cost considering these figures are for only 50 patients. It was also noted that a higher number of unnecessary blood tests were carried outat Manchester Royal Infirmary, where most patients underwent trauma surgery, compared to Trafford General Hospital, where most patients underwent elective surgery.
Conclusion:
This study identified that significant savings can be achieved if the practice of ordering unnecessary post-operative blood tests is eliminated. We therefore recommend: 1) Education of medical and nursing staff about the financial/clinical implication of unnecessary bloods 2) A protocol is developed,potentially on the type of operation done, to order post-operative bloods so as to limit unnecessary tests.

BAPIOAC19-P15

Improving documentation of regional anaesthesia catheter procedures at St George's Hospital, London

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Published 23.08.2020

Keywords: Regional anaesthesia

Background and aims:
Regional anaesthetic techniques provide effective analgesia post-operatively and in trauma patients such as those with multiple rib fractures. Documentation of the regional anaesthesia (RA) procedures is an issue due to the recent transition from paper to iCLIP computerised system to document electronically. Documentation of pain scores in patients before and after the block on the same day is also an issue. It is useful to create an 'Anaesthetic catheter procedure template' suited for iCLIP to improve documentation. This template will include pre and post block pain scores which can be documented adequately.Methods:This was a retrospective review of the available data from hospital paper notes and iCLIP from 13/05/19 to 24/05/19. A total of 21 patients were included in this study who needed a catheter for different reasons. The following were analysed: 1) documentation of catheter procedure and where it was documented, 2) documentation of pain scores pre and post catheter.

Results:
Differences werefound in the location of documentation varying from electronic to paper as well as variability in paper documentation. There was also considerable variation in how the electronic document was titled. A total of 12 out of 21 procedures were documented under documentation section within iCLIP. 11 out of 21 procedures were documented in paper. About 76% of the patients did not have pain scores documented prior to the nerve block. A total of 14 patients had their pain scores documented on day 0 post block.

Conclusion:
Documentation of RA procedures in St George's Hospital can be improved by introducing a template ensuring less inconsistency. This enables to document the procedure as well as pain scores before and after to measure effectiveness of the nerve block received by the patients. An audit will be conducted six months after the template is in place.

Conflict of Interests/Comments: Nothing to declare.

BAPIOAC19-P08

Relevance of FGFR1-NMDAR2B heteroreceptor complexes in treating major depressive disorder

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Published Aug'20

Background:
Major depressive disorder (MDD) is both a ubiquitous yet heterogeneous condition, affecting around 15% of individuals at least once in their lives, who may present with an array of physical and cognitive symptoms. Accumulating evidence posits that the N-methyl-D-aspartate (NMDA) receptor may play an important underlying role in the neurobiology and thus the treatment of this disease. In addition, the FGFR1 receptor tyrosine kinase was previously shown to produce antidepressant-like effects when bound by oneof its ligands. The formation of FGFR1-NMDA heteroreceptor complexes through allosteric receptor-receptor interactions may modulate downstream signalingpathways as well as recognition, trafficking and internalization of the constituent receptor protomers. Therefore we proposed the existence of a state of equilibrium between the FGFR1 and NMDA receptors and their heteroreceptor complex in the neuronal membrane, the balance of which may be altered in the depressed state.
Methods:
In our experiments, we used hippocampal and raphe nuclei sections from the brains of a wild-type Sprague-Dawley (SD) rat and in a selectively bred genetic rat model of depression, the Flinders Sensitive Line (FSL) rat, for comparison. We then localized and quantified the receptorcomplexes through immunofluorescence and in situ proximity ligation assay (PLA) techniques.
Results:
We obtained evidence for the existence of FGFR1-NMDAR2B heteroreceptor complexes in the hippocampus and midbrain areas of the adult rat brain. Analysisof the FGFR1 and NMDAR2B immunoreactivities indicate strong co-distribution of both receptor protomer in the same brain areas. Interestingly, NMDAR2B immunoreactivity studies suggest also a reduction in the expression level of the NMDAR2B subunit in the hippocampus and raphe brain regions of the FSL adult rats. Preliminary quantification analysis showed a significant reduction in the positive FGFR1-NMDAR2B PLA clusters in both studied areas in the genetic animal model for depression (FSL) with the exception of the molecular cell layer of the dentate gyrus.

Conclusions
Taken together, this concept could pave new avenues for therapeutic exploration in reducing the global occurrence, recurrence and severity of major depressive disorder.

BAPIOAC19-P04

Development of an acute general paediatrics service specification at a major London hospital

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Published 2020-07-30

Background and aims
Annually 28,000 patients between the ages of 0-18yearspresent acutely to St George's Hospital (mainly via the emergency department or following a GP consultation) and are the responsibility of the Acute General Paediatrics care group. They may be cared for in a number of settings and across a number ofpathways of care. To ensure the delivery of a safe, patient centred, high quality service, we created a service specification based on the present plethora of national standards. This would also provide a means for ongoing quality analysis.

Methods
Relevant guidance was identified through a variety of search methods: direct search of national bodies' websites, expert opinion and liaison with Trust managers to identify standards reported to regulators.

Results
Sixty two key standards were identified from six different guidelines. Thematic analysis of these standards identified nine overarching themes and within each, a number of sub-themes. A Red Amber Green (RAG) rating system was used to identify the performance of the service against each theme. An action plan has been created linked to the service governance strategy to ensure the standards can be achieved in the future.

Conclusion
The new service specification will be used by clinical staff to reflect on practice and outcomes. It enables clinicians to identify standards, rather than accessing them from various sources. It will aid planning, commissioning and provision of acute paediatric services and provide a framework against which to audit provision and demonstrate improvement. It would be possible to translate this for use across the UK.

BAPIOAC19-P03

Observational study of shoulder pain among patients undergoing cardiac procedure:

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https://doi.org/10.38192/1.6.2.7
Published 2020-07-26

Background:
Shoulder function and pain in patients undergoing cardiac procedures such as coronary artery bypass graft in poorly studied topic. Often due to lack of awareness of cardiac procedure complication or pre-existing shoulder pain, these patients are referred to the orthopaedics unnecessary in form of new shoulder problem. We carried out this study with an aim to identify prevalence of shoulder pain among patients undergoing elective cardiac procedure at a tertiary hospital.

Method:
A cross-sectional survey including a history and examination was carried out among patients undergoing a cardiac procedure at CIMS hospital, Ahmedabad, India. The face to face survey consisted of demographics, type of surgery, shoulder pain, past medical history including any interventions and a shoulder examination.

Result:
Thirty one patients were recruited and consented to the study who were undergoing an elective procedure. Therewere 25 (81%) men and 6(19%) women. Average age was 60years. Among the patients the most common cardiac diagnosis was coronary artery disease (77%) followed by valvular disease (16%) and acute coronary syndrome (6%). The most commonly performed procedure was coronary artery bypass graft (55%) followed by coronary angiography (29%) and valvular replacement (13%). Shoulder pain was reported by 11(35%) patients and clinically identified by the shoulder exam among 9(29%) patients. Left shoulder pain was reported by seven patients in comparison to right shoulder pain which was reported by one patient. Bilateral shoulder pain was reported by three patients. There were four out of ten diabetic patients who reported shoulder pain. The most commonly diagnosed musculoskeletal condition following the history and examination was osteoarthritis (4) followed by frozen shoulder (3) and impingement shoulder (2).
Conclusion:
This study demonstrates that shoulder pain is common among patients undergoing cardiac surgery. This study raises a key awarenessforpatients who may beunnecessary referred to orthopaedics following cardiac procedure.

BAPIOAC19-P13

Rapidly Growing Cutaneous Squamous Cell Carcinoma of the Nose in Chronic Lymphocytic Leukaemia:

Seth Dhillon

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Keywords: Chronic Lymphocytic leukaemia, Squamous cell carcinoma

Patients with chronic lymphocytic leukaemia (CLL) are at an increased risk of developing cutaneous squamous cell carcinoma (cSSC). In addition, the cSCCs appear to behave more aggressively, most likely due to the immunosuppressed state of the CLL patient.The literaturedocumenting the clinical course of cSCCs in CLL is sparse.

We present a case of an exceptionally fast growing cSCC of the nose in a patient with CLL.An 89-year old gentleman with a pre-existing diagnosis of CLL was referred to us with an cSCC of the dorsum of the nose. The tumour encompassed almost the entirety of the nose, extending to the right medial canthus. The lesion was identified as a local recurrence of a moderately-differentiated primary cSCC which was excised 11 months previously by curettage and cautery without further follow-up.

The cSCC subsequently recurred and underwent a period of exceptionally rapid growth. In consideration of the patient's age and comorbidities it was deemed that radical surgery, requiring total rhinectomy and right orbital exenteration, was not appropriate. The patient instead received palliative radiotherapy.

The current guidelines state that any cSCC in an immunocompromised patient should be treated as high-risk and managed accordingly.This case highlights the need for an increased awareness that CLL causes progressive immunodeficiency, hence all cSCCs in these patients should be treated as high risk. Most importantly, the chosen method of excision should allow marginal clearance to be established, significantly reducing the chance of local recurrence. The case also brings to the fore the challenges in making treatment decisions for patients nearing end of life with multiple co-morbidities.

BAPIOAC19-P16

Treatment Escalation Plan - Quality Improvement Project:

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Keywords: Treatment escalation

Background:
Treatment escalation describes the level of treatment intervention which would be appropriate, should the patient become acutely unwell. Patients may be subjected to inappropriate investigations and management by the 'on call' team as well as inappropriate referrals to ITU/HDU because there is often no clear documentation regarding the 'ceiling of care.' Furthermore, documentation of a treatment escalation plan (TEP) is often difficult to find and vague.

Methods:
Data was collected from three care of the elderly (CoE) wards for the presence of a documented TEP in the notes. A TEP proforma was designed through collaboration with staff. The agreed version was to be filled out by doctors, grade registrar and above. It was trialled on the same three CoE wards for four weeks. Post-intervention data was collected on rates and location of TEP documentation. Qualitative feedback was sought from staff.

Results:
Pre-intervention, data was collected from 58patient notes, 22 patients (37.9%) had a documented TEP. The location of the TEP varied. The documentation for 100% of patients simply stated "ward based ceiling of care." Following our intervention, data was collected from 48 patient notes and 35 patients (60.4%) had a documented TEP. The proforma was used in 100% of cases with a documented TEP. Overall, staff felt that the proforma was quick to fill out, clear and useful. The main issue raised was having to complete an additional form as well as the DNAR form.

Conclusion:
The new TEP proforma has improved documentation rates of TEPs providing clarity when dealing with deteriorating patients and therefore improving patient care. The next step will be to modify and review the proforma with consultation from the legal department to merge the DNAR and TEP proformas. This proforma is a major step in maintaining and improving patient safety.

Conflict of Interests/Comments: Nothing to declare.

BAPIOAC19-P10

Improving Patient Isolation Protocol Posters in a multicultural London Teaching Hospital:

Dijay Dave

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Background and Aims:
Side rooms are used to nurse patients with clinical needs that require isolation; often to prevent cross infection but sometimes for non-medical reasons such as bed availability. The reasons for isolation are thus varied and ensuring both patients and visitors are aware of their specific isolation protocols are essential in providing personalised care. Posters are often used to convey this information however ensuring proper communication across language barriers in a multicultural setting such as London can be difficult. We thus sought to both audit and improve the current posters used in our London teaching hospital setting.

Methods:
We interviewed 10 patients, visitors and doctors at our teaching hospital. Participants were asked about their experienceof side rooms, whether visitors (both personal and staff) followed trust isolation guidelines and their preference of the graphical posters we designed for both contact and airborne precautions. Current and new PPE (Personal Protective Equipment) posters for contact and airborne precautions

Results:
The majority of patients did not know the reason for themselves being in a side room and did not see visitors following isolation guidelines. All participants preferred the newly drafted posters over the current PPE posters.

Conclusion:
We discovered that in our multicultural hospital the majority of patients had decreased adherence and understanding of Patient Isolation protocols despite the presence of the posters. Our survey data showed that all patients, staff and visitors would prefer to have a new poster. Our newly drafted poster had overwhelming support from both patients and staff. The new Patient Isolation posters are in the process of being implemented at our teaching hospital.

BAPIOAC19-P06

Assessment of bowel motion in patients receiving pelvic stereotactic ablative radiotherapy (SABR)

Isobel Rycroft

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Background:
Stereotactic ablative body radiotherapy (SABR) is a novel technique that delivers high radiotherapy doses and is used to treat pelvic oligometastatic nodal disease. Pelvic radiotherapy can damage bowel. As a mobile structure, bowel position can change. It is unknown to what extent bowel mobility changes the dose it receives in SABR treatment. This study aimed to investigate the impact of bowel mobility on the dose it receives between and during (SABR) treatments.

Methods:
Planning CT plus pre and post-treatment Cone Beam CT (CBCT), for each fraction of treatment, were acquired for 5 patients. Bowel within a 3cm margin around the planning target volume (PTV) was contoured on all CBCTs and contours were superimposed onto the planning CT, to allow volumetric and dosimetric assessment. The volume of bowel within the 3cm margin, nearest edge of bowel to the PTV, mean dose and the maximum dose to 0.5cm2 were recorded. Measures for pre and post-treatment CBCTs were compared to determine motion during one treatment(intra-fraction). Measures for pre-treatment CBCTs and planning CT were compared to determine motion between treatments (inter-fraction). Wilcoxon signed-ranks tests were used for comparisons.

Results:
No significant differences in inter-or intra-fraction motion were noted for the whole population. However, for individual patients, bowel positions showed considerable variation and clinically relevant dosimetric changes were noted between and during treatment.

Conclusions:
Individual CBCT images should be reviewed for individual patients receiving pelvic SABR as in some cases the bowel may receive higher doses than intended.

BAPIOAC19-P12

Exploring Surgeon Burnout: Its Causes and How It Affects the Quality and Safety of Patient Care

Tmam Alghunian

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Keywords: Burnout, surgical training

Background:
Poor well-being may affect the performance of all types of workers. Surgeons, in particular, are inclined to suffer from burnout. However, a lack of definitive research on the link between burnout and patient care exists. Understanding this could help identify the outcomes of surgeon burnout and underline the need for interventions.Objective:The present study aimed to inform the design of a broader project investigating burnout in surgeons.

Methods:
A paper survey with 6 questions was developed after the review of the literature.The survey was conducted between January to March 2019 to design and develop an interview schedule and identify whether stress and burnout are issues in Yorkshire surgeons.

Results:
Eighty-three surgeons from different specialities, including urology, general surgery, trauma and orthopaedic surgery and neurosurgery, completed the survey. Of these 44% were consultants and 56 % were trainees. Ninety-two percent of participants believed that stress and burnout are issues for surgeons within the NHS. The results of the survey were used to develop a semi-structured interview study, which will include 15 to 20 surgeons from different specialities. The interview study will explore reasons for surgeon burnout and identify a mechanism to support surgeons inthe workplace to prevent or reduce burnout. The research may also be used to improve patient safety and quality of care.

Conclusions:
Surgeons are more likely to experience a high level of burnout. Further study is needed to explore factors responsible for the burnout and methods to help surgeons to manage it effectively.

Conflict of Interests/Comments: Nothing to declare.

BAPIOAC19-P10

Effectiveness of Peer-led Teaching for Medical Students

Naomi Melamed

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Background
In recent years, peer-led teaching has come to the forefront of medical education demonstrating advantages for both medical students and peer-tutors. Moreover, the General Medical Council has highlighted the importance of teaching colleagues to meet the standards proposed in 'Tomorrow's Doctors'. This innovation in medical education has been reflected by a vast increase in the number of peer-led teaching societies at medical schools. However, the effectiveness of peer-led tutoring has been contested.

Aim
Our study aims to explore the perspectives of third-year medical students and student tutors to evaluate the effectiveness of peer-tutoring programs. We also aim to identify potential obstacles peer-tutors may encounter within this process.

Methods
In 2019, 120 third-year medical students were invited to attend an extra-curricular session delivered by two fourth-year students from a London University. The session focused on developing clinical reasoning skills. All content was approved by a senior memberof academic staff. Students and peer-tutors were invited to complete questionnaires following the session to evaluate their teaching and learning experience.

Results
In total, 102 students attended the session delivered by two peer tutors. Questionnaire responses were received from 95 students and both student-teachers. Of these students, 99% reported they would attend another session. Around 98% agreed the session benefited their learning. Both student-teachers stated they feel more confident and competent in clinical reasoning. However, they reported that preparing this session was time consuming.

Conclusions
Our results suggest that peer-led teaching complements medical school curricula and provides benefits to both students and student-teachers. However, the process revealed several obstacles. These include the limited clinical experience of peer-tutors and time spent preparing sessions. Despite this, we propose that peer-led teaching is an innovative concept allowing students a platform to exchange clinical knowledge.

BAPIOACI9-P05

Machine learning approaches to analyse effect of ethnicity on outcomes following living kidney donation in the UK

Shanmugapriya Basker

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Background:
Despite thousands of kidney donations every year across the world, there is decline in donations particularly within the BAME (Black Asian Minority and Ethnic community) and also there is paucity of data for risk assessment within the South Asian ethnicity. This study aims to describe the risk basedon ethnicity, gender and regional variations and develop a predictive model.

Method:
This project uses Hospital Episode Statistics (HES) Admitted Patient Care (APC) data from 1997/8 to 2017/18 (20 years) with pseudo-anonymous data filtered by kidney donation codes. After trying several approaches to tackle extremely imbalanced dataset 'Weighted Random Forest' approach was selected as the final model.

Results:
Essential hypertension , End age and deprivation index ranked as three most important variables in risk of development of hypertension after donation in the Weighted Random Forest. The model has Negative Predictive Value (NPV) of 95% and True Negative Rate (TNR) of 77% proved that it was able to very well predict that the patients had 'Norisk of hypertension'. Also the Recall rate of 65% showed the model is not overfitting due to its imbalanced nature. The stability of the model was verified by running the algorithm several times with k-fold cross validation and AUC as well. AUC was between 75% to 76% after running through 100 iterations with different set of data.

Essential hypertension, End age and deprivation index ranked as three most important variables in risk of development of hypertension after donation. Logistic regression analysis showed that pre-existing essential hypertension, male gender, age at kidney donation and low numbers of transplant providers are important risk factors for long term hypertension risk. In sub analysis, we found that South Asian ethnicity and obesity areadditional risk factors.

BAPIOAC19-P01

Incidence of prosthetic graft infection following lower limb and open AAA repair surgery at the Manchester Vascular Centre

Basim Ali

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Published 2020-07-25

BACKGROUND
Prosthetic graft infection is a major complication of vascular surgery. Infection is associated with higher morbidity and mortality along with prolonged hospital stay. We investigated the incidence of prosthetic graft infections within a tertiary vascular centre over a 40 month period, from 2016 to 2019.
METHOD
This is a retrospective cohort single site study of prosthetic vascular grafts involving the lower limb, abdominal and axillary arteries. The primary objective was to find the incidence of vascular graft infection in patients undergoing graft procedures at the Manchester Vascular Centre. The outcome of each prosthetic graft infection was evaluated. Patient age, location of graft, type of prosthetic material and pathogen isolated were recorded. Data was extracted from the vascular activity log.
RESULTS
Of the 427 graft procedures performed between 2016 and 2019, 254 prosthetic grafts were identified. Procedures included were axillo-femoral, abdominal aorta and all lower limb interventions. There was a graft infection incidence rate of 4.7%. Patient outcomes ranged from recovery with antibiotic therapy, surgical intervention, amputation and death. The most common pathogens isolated were Enterococcus faecalis and Staphylococcus aureus.
DISCUSSION
The incidence of prosthetic graft infection identified here is 4.7%. After review of available literature, we have only been able to identify some studies which have looked at some but not the entire range of graft areas, notably we included abdominal aortic aneurysm repairs. The incidence of prosthetic graft infection at our centre may be a reflection of the wide anatomical rangeof prosthetic grafts considered but may also reflect the significant burden of smoking, illicit drug use, diabetes and chronic kidney disease in our patient population.
KEY MESSAGES
Prosthetic graft infections lead to significant morbidity, mortality and overall poor outcome for patients. Further research is needed into factors contributing to these adverse outcomes so that effective measures can be taken to improve end results.

BAPIOAC19-P07

Re-audit of variations in written consent for Laparoscopic Cholecystectomy and Inguinal Hernia Repair

Vikramman Vignaraja

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Background
Laparoscopic cholecystectomy and inguinal hernia repair are two very common elective operations performed in general surgery. General Medical Council guidance emphasises the process of informed consent and shared decision making. Failure to warn patients of a significant complication has ethical and medico-legal implications.

Aim
Re-audit the quality of written consent forms for elective Laparoscopic cholecystectomy and inguinal hernia repair at a District General Hospital, against procedure specific consent forms (PSCF) that are being adopted in trusts nationally.

Method
We performed a retrospective analysis of written consent forms for elective Laparoscopic cholecystectomies and inguinal hernia repairs for the month of November 2018, which included28 and 23 cases respectively. We analysed each consent form and listed all complications consented for. This was benchmarked against studies listing all of the complications consented for in PSCFs.

Results
Laparoscopic cholecystectomy -Between 6 and 11 complications were listed out of a possible 17 seen in PSCF. Four complications were consented for in the above 90% of forms. The other 13 complications ranged from being present in 88% to 0%. Inguinal Hernia Repair -Between 5 and 11 complications were listed out of a possible 14 seen in PSCF. Twocomplications were consented for in above 90% of forms. The other 12 complications ranged from being present in 69% of forms to 3%.

Discussion
Our results show huge variations between consent forms. Consent documentation may not have a direct effect on patient care and outcomes buthas ethical and medico-legal implications. Information regarding the risks of a procedure is important to the patient-physician shared decision-making process about the procedure. Patients may have decided not to proceed having known about a certain risk and thus may have avoided a surgical complication deemed personally unacceptable. In response the surgical department has plans to adopt formal PSCF provided by the Royal College of Surgeons.

BAPIOAC19-P14

Calcium imbalance in Sarcoidosis and Renal Failure

Abilash Sathyanarayan

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Keywords: Calcium metabolism, Sarcoidosis, Renal Failure

Case details:
A 59 year old gentleman with a background history of chronic kidney disease stage (CKD) 4, type 2 diabetes mellitus, hypertension, congestive cardiac failure and bilateral lower limb below knee amputations, presented with hypercalcaemia of 3.30 mmol/L (reference range 2.20 -2.60) and suppressed PTH at 12 ng/l (reference range 15-65),from a previously raised PTH level of 162 due to CKD.

Investigations showed raised ACE levels of 106 U/l (reference range 10-52), enlarged mediastinal and hilar lymph nodes on CT. A presumptive diagnosis of sarcoidosis was made in view of patient's reluctance to undergo invasive biopsy.

He was treated with oral prednisolone 60 mg od. Calcium normalised to 2.56 mmol/L within one week and continued to drop further leading to symptomatic hypocalcaemia at 1.87 mmol/L in 3 weeks. The PTH rose to 268 ng/l. This was treated with alfacalcidol and the calcium normalised. He was weaned off prednisoloneand patient stopped alfacalcidol in few months and the calcium remains normal with a raised PTH.

Discussion:
We hypothesise that, on administering the prednisolone in this patient, there was inhibition of extra renal 1,25-OH-Vitamin D synthesis in the sarcoid granulomas. The CKD induced Vitamin D deficiency in the background was unmasked by amputating the predominantly extra-renal source of Vitamin D in this patient by treatment with prednisolone. This explains the presentation of hypercalcaemia with a suppressed PTH level initially, which then reversed. On treatment there was a high PTH secondary to low 1,25 OH Vitamin D.

It interesting to note that there is one case report of sarcoidosis ameliorating the symptoms of hypoparathyroidism.

Conclusion:
We discuss the complex interactions between renal and extra renal 1-alpha-hydroxylases and the need for vigilance if multiple mechanisms of calcium homeostasis are affected in a patient.

My tête-à-tête with COVID...!

Mohor Mukherjee
https://doi.org/10.38192/1.6.2.27

The dilemma of a persistent post-viral syndrome experienced by many remains highly suggestive of Long-COVID-19 yet, the confusion with timing, accuracy, and ability of the UK to provide for a responsive testing system has posed a huge burden on many battling with debilitating hurdles in daily life. This original account from a patient's perspective offers a window to understand the human emotions as unleashed by this viral pandemic. We invite personal stories of how the virus has affected people to help the scientific community understand the range of human experience.

Looking back, it must have been on that warm May evening when Ifelt drained of energy whilst watching a film with my daughter. She had been waiting for that Friday evening to spend time with me and I didn't have the heart to tell herI needed to go to bed. I survived the film, but the weekend was spent in bed. Whilst I did think of COVID (remember this was in May and the pandemic was raging in the UK!), I had no COVID related symptoms and thereforepassed it on as a combination of work, chores and childcare–nothing a lazy restful weekend can't fix, right? And so it did! Got back to the 'new normal' on Monday – working from home, home schooling, long bike rides/walks over the weekend.

A good few weeks passed, and I felt a similar state of exhaustion at the start of the week, butthis time with greater intensity. This was compounded by a severe headache- I remember complaining to my colleagues about it. By mid-week, my asthma wasn't great either and I asked my respiratory consultant for advice (this was my week one). Although still not feeling a hundred percent, by the end of the week, I felt I was recovering. I rested over the weekend, but could not start work in earnest the following Monday on account of breathlessness, intense and insistent fatigue.

My GP suggested I see a doctor at a local respiratory center, where the checks came normal but decided I should go to the hospital for some further checks as a precaution. The test results seemed to suggest my lungs were not a concern. I was able to convince them to allow me to get back home, although I was put on their radar, as they suspected it may be post-COVID recovery, so passed the point of infection and therefore not required to self-isolate.

It was difficult for me to fathom that my increasing weakness was anything to do with COVID (and must admit I was in denial to start with!), given I had very limited interaction with the world since March, I am fit and lead a healthy lifestyle. Touchwood the family was safe. I took a swab test that week (admittedly had to tweak my answers online to get a test as I had no COVID symptoms) and as was expected by the medical professionals my test results were negative.

Things went steadily downhill from here and the next few weeks were a blur! I went suddenly from someone who regularly ran or cycled a good distance to someone who could not walk a flight of ten stairs without stopping multiple times to catch my breath. I was fatigued and breathless, like I have never experienced before. Lifting my head, walking a couple of steps, eating a few spoonful of food, and lifting my phone seemed like a big achievement. I would wake up in the morning, feel less tired for about ten minutes before being exhausted again!

My Tete a Tete with COVID -continued

The steroids and antibiotics along with increased dosage of my corticosteroid inhalers and tablets helped but made minimal difference in reducing my condition. My blood pressure was low below acceptable limits and I also developed a severe reflux. Frankly, I felt battered! My general state of severe breathlessness, fatigue and weakness continued for almost a month.

It was only from the fifth week onward that I started feeling a bit human again. I could take a few steps, could go out to the garden (for the first time in weeks) and sit up with the family, although I still needed to rest frequently. 11 weeks on it is comforting to say, I am recovering, albeit slowly with some good and some less good days. I have got back to working from home, can walk for about 20 mins, do some household chores, bake (as that is my hobby) and can usually pull through the day. Having said that, my energy levels are nowhere close to normal me and I have understood I need to be patient with myself. The recovery is not a sprint and I gradually need to condition myself back to normalcy. I can't imaginegetting on a bike or go out for my runs, and I have been advised by the doctors that I should not push to do that just yet!

So while the jury is still out on the all-important question on whether I had COVID or not, I was introduced to the concept of 'Long-COVID' by my consultant. He suggested I write this article to raise awareness and make sure that people understand that this unexplained suffering is 'real'. What was also difficult was explaining everyone around me, trying to help solve it for me with logical explainable conditions (could it be fatigue, stress or some other condition).

COVID has been so hard on most people in many ways. I am managing to pull through because of my amazing family, my wonderful friends, my supportive colleagues and mydoctors at the surgery (doctors' clinic), at the respiratory center and my consultant. This article is for you people out there, who I hope don't experience any of this but if you do, hang in there –you may not be part of the "official count" but you are certainly not alone! Rest up, give it time and you will eventually overcome it.

What are the social, psychological and physical health challenges facing adolescents in the UK?

Triya Chakravorty
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Abstract

The ages of ten to nineteen are monopolised by biological, psychological and sociocultural changes, all of which impact health in the present and future. Behaviours and habits acquired during adolescence can have long-term impacts. Smoking, alcohol use, obesity and physical inactivity are all examples of health-related behaviours that usually start in adolescence and contribute to the global epidemic of non-communicable diseases in adults. These behaviours are influenced by socioeconomic and cultural factors and are major determinants of future health inequalities.

Introduction

To say that adolescence is an important time of life is a colossal understatement. The ages of ten to nineteen are monopolised by biological, psychological and sociocultural changes, all of which impact health in the present and future. Adolescents have specific health needs that differ from children and adults[1]. The notion that adolescence is a unique part of life is not limited to humans.

In fact, many of the behaviours stereotypically associated with adolescence (for example, increased risk taking) are seen in other species too[2]. Physically, adolescents go through several changes, such as the development of secondary sexual characteristics and growth to a final height[3]. These changes do not occur in uniform amongst all adolescents; they depend on factors such as ethnicity, gender and body mass index, as well as external factors such as nutrition and the social environment [4-6]. Brain maturation is not complete until around twenty-five, which suggests that experiences which occur during adolescence can significantly impact neural development[7]. There are many sociocultural changes that occur also.

Adolescence is a time to develop a self-identity, acquire skills and knowledge and begin to assume adult roles in society [8]. Behaviours and habits acquired during adolescence can have long-term impacts [9]. Smoking, alcohol use, obesity and physical inactivity are all examples of health-related behaviours that usually start in adolescence and contribute to the global epidemic of non-communicable diseases in adults [10,11].

These behaviours are influenced by socioeconomic and cultural factors and are major determinants of future health inequalities[12]. This essay will outline some key challenges facing adolescents in the United Kingdom (UK) today.

Mental Health

Mental health disorders are one of the largest contributors to the burden of disease in adolescence globally[13]. The World Health Organisation (WHO) estimate that 10-20% of all children and adolescents experience mental health problems [14]. It is estimated that half of all mental health disorders are established by fourteen years [15,16]. Furthermore, the prevalence of depression and anxiety in adolescence has increased significantly in the past twenty-five years, and in the UK, the rate of self-harm in girls aged 13-16 has risen by 68% in the past decade [17,18]. The reasons for these increases are not fully known.

However, depression and anxiety have several adverse consequences on development, such as lower academic performance, impaired social relationships, increased risk of substance abuse and suicide[18]. Therefore, understanding the impact of mental health disorders on adolescent health is a priority.

Social Determinants

The WHO defines the social determinants of health as *"the conditions in which people are born, grow, live, work and age"* [5]. Education is one of the strongest social determinants of health[19], and completing secondary school is associated with improved health outcomes [9]. This is particularly relevant in England, since changes in the education system have led to the extension of the age for compulsory participation in education or training to eighteen, making this a positive initiative for health reasons also [20].

The impact of education is vast and exceeds beyond gaining qualifications. School is an important social environment which can influence peer connections, emotional wellbeing and health. A stronger engagement of adolescents and their families with school positively effects health outcomes directly [9,21].

In the UK, poor academic performance is a risk factor for adolescent smoking. Furthermore, adolescents tend to have friendship ties with people of the same smoking status and level of academic performance [22]. Therefore, anti-smoking interventions that target poor academic performance specifically may be beneficial to decrease smoking related heath inequalities in the long-term.

Socioeconomic Status

Living arrangements and employment status are important determinants of health. Whilst youth homelessness in the UK is difficult to quantify, several reports indicate a recent increase [23]. Homelessness during adolescence has several detrimental effects, such as an increased risk of infectious diseases, alcohol use and mental health disorders [20]. Furthermore, many homeless adolescents may go undetected by official counts20. Adolescents who report sleeping on sofas of friends or on public transport are termed "hidden homeless" [20]. This is a serious issue, as they may not receive the support they require.

Overall, those who are long-term unemployed have a lower life expectancy and worse health [24]. However, there is limited research into the impact of unemployment on adolescents specifically [20]. The recent shift in working patterns in the UK has seen more businesses using zero-hour contracts [20]. This may be particularly relevant to adolescent health, as adolescents on zero-hour contracts are more at risk of health problems compared to their peers [25].

Relationships

Relationships with family, teachers, peers can affect adolescents mentally and physically. It is of no surprise that family structure plays an important role in human development, and can impact health in the long-term [20]. An observational study conducted in the United States of Americashowed that adolescents from two-parent households have higher self-rated health scores at age thirteen and in adulthood [26]. Parental behaviours also impact health. Adolescents whose parents smoke, drink or engage in violence are more likely toengage in these behaviours themselves [9].

This suggests that public health interventions that target both parents and adolescents may be useful in reducing these behaviours. The formation of peer relationships is one of the key developmental changes of adolescence. This is important, since peers can have both positive and negative influences on health [9]. Peer relationships allow adolescents to buffer the effects of life stressors, however, peer rejection can cause considerable distress [9,27].

There is also significant evidence showing the role of peer influence in the development of antisocial behaviour, substance misuse and participating in criminal activity [9,20].

One challenge facing adolescents regarding peer dynamics is bullying. In the UK, victims of bullying are more likely to be absent from school, have lower educational qualifications and increased mental health problems [28]. Although the UK government requires state-funded schools to include anti-bullying measures in their policies [29], the rapid development of technology means that cyberbullying is a rising concern; the impacts of which are less documented.

Technology

What it means to be an adolescent today is vastly different compared to even the previous generation. This is partially due to technological innovations which have allowed for increased global connectivity, internet access and social media use [7]. Social media gives adolescents a platform with which to actively engage with world affairs and each other. However, its use can also negatively influence health. For example, several studies show a significant link between adolescent social media use and depression[18]. The reasons for this have not been completely elucidated, but the impact is likely multifactorial, involving factors such as impaired sleep, sedentary habits and addictive behaviour[18]. Nevertheless, social media is an intensely powerful platform that can be used promote the health of adolescents[30]. For example, South African multimedia "edutainment" programme Soul City helped to change stereotypes about Acquired Immunodeficiency Syndrome and domestic violence, and has contributed to the empowerment of local communities[31].

Adolescents should beincluded in the development of future interventions so as to accurately reflect their needs. Internet addiction is an increasingly

prevalent concern. Problematic internet use (PIU), defined as a psychological dependence and lack of control over the timespent online, is an important area of research, as it can impact emotional well-being, relationships and everyday functioning of adolescents[32]. The symptoms of PIU are similar to those of substance-related addictions, including unpredictable behaviour and mood. Addictive behaviours that are developed in adolescence are likely to continue into adulthood, making this a particularly important issue[33]. Excessive use of technology can also impact physical health via sleep disturbance. Sleep disturbance is associated with poor academic performance, increased risk of mood disorders and obesity[34]. As a result, the American Academy of Paediatrics recommend that young people should limit their screen time to avoid sleep disruption[35].

Furthermore, the use of behavioural modification strategies to improve sleep may have several benefitsfor adolescents.

Environmental Factors

Air pollution is a worldwide environmental health issue, with particular concerns in large cities, where the air quality is relatively worse[36]. It is well known that air pollution is a strong risk factor for poor cardiovascular andrespiratory health[37]. However, there is increasing evidence to suggest that air pollution is associated with mental health problems in adolescents as well[38]. The pathophysiology may involve the effect of inflammatory stimuli such as inhaled pollutants on the brain[39]. Roberts et al[38] investigated the associations between air pollution exposure during childhood with concurrent and later mental health problems in a cohort from London. They found that pollution concentration levels at age twelve were associated with an increased risk of depression at eighteen. Although further investigation is required to understand the mechanism of this association, this finding adds to the growing list of reasons why tackling pollution should be a top priority for the UK government.

Conclusion

The range of factors that affect adolescent health are vast. How adolescents develop is rapidly changing, and the link between health outcomes and social determinants is increasingly complex.

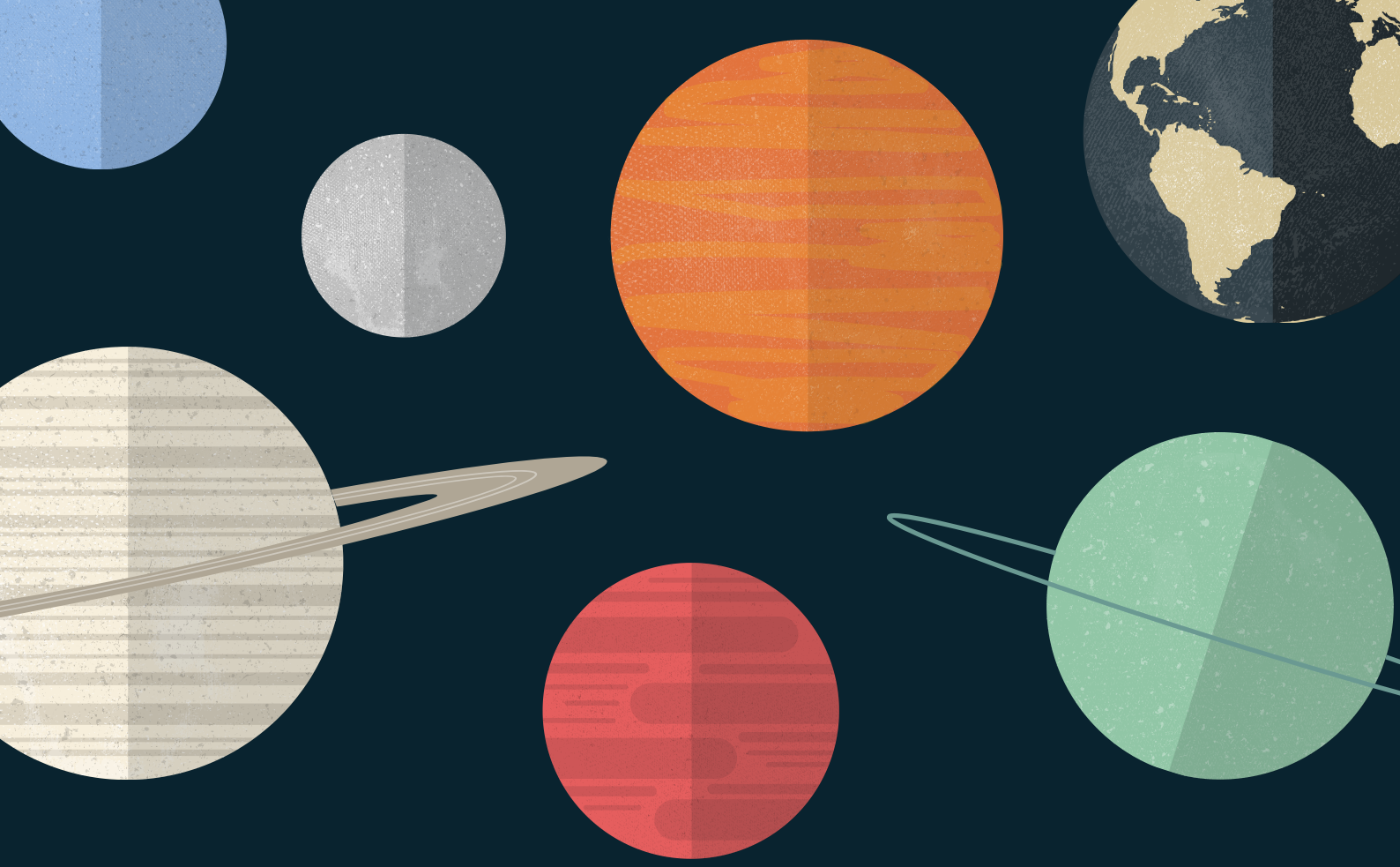
The current generation of adolescents are uniquely affected by contemporary factors such as social media and air pollution, the impacts of which have yet to be fully unravelled. As a result, interventions aimed at improving adolescent health will need to evolve to remain relevant.

References:

1. World Health Organisation Sixty-fourth World Health Assembly. Resolution WHA 64.28: Youth and health risks., <http://apps.who.int/gb/ebwha/pdf_files/WHA64/A64_R28-en.pdf> (2011).
2. Spear, L. P. The behavioral neuroscience of adolescence., (Norton, 2010).
3. Susman, E. J. Modeling developmental complexity in adolescence: Hormones and behavior in context. Journal of Research on Adolescence7, 283-306, doi:10.1207/s15327795jra0703_3(1997).
4. Wang, Y. Is obesity associated with early sexual maturation? A comparison of the association in American boys versus girls. Pediatrics110, 903-910, doi:10.1542/peds.110.5.903 (2002).
5. World Health Organisation -Health For The World's Adolescents -A second chance in the second decade, <http://apps.who.int/adolescent/second-decade/> (2014)
6. Perry, C. L. in Promoting Health: Intervention Strategies from Social and Behavioral Research. Institute of Medicine (US) Committee on Capitalizing on Social Science and Behavioral Research to Improve the Public's Health(eds B.D. Smedley & S.L. Syme) (National Academies Press (US), 2000).
7. Blum, R. W., Bastos, F. I., Kabiru, C. W. & Le, L. C. Adolescent health in the 21st century. Lancet379, 1567-1568, doi:10.1016/S0140-6736(12)60407-3 (2012).
8. National Research Council and Institute of Medicine. Growing Up Global: The Changing Transitionsto Adulthood in Developing Countries. . (The National Academies Press, 2005).
9. Viner, R. M.et al.Adolescence and the social determinants of health. Lancet379, 1641-1652, doi:10.1016/S0140-6736(12)60149-4 (2012).
10. Beaglehole, R.et al.Priority actions for the non-communicable disease crisis. Lancet 377, 1438-1447, doi:10.1016/S0140-6736(11)60393-0 (2011).
11. Sawyer, S. M.et al.Adolescence: a foundation for future health. Lancet379, 1630-1640, doi:10.1016/S0140-6736(12)60072-5 (2012).
12. Mackenbach, J. P.et al.Socioeconomic inequalities in health in 22 European countries. N Engl J Med358, 2468-2481, doi:10.1056/NEJMsa0707519 (2008).
13. Gore, F. M.et al.Global burden of disease in young people aged 10-24 years: a systematic analysis. Lancet 377, 2093-2102, doi:10.1016/S0140-6736(11)60512-6 (2011).
14. WHO. Maternal, newborn, child and adolescent health. , <https://www.who.int/maternal_child_adolescent/topics/adolescence/mental_health/en/> (2017).
15. Kessler, R. C.et al.Age of onset of mental disorders: a review of recent literature. Curr Opin Psychiatry20, 359-364, doi:10.1097/YCO.0b013e32816ebc8c (2007).
16. Kim-Cohen, J.et al.Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. Arch Gen Psychiatry 60, 709-717, doi:10.1001/archpsyc.60.7.709 (2003).
17. Morgan, C.et al.Incidence, clinical management, and mortality risk following self harm among children and adolescents: cohort study in primary care. BMJ 359, j4351, doi:10.1136/bmj.j4351 (2017).
18. Keles, B., McCrae, N. & Grealish, A. A systematic review: the influence of social media on depression, anxiety and psychological distress in adolescents. International Journal of Adolescence and Youth25, 79-93, doi:10.1080/02673843.2019.1590851 (2020).
19. Feinstein, L.et al.What are the effects of education on health? , <http://www1.oecd.org/education/innovation-education/37425753.pdf> (2006).
20. Shah, R.et al.The social determinants of young people's health. Identifying the key issues and assessing how young people are doing in the 2010s, <https://www.health.org.uk/publications/the-social-determinants-of-young-people%E2%80%99s-health> (2018).
21. Flay, B. R.et al.Effects of 2 prevention programs on high-risk behaviors among African American youth: a randomized trial. Arch Pediatr Adolesc Med158, 377-384, doi:10.1001/archpedi.158.4.377 (2004).
22. Robert, P.-O.et al. Academic performance and adolescent smoking in 6 European cities: the role of friendship ties. International Journal of Adolescence and Youth24, 125-135, doi:10.1080/02673843.2018.1475288 (2019).
23. Young and homeless research -Young & Homeless report 2018, <https://www.homeless.org.uk/facts/our-research/young-and-homeless-research> (2018).
24. Bartley, M. Health Inequality: An Introduction to Concepts, Theories andMethods, 2nd Edition. (2016).
25. UCL. Being on a zero-hours contract is bad for your health. UCL News,

<https://www.ucl.ac.uk/news/2017/jul/being-zero-hours-contract-bad-your-health> (2017).

26. Sokol, R., Ennett, S., Gottfredson, N. & Halpern, C. Variability in self-rated health trajectories from adolescence to young adulthood by demographic factors. Prev Med105, 73-76, doi:10.1016/j.ypmed.2017.08.015 (2017).
27. Acquah, E. O., Topalli, P.-Z., Wilson, M. L., Junttila, N. & Niemi, P. M. Adolescent loneliness and social anxiety as predictors of bullying victimisation. International Journal of Adolescence and Youth 21, 320-331, doi:10.1080/02673843.2015.1083449 (2016).
28. Wolke, D. & Lereya, S. T. Long-term effects of bullying. Arch Dis Child100, 879-885, doi:10.1136/archdischild-2014-306667 (2015).
29. Education Policy Institiute -Bullying: A review of the evidence, <https://epi.org.uk/publications-and-research/bullying-a-review-of-the-evidence/> (2018).
30. Lau, P. W., Lau, E. Y., Wong del, P. & Ransdell, L. A systematic review of information and communication technology-based interventions for promoting physical activity behavior change in children and adolescents. J Med Internet Res13, e48, doi:10.2196/jmir.1533 (2011).
31. Scheepers, E.et al.Evaluating health communication –a holistic overview of the impact of Soul City IV. Health Promotion Journal of Australia15, 121-133, doi:10.1071/he04121 (2004).
32. Anderson, E. L., Steen, E. & Stavropoulos, V. Internet use and Problematic Internet Use: a systematic review of longitudinal research trends in adolescence and emergent adulthood. International Journal of Adolescence and Youth22, 430-454, doi:10.1080/02673843.2016.1227716 (2017).
33. Coffey, C., Carlin, J. B., Lynskey, M., Li, N. & Patton, G. C. Adolescent precursors of cannabis dependence: findings from the Victorian Adolescent Health Cohort Study. Br J Psychiatry182,330-336, doi:10.1192/bjp.182.4.330 (2003).
34. Kubiszewski, V., Fontaine, R., Rusch, E. & Hazouard, E. Association between electronic media use and sleep habits: an eight-day follow-up study. International Journal of Adolescence and Youth19, 395-407, doi:10.1080/02673843.2012.751039 (2014).
35. Children, Adolescents, and Television. Pediatrics107, 423-426, doi:10.1542/peds.107.2.423 (2001).
36. Review of evidence on health aspects of air pollution –REVIHAAP Project: Technical Report [Internet]. (WHO Regional Office for Europe, Copenhagen, 2013).
37. Kelly, F. J. & Fussell, J. C. Air pollution and public health: emerging hazards and improved understanding of risk. Environmental Geochemistry and Health 37, 631-649, doi:10.1007/s10653-015-9720-1 (2015).
38. Roberts, S.et al.Exploration of NO2 and PM2.5 air pollution and mental health problems using high-resolution data in London-based children from a UK longitudinal cohort study. Psychiatry Res272, 8-17, doi:10.1016/j.psychres.2018.12.050 (2019).
39. Danese, A.& Baldwin, J. R. Hidden Wounds? Inflammatory Links Between Childhood Trauma and Psychopathology. Annu Rev Psychol 68, 517-544, doi:10.1146/annurev-psych-010416-044208 (2017).



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