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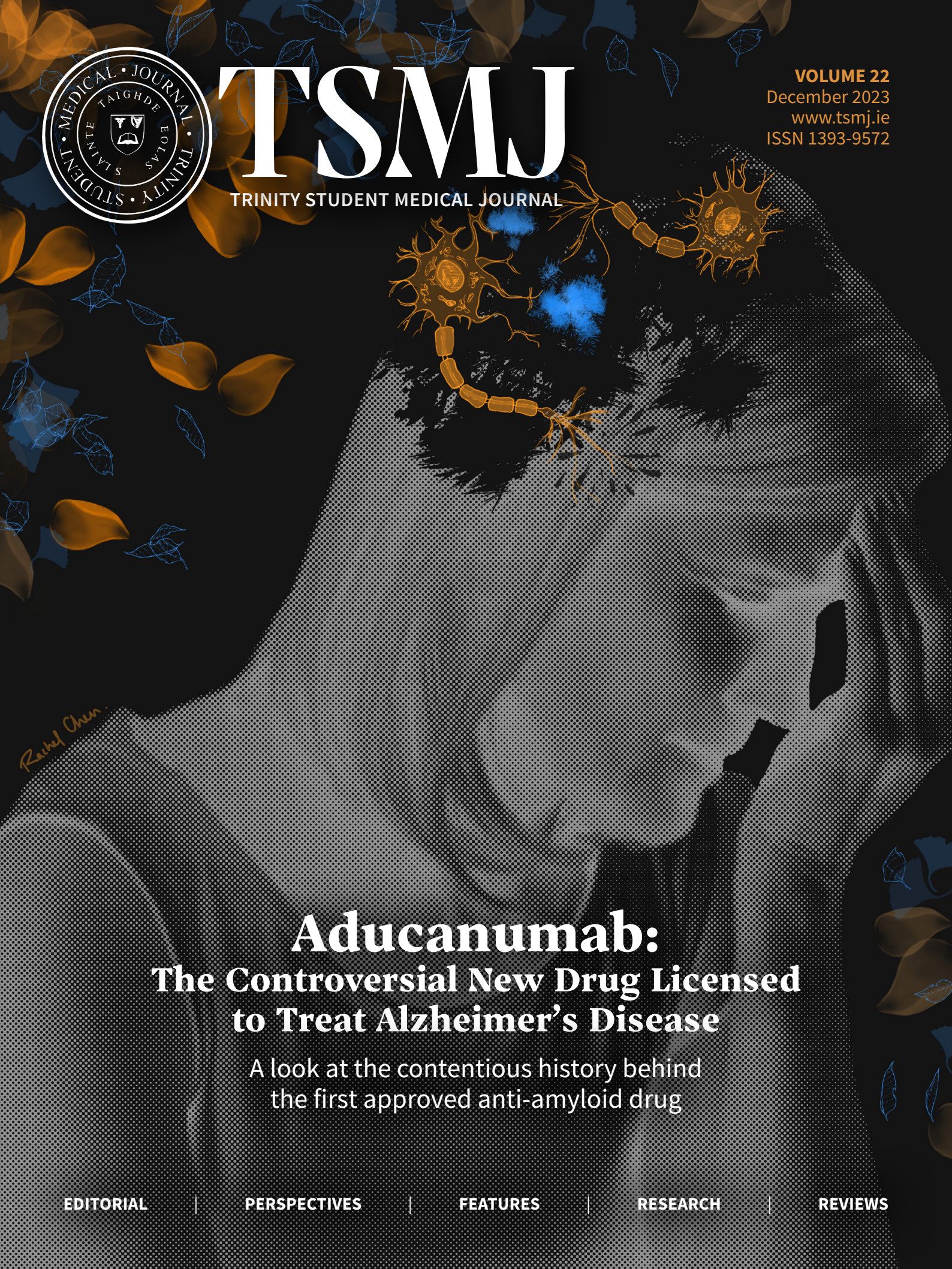

Aducanumab:
The Controversial New Drug Licensed to Treat Alzheimer's Disease

A look at the contentious history behind the first approved anti-amyloid drug

TSMJ
TRINITY STUDENT MEDICAL JOURNAL

The Trinity Student Medical Journal is intended to provide an inclusive platform for students to communicate current medical research, opinions and thoughts to other students, faculty members and faculty of affiliated hospitals and institutions. We publish articles related to many aspects of medicine and healthcare including scientific research and clinical experience. Articles are accepted from students in medicine and other related fields, as it is our view that medicine is the meeting point of many disciplines. The aim of the journal is to provide a medium that is responsive to the rapidly changing face of contemporary medicine, and is able to grow and expand as rapidly as the subject.

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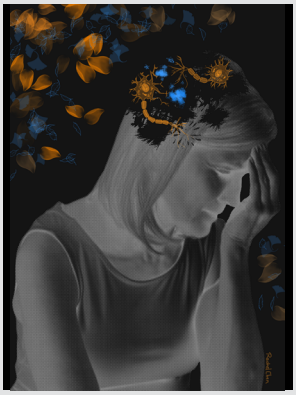
Cover Art



◄ **"BLOSSOM"** by **RACHEL CHEN**

In a recent study led by the neuroscientist Dr Ju-Hyun Lee[1], 'flower-like' rosettes were observed in the heavily damaged neurons of victims suffering from Alzheimer's disease. This unique pattern was dubbed 'poisonous flowers'. I was inspired by the striking imaging studies he produced, and decided to incorporate this motif into the piece. The blue petals in this piece allude to 'forget-me-nots'. These small blue flowers represent memory loss, and are also symbols commonly associated with Alzheimer's. I chose to employ a monochrome halftone composition in order to draw more attention to the details highlighted by the two complementary colours. They illuminate the build-up of amyloid plaques between neurons, which aducanumab has been described to remove.

1. Lee, J. H., Yang, D. S., Goulbourne, C. N., Im, E., Stavrides, P., Pensalfini, A., Chan, H., Bouchet-Marquis, C., Bleiwas, C., Berg, M. J., Huo, C., Peddy, J., Pawlik, M., Levy, E., Rao, M., Staufenbiel, M., & Nixon, R. A. (2022). Faulty autolysosome acidification in Alzheimer's disease mouse models induces autophagic build-up of Aβ in neurons, yielding senile plaques. Nature neuroscience, 25(6), 688–701. https://doi.org/10.1038/s41593-022-01084-8

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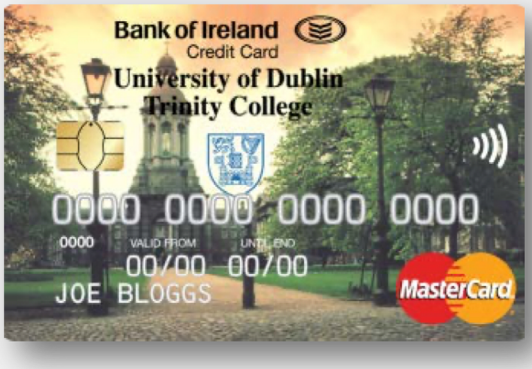

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Editorial Team & Advisory Board

EDITORIAL

Editor's Foreword:

Asten Yeo

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I am pleased to say that this issue of the TSMJ is one of the most diverse issues of the TSMJ thus far, not only because of the range of article types, but from the range of contributing authors from the various health science disciplines here in Trinity. Though some might assume that we only publish articles written by medical students, the TSMJ remains an inclusive open-access student journal covering all fields related to medicine and biomedical science, and it is encouraging to see a return to such.

While the COVID-19 pandemic has certainly made original clinical research difficult for students, we have nonetheless continued to find ways to contribute. In this issue, we featured systematic reviews looking at the role of prophylactic vaccination against shingles in autoimmune patients undergoing biologic therapy and whether antibiotics or surgery should be first-line for acute uncomplicated appendicitis. Also featured is a brilliant full-cycle clinical improvement project report on the use of the $ISBAR_3$ handover technique in a tertiary paediatric centre, which goes to show the value that medical students can have in contributing to clinical practice outside of primary research. For those interested in public health or immunopathology, we also have two detailed reviews looking at maternal mortality in Sweden, India, and Rwanda and at the role of Th17 lineage cells in the pathogenesis of COVID-19.

I am also pleased to see the return of the interview article which has been absent from the TSMJ for some time. Interviews are great for providing a concise and often personal view of hot topics in medicine. In this issue, our staff writers spoke to Anna Rafferty from Johnson & Johnson about their undergraduate women in STEM programme and Dr Ian Fraser—consultant radiation oncologist at the Hermitage Medical Clinic—about CyberKnife, the first fully robotic radiotherapy device.

While original research and reviews nonetheless remain the focus of TSMJ, we are also proud to present perspectives written by our staff writers on recent and topical events, such as our cover piece on newly approved anti-amyloid drug aducanumab, or our other fantastic piece on emerging infectious diseases.

To end, I would like to thank the School of Medicine of Trinity College Dublin and our advisors for supporting the TSMJ and ensuring that it meets high editorial standards. Many thanks to the TCD Student Open Access Project, which has supported the online publication of the TSMJ, as well as other student open-access journals from various faculties around Trinity. I would also like to thank our sponsors from Johnson and Johnson, the Medical Protection Society, and the Trinity Association and Trust. Without their generosity, it would not be possible to print, produce, and publish, either in print or online.

Last, but not least, I would like to express my deepest gratitude and appreciation towards the whole TSMJ committee. I am incredibly grateful to have been able to work—with and for—all the talented directors, editors and reviewers who have so graciously volunteered with us this year. To our directors: your time and effort have gone towards not only producing this volume but also the myriad background tasks that keep the TSMJ running, from organising events and journal clubs to running our social media accounts and website. As one of the largest committees in recent years (with an equally large agenda), this must have been no easy feat. A special commendation should also go out to our Media Director, Rachel Chen, who was also responsible for the wonderful artwork that adorns the cover of this issue.

As for our editors and reviewers, you have been—now and always—the driving force of the TSMJ. As well as our appreciation, you have also my sincerest apologies, for the sheer size of this year's volume should elucidate just how much has been edited, reviewed and formatted over countless drafts. Thank you for the many hours spent reading and re-reading manuscripts, figuring out how to best showcase the work of the authors.

I hope that this volume is as much a pleasure to read as it was for us to work on, and that Volume 22 stands as a testament to what can be achieved from the cumulative talent and hard work of all the brilliant medicine and health science students that we have here in Trinity. I look forward to what the next committee has to offer. ◄

STAFF PERSPECTIVE

Aducanumab: The Controversial New Drug Licensed to Treat Alzheimer's Disease

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Key Points

- Alzheimer's Disease is a neurodegenerative condition that results in both cognitive and functional decline. It has a high prevalence in the developed world, accompanied by a large burden of disease.
- There are few treatment options for Alzheimer's Disease which has led to a high interest in Aducanumab, a monoclonal antibody designed by Biogen Incorporated and Eisai Corporation Limited. It selectively targets the aggregated forms of β-amyloid and decreases plaques, which is a pathological feature of Alzheimer's Disease.
- Trials of Aducanumab showed significant reductions in amyloid plaque (61%; p<0.0001] in PRIME, 59%; p<0.0001 in ENGAGE, 71%; p<0.0001 in EMERGE), but proved inconclusive when determining if there was any clinical benefit associated with this mechanism.
- These results, accompanied by various events in the history of this drug, namely its approval by the United States Food and Drug Administration through an accelerated pathway and the subsequent resignation of three panel members, has aroused controversy.

Keywords: **Aducanumab, Alzheimer's Disease**

Introduction

Alzheimer's Disease is a neurodegenerative condition associated with cognitive and functional decline, largely involving memory, visuospatial aptitude, language, and executive functioning. With an insidious onset, the condition often presents after the age of 65 years, and accounts for around two-thirds of all dementias[1]. Its already high prevalence in the developed world, with an estimated 5.5 million currently living with diagnosis of Alzheimer's Disease in the US, is believed to rise significantly by 2050. Furthermore, being the sixth-leading cause of death in the US, with an average life expectancy of four to eight years and estimated economic cost of $259 billion[2], the burden of the condition is great. Despite this, Alzheimer's Disease has no cure. Therefore, the proposition of any new treatment is the subject of much interest.

In 2020, aducanumab set the medical community ablaze for its potential to be the first medication for Alzheimer's Disease approved by the United States Food and Drug Administration (FDA) in 18 years. On June 7th 2021, that potential became a reality. Met with both delight and disapproval, the drug was passed through an unconventional, accelerated pathway as compared to the more traditional pathway used for most other drugs, a decision taken by the FDA owing to the potential benefits that the drug could contribute to those diagnosed with a disease that has no current cure. However, questions relating to the efficacy and safety of aducanumab, supported by the subsequent resignation of three FDA advisory panel members in response to its approval[3], resulted in this drug that once stirred much interest becoming the subject of great controversy.

This review aims to clarify the events involved in development of aducanumab, the difficulties in getting approval for the drug, and what this means for its future as a treatment for Alzheimer's Disease.

What is Aducanumab?

Aducanumab, sold under the brand name Aduhelm, was developed by Biogen Incorporated (Biogen) in collaboration with Eisai Corporation Limited (Eisai Co.), as the "first and only" treatment to address a "defining pathology" of Alzheimer's Disease[4]. Aducanumab is a recombinant, fully-human IgG1 monoclonal antibody originally developed by Neurimmune and later licensed by Biogen in 2007. Neurimmune, in collaboration with the University of Zurich, had previously identified the presence of anti-amyloid antibodies in otherwise healthy individuals with slowly progressing dementia[5]. The protective function of these antibodies inspired the development of Aducanumab.

The monoclonal antibody is designed to, like these other anti-amyloid protective antibodies, enter the brain and target parenchymal β-amyloid (Aβ), reducing both soluble and insoluble Aβ in a dose-dependent manner[6]. Aβ is a fragment of amyloid precursor protein (APP) implicated by the amyloid cascade hypothesis as a prime culprit in the pathogenesis of Alzheimer's Disease[7]. This hypothesis claims that cleavage of APP by the endosomal-lysosomal pathway results in the production of an intact Aβ protein which is deposited in the brain to form plaques, leading to the formation of neurofibrillary tangles and cell death[7]. This disrupts cell-to-cell

communication and causes inflammation, resulting in damage to neuronal tissue and the subsequent presentation of cognitive decline.

Aducanumab initially proved favourable as trials removed any doubt as to its role in selectively targeting aggregated forms of Aβ to decrease plaques[6]. It was a question of whether there was any clinical benefit linked to this clearance of Aβ that led to skepticism surrounding its approval by the FDA, especially considering its original price at US$56,000 per year per patient[3], a number that far exceeds cost-efficacy despite the potential benefits aducanumab could offer[8]. Furthermore, the results of the trials appeared to align with previous studies that investigated the effects of other anti-amyloid antibodies on Alzheimer's Disease[9].

A Promising Start

While not unanimously considered to be the primary cause of Alzheimer's Disease, it is widely supported that Aβ plaques are a key pathological feature of the condition[10]. It was based on this principle that the PRIME study, phase Ib clinical trials of aducanumab, was initiated in 2012.

The study examined the effects of monthly IV infusions of 1, 3, 6, and 10 mg/kg doses of Aducanumab[6] on the levels of Aβ in patients with a clinical diagnosis of prodromal or mild Alzheimer's Disease and a positive Aβ PET scan[11]. Results showed that, following 54 weeks of therapy, the drug had an effect on reducing the levels of Aβ plaques by 61% ($p<0.0001$) in a time- and dose-dependent manner[4], particularly in the 3, 6 and 10 mg/kg dose groups, as measured by florbetapir PET imaging[11]. The results also suggested that Aβ clearance by aducanumab could potentially slow the clinical decline of an individual with Alzheimer's Disease in accordance with the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score and Mini-Mental State exam (MMSE). However, these findings were only exploratory as the PRIME trial was not designed to assess clinical outcome and further studies were required to investigate this clinical potential[6].

The primary drawback of aducanumab therapy indicated by the PRIME trial was the development of amyloid-related imaging abnormality-edema (ARIA-E). This was found to be a dose-dependent adverse effect more frequently occurring in ApoE ε4 carriers, in line with previous studies of anti-amyloid antibodies such as Bapineuzumab[12]. It presents as hyperintensity in T2-weighted sequences, observed in the parenchyma and/or leptomeninges in various regions of the brain, including the frontal, parietal, and occipital lobes[13]. Limited data on the physical manifestation of ARIA-E has led to uncertainty surrounding the potential severity of its clinical course. What data is available describes symptoms such as headaches, altered mentation, nausea, and gait disturbances.

A phase II clinical study, EVOLVE, was designed to determine the clinical significance of aducanumab-induced ARIA-E. It was commenced in December 2018, but terminated prematurely in 2019 in line with the discontinuation of phase III clinical trials (which had been going on simultaneously) following a prediction of futility[14]. EVOLVE was set to be evaluated by an independent Adjudication Committee. However, this committee had not been assembled by the time that the study, along with all other ongoing aducanumab trials, was terminated by Biogen and Eisai Co. As such, no assessment of the EVOLVE study occurred[14].

While the PRIME trial indicated a reduction in Aβ levels, and the EVOLVE study was looking set to investigate the safety of the aducanumab, the unanswered question remained as to whether a decrease in Aβ plaque slows down cognitive and functional decline in Alzheimer's Disease. This was to be determined by two large phase III clinical trials, EMERGE and ENGAGE.

EMERGE and ENGAGE

EMERGE and ENGAGE, initiated in 2015, were two identically designed trials that aimed to determine the ability of aducanumab to slow cognitive and functional decline in participants with early Alzheimer's Disease. Before aducanumab, all other trials of anti-Aβ treatments had failed to prove clinical efficacy in their larger phase III stages, despite promising results from earlier phases[15]. Therefore, the question lay in whether the EMERGE and ENGAGE studies would prove any different. To great surprise, Biogen announced in October 2019 that their EMERGE study had done just this, several months after terminating all ongoing aducanumab trials due to a prediction of futility made on the grounds that one trial was not demonstrating clinical benefit in an interim analysis, even though the other was trending positive[16].

The results of both trials were assessed based on changes from patient baseline by the CDR-SB score. A secondary outcome was to assess the effects of aducanumab on the clinical progression of the disease, as measured by MMSE, AD Assessment Scale-Cognitive Subscale (ADAS-Cog 13), and AD Cooperative Study-Activities of Daily Living Inventory for MCI (ADCS-ADL-MCI). While both studies showed a significant decrease in Aβ (59%; $p<0.0001$ in ENGAGE, 71%; $p<0.0001$ in EMERGE)[4], it was only the EMERGE trial that met its primary endpoint, that is, a slowing of cognitive and functional decline. ENGAGE, on the other hand, showed no benefit of aducanumab therapy on cognition and functioning, a result that raises doubt about the causal link between lowering Aβ levels and clinical improvement.

This difference in result was not anticipated as both were randomized, double-blind, and involved the use of a placebo. However, post-hoc analysis of the trials found that while their designs were identical, the implementation of them was not. At baseline, ENGAGE was initiated one month earlier than EMERGE[17]. Additionally, ENGAGE enrolled more participants overall, and with the introduction of protocol amendments at different stages along the timelines of each trial, discrepancies arose between them concerning the duration that patients were exposed to high-dose Aducanumab[16]. In line with this, post-hoc analysis of the ENGAGE study found that results from a subset of patients exposed to high-dose aducanumab supported the positive findings from the EMERGE trial. This difference in dose-dependent

aducanumab exposure was the variable proposed by Biogen as the critical cause of the initial failure of the ENGAGE study[16]. Furthermore, it was revealed that the placebo groups in each trial responded differently to each other, where less progression of disease was seen in the ENGAGE placebo group as compared to those in the EMERGE trial, a result most likely due to the heterogeneity of the Alzheimer's Disease phenotype[16]. Finally, the futility analysis was based only on data from 1,748 participants, rather than the full 3,285 participants[18].

Given the FDA's requirement for two positive studies to pass a treatment, aducanumab appeared to follow in the footsteps of other anti-amyloid antibodies that showed to reduce levels of amyloid deposits in phase I and II trials, but did not have a significant impact on cognitive and functional decline in phase III trials[19]. However, following Biogen's announcement to pursue approval for the drug, the results of the phase III trials were presented publicly in December 2019, during which Biogen concluded that the EMERGE trial met both its primary and secondary endpoints when using high-dose aducanumab while the ENGAGE study did not, except in a subset of patients exposed to high-dose aducanumab as revealed by the post-hoc analysis. It was here that the medical community split into those hopeful for an innovative new treatment for a high-burden disease, and those more skeptical given the initial prediction of futility.

This division became more apparent following the rejection of aducanumab by the FDA Peripheral and Central Nervous System Drugs Advisory Committee, where ten out of eleven members voted against the approval of the drug, and the last voted uncertain. Concerning this, the Advisory Committee said, "Does Study 302 (EMERGE), viewed independently and without regard for Study 301 (ENGAGE), provide strong evidence that supports the effectiveness of aducanumab for the treatment of Alzheimer's Disease?"[20]. In answer to this, they determined that the positive EMERGE study, paired with the negative ENGAGE study, resulted in "a statement of inconclusiveness"[21].

Additionally, the side effects observed in the PRIME study were evident in the phase III trials, most notably ARIA-E, along with the development of microhaemorrhages accompanied by haemosiderosis, an effect known as amyloid-related imaging abnormality-haemorrhage (ARIA-H). This was seen in 41% of participants who were treated with the highest aducanumab dose (10 mg/kg), in comparison to 10% on placebo[22]. While the majority of these cases were asymptomatic, the effects of these reactions have yet to be fully established, which further complicates the calculation of a benefit to risk ratio[23].

Resignation of FDA Panel Members

Despite the FDA requiring two positive studies to pass a treatment, in June 2021 aducanumab was approved under an accelerated pathway, granted based on evidence from clinical trials that show the effect that aducanumab has on lowering levels of Aβ, a result that is "reasonably likely" to predict slow clinical decline[4]. This unconventional approval of aducanumab by the FDA was described by George Vradenburg, Chairman and Co-Founder of UsAgainstAlzheimer's, as a "transformational breakthrough" that offers "new hope" for all those affected by the disease[4]. Others were left feeling less than enthusiastic.

Three FDA panel members resigned following this approval, all of whom were members of the FDA Peripheral and Central Nervous System Drugs Advisory Committee[3]. One member, Mayo Clinic neurologist David Knopman, explained how he felt the Advisory Committee's opinions were disregarded by the FDA's ruling on aducanumab given the strong objection delivered by the committee which was composed of experts in the fields of neurology and medicine[3]. These feelings were further amplified by the inconclusive results of both the aducanumab-related trials and those of other anti-amyloid antibodies.

Lon Schneider, Professor of Psychiatry, Neurology, and Gerontology at the Keck School of Medicine of the University of Southern California, also vocalized disapproval for the decision made by the FDA. He remarked that the existing controversy should not exist in the first place as the phase III clinical trials were never completed, instead terminated for futility before all data could be collected. As such, all subsequent discussions about Aducanumab concerned data from "incomplete" studies[21].

Schneider and Knopman have both advocated in favour of another phase III trial being carried out. The results of such a study would help to clarify whether aducanumab should be supported or rejected for the treatment of Alzheimer's Disease. They, like others who objected to the FDA's approval of aducanumab, are not opposed to the drug's potential use in the treatment of Alzheimer's Disease. Instead they are uncertain as to whether it should have been approved now, given the inconclusive results concerning its clinical benefit. As such, there is concern that its approval may cause more emotional, medical, and economic harm than good.

An Ethical Dilemma

In contrast to healthcare professionals who appear divided in opinion concerning the approval of aducanumab, patient advocacy groups have largely been supportive of the decision made by the FDA. COO of UsAgainstAlzheimer's, Russ Paulsen, has advocated in favour of patient autonomy, that being the right of a patient to make a "free and voluntary act" where correctly informed and considered to have full capacity[24]. He has stated that some patients have expressed the wish to "have that choice" and to "have a chance"[25], given that Alzheimer's Disease is a fatal condition that can have a massive impact on patients and families.

On the other hand, the ethical principle of nonmaleficence, which is described as the obligation to avoid "harm or injury to the patient" that may occur through acts of "commission or omission"[24], is seen by some to be threatened by the approval of aducanumab Joel Perlmutter, a neurologist at Washington University who was among the three Advisory Committee members

to resign, expressed concern that offering patients false hope may cause emotional harm that could have otherwise be prevented, especially given that autonomy itself is not absolute as medical professionals are not obliged to administer a certain treatment that is seen to have a negative benefit to risk ratio. He described the responsibility of the FDA and Advisory Committee to "protect these patients and families" even if at times this requires "facing difficult decisions"[25].

This ethical discussion is yet another topic of debate alongside the scientific basis of aducanumab, and one which has no simple answer.

Further Obstacles

The FDA's approval of aducanumab did not come without stipulations. The agency granted this approval on the condition that phase IV confirmatory studies be conducted with the aim of collecting "real-world" data to evaluate the long-term effectiveness and safety" of aducanumab in clinical practice[26]. Of these, the ICARE AD-US trial was terminated the following year, while the ENVISION trial was initiated in May 2022. The aim of this latter 18 month trial is to enroll around 1500 patients with early Alzheimer's Disease and confirmed Aβ pathology, with at least 18% of the participants being from Black/African American and Latino communities[27]. Biogen's decision to increase participation among previously underrepresented communities was made with the aim of better assessing the efficacy and safety of the drug when considering health disparities. This is significant given that individuals of such ethnicities are at a higher risk of developing Alzheimer's Disease than Non-Hispanic Whites[28].

A phase IIIb trial known as EMBARK, another trial required by the FDA, is a re-dosing study that aims to investigate the data from previous trials of aducanumab, particularly the phase III trials EMERGE and ENGAGE. It involves monthly administration of the highest dose assessed in these trials (10 mg/kg) for 100 weeks to patients involved in the previous trials[29]. This will allow for the assessment of the long-term tolerability and safety of aducanumab after a wash-out period, as well as its efficacy in those with more advanced Alzheimer's Disease.

Progress concerning the authorization of the marketing of aducanumab has been slower outside of the US. In a meeting of the Committee for Medicinal Products for Human Use (CHMP) in December 2021, an official announcement was made against the approval of licensing aducanumab by the European Medicines Agency (EMA). The EMA's particular concerns regarding the drug involved the dominant side effect, ARIA-E, and the lack of clarity on whether such an abnormality can be effectively monitored and managed[30]. As such, it was rejected on the grounds that any potential benefits of the drug were not shown to outweigh the risks to health. In response, Biogen Inc. asked for this decision, along with their marketing authorisation application (MAA) for aducanumab, to be re-examined[31]. They also declared their intention to obtain initial results from their confirmatory phase IV trials in 2026, five years ahead of the deadline granted to them by the FDA[32]. Just under half a year later, Biogen announced the withdrawal of their MAA[33].

In addition to this rejection by the CHMP, aducanumab's launch fell short of predictions, making third quarter sales of only $0.3 million[34]. Biogen's aducanumab also faces competition from other drugs designed to treat Alzheimer's Disease, such as donanemab, a monoclonal antibody created by Eli Lilly and Co. that also targets deposited Aβ and was granted the status of "Breakthrough Therapy" by the FDA in June 2021[35].

Where Does Its Future lie?

With the recent approval of Biogen and Eisai's lecanemab (brand name Leqembi) by the FDA in January 2023 through a similar accelerated approval pathway, any future progress that aducanumab could make may well be overshadowed[36]. As is the case with aducanumab, lecanemab is a humanized IgG1 monoclonal antibody found to decrease Aβ plaques in the brain. However, unlike its predecessor, Lecanemab proved itself to be the first drug of its kind to demonstrate a slowing of cognitive decline in the early stages of Alzheimer's Disease when compared to placebo[37]. This may potentially be explained by a difference in binding profiles to different forms of Aβ between the two drugs. Furthermore, Lecanemab is expected to cost around half of the original price of aducanumab at an estimated US$26,500[37]. However, safety risks that require further investigation may present a future obstacle for this new drug and potentially allow attention to return to aducanumab once again[37].

Despite these recent events, the development of aducanumab has evidently sparked hope that future studies might focus on the development of drugs that can treat the pre-clinical stages of dementia before the manifestation of debilitating symptoms. At the very least, the controversy has brought to light the challenges of studies concerning Alzheimer's Disease, caused by the heterogeneity of phenotypes and the influence that sex and ethnicity has on the impact of disease[21]. Lastly, it may set a precedent for the future of such research[21].

Conclusion

Alzheimer's Disease continues to be a pressing issue in the Western World due to its heavy burden, yet still there remains no cure. Despite the initial promise that aducanumab presented in this avenue, evidenced by the results of its phase I trial, the process of its development and approval since has been fraught with disagreements both between healthcare professionals as well as those outside of this sector. This has only been heightened by the question mark surrounding the validity of its phase III trials, EMERGE and ENGAGE, furthered by the subsequent resignation of three FDA panel members. More recently its reputation received a blow when its third quarter revenue fell far short of its predicted sales.

With further trials in progress, the future of aducanumab remains unclear. However, the significance that its development holds should not be underestimated. As expressed by Marwan Sabbagh, director of Cleveland

Clinic Lou Ruvo Centre for Brain Health in Las Vegas, and Jeffrey Cummings, research professor at the University of Nevada in Las Vegas, aducanumab's approval is not indicative of a cure, but is instead "the first incremental step in transforming the disease from an untreatable terminal illness to a manageable chronic disease"[38]. Having prompted further research by Biogen Inc. and other pharmaceutical companies, it represents a stepping stone to an uncertain but hopeful future for Alzheimer's Disease. ◄

Declarations

Ava Janes is a staff writer on the editorial board of the TSMJ, and was asked to contribute an invited Staff Feature to the TSMJ Volume 22. The author declares that the article was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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STAFF PERSPECTIVE

Ignoring Emerging Infectious Diseases: The Fatal Error That Could Lead to the Next Pandemic

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Key Points

- Emerging Infectious Diseases (EIDs) are a group of novel or re-surging infectious pathogens which primarily originate from animal populations.
- Many EIDs have a pandemic-causing ability and should be a top priority for governments worldwide.
- The primary strategies that should be implemented to prevent a pandemic caused by emerging pathogens revolve around preventing the transfer of zoonoses via diligent surveillance methods involving classical tools, data science, and artificial intelligence.
- The equitable use of mRNA vaccine templates can decrease the spread, morbidity, and mortality of viral and possibly other pathogenic EIDs.
- Governments must invest in creating stable healthcare systems and well-equipped research facilities to handle the burden of EID outbreaks.

Keywords: **Emerging Infectious Diseases, Pandemic Preparedness, Vaccines, Epidemiology**

Introduction

In an October 2019 interview, the Director-General of the World Health Organization, Dr Tedros Adhanom Gebreyesus, warned that the world was dangerously unprepared for the next flu pandemic[1]. At the time, this message was not taken seriously. 25 months later, global healthcare systems and economies suffered substantial damage, and over 5 million people died of Coronavirus Disease 2019 (COVID-19)[2]. Despite the harm that has already been done, it is unproductive to belabour the past and assign blame. Instead, nations should reflect on COVID-19 and their response to the initial outbreaks of the virus.

Despite almost 2 years of first-hand experience, most countries remain unprepared for the next pandemic. Even before COVID-19, significant funds went into infectious disease research, however, the outcomes of considerable investments did not translate into effective pandemic preparedness plans. In their 2020 study, Head et al. found that between the years 2000 and 2017, G20 countries invested USD 104.9 billion into infectious disease research[3]. Between these years, G20 countries failed to eradicate any Emerging Infectious Diseases (EIDs) and, in 2020, failed to prevent the COVID-19 pandemic. Considering that it took the United States only 0.288% of the G20 investment to eradicate smallpox in a period of ten years[4], it would be expected that more progress would have been made in tackling EIDs. The failure of the G20 countries is primarily due to two reasons: poor strategy, and inadequate allocation of funds. Head et al. reported that the highest fraction of investments went to HIV, while EIDs like ebolaviruses or coronaviruses only received funds in situational circumstances (e.g. in response to an outbreak)[3]. Despite the world's researchers and healthcare systems increasing their investments and research efforts on coronaviruses, many EIDs continue to be ignored by the scientific community. These diseases pose a constant threat to global health and well-being. The 'sit-and-wait' approach, which ultimately led to COVID-19, needs to be reformed with a greater emphasis on proactive prevention methods rather than post-outbreak reactions. However, before drafting policy plans on how to effectively intercept outbreaks, it is important to return to the fundamentals of EID biology and epidemiology to truly understand the dynamics of these pathogens.

The Current State of EIDs

Definition

EIDs are contagious pathogens which have either been identified for the first time in a specific community or have previously existed but are increasing in prevalence or geographic radius[5]. The US National Institute of Allergy and Infectious Diseases (NIAID) classifies EIDs into three categories based on their threat to public health[6]. Category A pathogens require particular attention from a public health point of view as they are easily transmitted and have high mortality rates. These pathogens are characterized by their ability to cause outbreaks of varying severity, with some having

pandemic-causing ability. Examples of diseases and pathogens that fall into this group are anthrax (*Bacillus anthracis*), Ebola Virus Disease (Ebola virus), and Dengue Fever (Flaviviruses). Category B infections have lower transmissibility than those in category A, may result in moderate morbidity and mortality rates, and require some additional tools for surveillance. Some diseases in this group are Hepatitis A (Hepatovirus A), West Nile Fever (West Nile Virus), and Zika Virus Disease (Zika Virus). The pathogens classified in group C may evolve in the future to become more transmissible or virulent and pose a large pandemic threat. Some examples of these pathogens are prion diseases, antibiotically-resistant bacteria, coronaviruses and HIV. While there is vast diversity in the pathogens that are considered EIDs, one similarity that almost all of them share is that they are passed from animals to humans.

Transmission—Zoonosis

Zoonotic diseases are introduced into the human population via direct contact with infected animals, water sources, food sources, or environmental factors[6]. Zoonotic pathogens are grouped into five stages based on how they spread. Stages 1 and 2 diseases may only be acquired from animals, while stage 5 pathogens are endemic human diseases (e.g. can only be spread between humans). Pathogens that can infect both humans and animals at different rates are grouped into stages 3 and 4. Since SARS-CoV-2, the virus causing COVID-19 was likely passed onto humans from bats via an intermediate host, zoonoses have become a topic of interest in the scientific community.

When an EID is passed onto a human host, it can only spread further if it is able to effectively spread between individuals. Modes of transmission differ radically between diseases, but some routes are common to all EIDs. Between humans, pathogens can be spread through direct contact, respiratory droplets, and bodily fluids, amongst other methods. The rate of transmission between various pathogens differs greatly, but there are certain human and environmental considerations that increase the risk of a spillover event and the subsequent spread of the infection between humans.

Factors Contributing to the Outbreaks of EIDs

Globalization has completely redefined the state of infectious diseases in the 21st century. Though international partnerships are at the heart of scientific and medical advancement, higher levels of human contact as well as changes to patterns of international travel have greatly contributed to the emergence of EIDs[7]. Indeed, in the early stages of the COVID-19 pandemic, air travel likely played a major role in the dispersion of SARS-CoV-2. In addition, global movement may lead to the introduction of vectors carrying pathogens to regions they previously did not inhabit via an intermediate human host. Perhaps the most important risk factor to consider is the increase in the international wildlife trade. As there is increased contact between humans and animals that may act as reservoirs of infectious pathogens, the risk of an infection being transferred is much greater. Most EIDs are zoonoses, so naturally targeting the international wildlife trade has been implicated as a possible deterrent to the outbreaks of emerging pathogens. When considering human risk factors in EID outbreaks, it is also critical to take into account host-pathogen dynamics. In many countries with ageing populations, there is a higher risk of EID spillover from animals to humans as more individuals experience immunosenescence in old age and do not mount a strong immune response. The burden of EIDs on these nations may also be greater due to the increased morbidity and mortality associated with many EIDs and advanced age.

Moving away from human factors, a pathogen's environment may also play a role in driving outbreaks. For instance, it is likely that with climate changes, infectious agents that favour tropical environments will evolve and become more prominent. Environmental changes may also impact a pathogen's reservoir, and for vector-borne diseases, their transmission-related characteristics.

The risk factors for EID outbreaks must be carefully considered while planning policy for pandemic prevention. While it may be useful to tackle them individually, most public health experts have suggested that preventing spillover events, the core of EIDs, may alleviate the need to modify other human behaviours. At the same time, focusing solely on zoonoses is unproductive, and countries must be urged to evaluate and invest in other pandemic-preparedness measures.

Tackling EIDs

In the past, global strategies for dealing with EIDs have relied on the 'sit-and-wait' approach[8]. If an outbreak occurs, governments impose local or national restrictions while the scientific community focuses their efforts on drug and vaccine development. This strategy has proven to be ineffective. Even slight delays in detection and the subsequent response, for example, due to long pathogen incubation periods, or the lack of appropriate diagnostic tools, can cause considerable damage to healthcare systems and economies. The lack of a proper preparedness plan can allow pathogens to transition from being rare tropical infections to top priorities of global well-being in a matter of days. Despite the lessons learnt from COVID-19, the world remains unprepared to tackle the next emerging pathogen. While there are differing opinions on how best to prepare for or respond to infectious outbreaks, experts agree on several overarching strategies which would greatly benefit countries' responses to clusters of pathogens: i) preventing the spread of zoonoses, ii) vaccine development, and iii) investment in healthcare systems.

Preventing the Spread of Zoonoses & Surveillance

Over the past two years, addressing zoonotic pathogens has dominated the keynote speeches and information booklets of medical conferences worldwide. While the literature contains differing opinions on how best to tackle zoonotic transfer, there are common topics that are emphasized in numerous studies.

The cessation of the illegal animal trade is a logical step to reduce the risk of zoonotic events. Due to increased globalization and international travel, the movement of pathogens outside of their normal ecological and geographical boundaries via animal hosts is inevitable. Unfortunately, most governments do not have an agency that detects pathogens in imported wildlife, creating a loophole which may lead to the emergence of EIDs[9]. Moreover, the legal wildlife trade was also identified as a potential risk factor for the transfer of zoonoses. It is likely that SARS-CoV-2 emerged in a Wuhan wet market which cultivated perfect conditions for the transfer of an animal coronavirus to humans[10]. Based on the severe risk it poses, it has become clear that the best option to decrease the risk of zoonosis would be to terminate all wildlife trade[9]. However, this approach is highly unrealistic, and many countries would refuse to agree to these terms. Instead, a 'clean trade' scheme should be implemented to initiate safe and diligent strategies in wildlife commerce, including policy-making and surveillance.

One of the major strategies proposed to combat zoonotic diseases is the umbrella approach suggested by Shiferaw et al[11]. The plan brings together governments, scientific/medical personnel, as well as the general public to improve the state of EIDs via surveillance, education, laboratory work, and legislation. Despite some success of these methods in controlling endemic zoonoses, it may be difficult to implement them in the monitoring of emerging infections. Most novel EIDs arise in low-income countries which do not have the funds or resources to carry out the plan outlined by Shiferaw et al. To combat this issue, Ellwanger et al. have suggested that only the highest risk animal and human populations should be monitored for emerging infections, decreasing the financial burden on developing countries[12]. This targeted surveillance would focus on pathogens that are known to have crossed the species barrier and their animal hosts which make the most contact with humans (companion animals, livestock, some wild animals). In addition, specific human populations, specifically those who are in close contact with wild animals and a select group from the general population, may be closely monitored for infection. This method may be effective for already known pathogens, yet falls short of identifying novel pathogens, meaning that other prevention strategies are required.

Following COVID-19's exposure to poor surveillance concerning infectious diseases, multiple approaches using new technology have been suggested to ameliorate the monitoring of emerging pathogens. Data science approaches use human behaviour patterns, clinical records, as well as scientific literature to track and model the courses of EID outbreaks[13]. The findings of these studies could be used to inform how governments should handle clusters of disease, travel restrictions, and quarantine measures. Data science may also be used to monitor the movements and infections within non-human disease hosts. Akinyi et al. monitored non-human primates in Kenya for gastrointestinal protozoa and viruses using simple diagnostic tools such as microscopy, ELISA, and PCR[14]. While these tools may pose financial issues for laboratories in lower-income countries, they are more cost-effective than techniques such as sequencing and yet produce similar diagnostic value. While data science strategies require a large quantity of trained workers as well as robust laboratories, they can be effectively employed in tackling a large variety of human viruses such as SARS-CoV-2, Ebola virus, and HIV, and may be used for other non-viral pathogens in the future. Vigorous monitoring of infection dynamics among animal and human hosts allows for the rapid identification of pathogens but also has a prognostic value which facilitates accurate predictions of EID outbreak patterns.

Along with data science and traditional monitoring methods, artificial intelligence (AI) has also emerged as a new field in infectious disease biology. AI uses public health surveillance data to model infectious disease spread and conduct experimental analyses and evaluation which could inform public policy to establish optimal infectious disease control measures[15]. So-called 'hybrid models' which take into account various environmental factors in addition to human and animal behaviour have also been suggested to more accurately model pathogen spread under different climatic conditions. These prediction methods have already been successful in monitoring viral and parasitic outbreaks and holds promise in the surveillance of other types of EIDs.

It is conceivable that data science, AI, and traditional methods used in combination may be the key to preventing the next type of zoonotic event as they take into account all risk factors and contributors to EID spread. Findings from various studies have already informed databases evaluating zoonosis risk. For example, the *Spillover* database ranks known viral pathogens based on eight factors: host genetics, host epidemiology, host ecology, environmental factors, virus genetics, virology, virus ecology, and virus epidemiology. In the future, these databases may be used to classify novel pathogens, but also monitor the currently known ones to identify those at highest risk for a zoonotic transfer[16].

Vaccine Development

Vaccination is an effective tool used to decrease the transmission and mortality rate of a pathogenic infection. The testing and manufacturing of a vaccine used to be a lengthy process; usually, it would take about ten years to produce a suitable antigen and to group it with the correct adjuvant and delivery method[17]. The COVID-19 pandemic markedly accelerated this process as the vaccines used to fight SARS-CoV-2 were synthesized and brought through meticulous clinical testing in less than a year. The molecular mechanisms behind mRNA vaccines allow for this rapid development. mRNA vaccines only differ by the RNA sequence, not by the method of administration, meaning that their base sequence can be quickly modified should a new pathogen emerge. In addition, the adjustable quality of mRNA vaccines allows them to combat mutations in pathogens as their base

sequence can be altered to counter the effects of genetic variants[18]. Editing the mRNA is much simpler than editing an entire protein or its subunits, simplifying and accelerating the vaccine production pipeline. Multiple mRNA vaccines can also be manufactured in the same facility, allowing for efficient mass production. So how can we harness the benefits of mRNA vaccines to combat emerging pathogens? The best proposed method is a blueprint vaccine which can be modified based on a pathogen-specific antigen. This prophylactic measure could further reduce the time between outbreak and vaccine availability as the vaccine would already have undergone rigorous testing – the only modification that would have to be made is the genetic code. Some experts argue that despite the success of mRNA technology in the battle against SARS-CoV-2, there is not enough evidence to optimistically declare that this methodology could function against other pathogens[19]. Bacteria are far more structurally and functionally complex than viruses, making it difficult to synthesize an antigen with high enough levels of immunogenicity. The same line of argument can be used for emerging infections caused by parasites characterized by their elaborate life cycles and immune evasion. In summary, while mRNA vaccines may not be applicable to all pathogens, their high effectiveness logistical advantages make them a promising tool in the fight against viral EIDs.

Despite the favourable clinical outcomes against pathogens, the success of vaccination is often limited by the issue of proper vaccine distribution. Global vaccine equity is one of the greatest challenges that we are currently facing and will continue to confront in the future. The primary aetiology of vaccine inequity is caused by a small supply and the unjust allotment of doses[20]. While the synthesis and production of mRNA vaccines are fast-moving, supply-chain issues and the economic challenges that came with the pandemic limited the supply of doses of many vaccines which are available on the market. Additionally, in the case of SARS-CoV-2 vaccines, high-income countries pre-ordered large quantities of doses for their populations while low-income countries received only 1.2% of the world's vaccines despite making up 40% of the global population. The unfair allocation of vaccines leads to infection hot spots in areas with poor vaccine uptake. Additionally, areas with low vaccination rates could be the source of new viral variants as higher levels of intracellular replication is responsible for higher mutation frequencies. In the short-term, strategies to improve the state of vaccine distribution are to re-allocate stockpiles to areas with the highest infection rates and lowest vaccine uptake. In the long-term, plans should seek to target areas which are at risk of housing severe outbreaks before an infectious wave takes over.

In summary, as demonstrated in the COVID-19 pandemic, mRNA vaccines are an effective manner of combatting emerging viral pathogens. Their ease of manufacture and flexibility could greatly contribute to rapidly addressing explosive outbreaks. However, the unjust distribution of vaccines puts a brake on its success as a strategy for combatting EIDs. Additionally, there may still be gaps between the time at which an outbreak occurs, and when a vaccine is made available. Therefore, it is also crucial to invest in healthcare systems capable of effectually caring for a population until a vaccine is fully approved.

Investing in Healthcare Systems & Preparedness Plans

High-income countries that remain overly confident in their strong healthcare systems are not actively preparing for the next pandemic in terms of both surveillance and response measures[21]. This flaw was particularly seen when many high-income nations, including Ireland, saw their healthcare systems crumble during various phases of the COVID-19 pandemic. Inadequate numbers of clinicians and healthcare professionals, as well as burn-out and a lack of hospital beds and medical equipment led to many hospitals being stretched thin and unable to provide enough care to patients. Peaks of infection cannot always be predicted, so it is critical to be on constant lookout for possible outbreaks as even the strongest of systems have a breaking point. A key feature of a strong pandemic response is the establishment of well-equipped and personnel-rich scientific, medical, and translational institutions[22]. Continuous investment in healthcare systems may reduce patient mortality should an outbreak occur. Additionally, higher expenditure on research facilities would accelerate the creation of safe and effective vaccines and other pharmacological interventions. It is important to note that even with substantial preparations for a pandemic, it is still crucial to employ classical public health manoeuvres to drive down the spread of an EID should it emerge.

Conclusion

In summary, EIDs are a constant global threat that is frequently ignored by the scientific community and governments across the world. Increased globalization and contact between humans as well as animal-to-human contact have greatly increased the risk of zoonotic events and subsequent EID outbreaks. Despite over two years of first-hand experience, the world remains severely unprepared to tackle the next pandemic. The 'sit-and-wait' approach needs to come to an end, and proper pandemic policies need to be implemented. Zoonoses should be targeted using robust surveillance tools including classical diagnostic measures, data science methods, and artificial intelligence.

In addition, an mRNA vaccine blueprint should be established before an outbreak occurs to minimize the time between outbreak onset and vaccine availability. Vaccine equity should also be tackled by appropriate needs-based distribution doses. Finally, governments should provide substantial funding and recruit sufficient personnel to tackle an EID outbreak. Epidemiological measures and organized health facilities should be appropriately employed to reduce transmission and mortality before a vaccine becomes available. We need to retrace our steps with COVID-19 and use the lessons learnt to prepare for the next pandemic. Diseases do not respect borders or take turns, and for this reason, this piece is not merely an opinion, but a call for action. ◄

Declarations

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SPONSORED INTERVIEW: ANNA RAFFERTY

Women In STEM

by Kristen Andersen* and Ava Janes

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Encouraging diversity in the workplace has the potential to "change the trajectory of health for humanity" says Anna Rafferty, Director of Strategy at Johnson & Johnson Campus, Ireland. Promoting such representation, particularly in the area of STEM, has been one of the key aims of Johnson & Johnson's WiSTEM²D undergraduate programme since its creation in 2016.

As a leader of this programme, Anna started her career with Johnson & Johnson in 2003 after graduating with a BSc in Biotechnology from the National University of Ireland, Galway, and later a Graduateship in Marketing from the Technological University of Dublin. She is now a central figure in the undergraduate WiSTEM²D programme in Ireland.

We spoke to Anna about the about the WiSTEM²D programme, the difficulties and challenges faced by women in STEM careers, and what she believes universities can do about it.

Can you tell us about the programme? How does it work and what is it trying to achieve?

The undergraduate programme is all about inspiring young women to pursue a career in STEM in order to encourage the growth of a workforce that more truthfully reflects and understands the communities and individuals that they are trying to benefit. In this way, we hope to enhance and expand the positive impact that STEM can have on healthcare and so positively alter the trajectory of health for humanity.

It's a high intensity programme run in various universities that provides multiple opportunities for those involved, such as site tours, mentoring, and research. It is quite a selective programme, but our aim is to take on young women with a spark in them rather than basing success on academic grades alone. We believe that it is so important to broaden the accessibility of the programme, and for this reason a bursary is also offered which attempts to reduce economic barriers and allow the participants to truly immerse themselves in the experience.

What obstacles do you believe women currently face when pursuing a career in STEM?

Stereotypes are a large barrier that many women face, and the site visits that we arrange are incredibly important in tackling this as they allow the young women to challenge these stereotypes, especially the ones that they themselves may have created. Often exceptional women, such as Marie Curie, are promoted as role models for young girls which fosters beliefs and pressures that aren't reflective of what working in STEM is actually like. Many young women believe that if they cannot achieve such expectations, there is no place for them in STEM. We are therefore trying to break down these unrealistic beliefs and encourage self-value among young women.

On a more recent note, I think that women of all socioeconomic backgrounds, particularly those in lower classes, have been adversely affected by the COVID-19 pandemic. Given that approximately 70% of those employed in the Irish healthcare system are female, coupled with the added burden of home life brought about by the pandemic, the pressure of balancing both work and home duties has increased, with many women prioritising the latter. This makes the work that we do even more important to ensure that women feel empowered and valued within the area of STEM.

What impacts has this programme had to date?

The impact that has meant the most to me by far is the change that I have seen in young women who have participated in the programme, especially concerning their own sense of purpose and potential. Many of them couldn't see a place for themselves within STEM because they believed that they didn't fulfil the requirements expected of a person entering the field. They also weren't attracted to these requirements as they believed that they would have to forfeit aspects of their personal life to achieve them. But when these young women start to meet others like them who are pursuing a career in STEM, they realise the potential that the field has to offer. Bolstering the confidence of the participants through celebrating their achievements within the programme also has a great impact. The pride and energy you can see in these young women at the very end is incredibly special. It opens the road to them pursuing studies in STEM.

What can universities do to promote women in STEM?

The network is everything. You know we're always saying make sure to continue to make those connections with your mentor and others in the group. Everyone thinks of networking as being this arduous thing, who wants to do it, but when you get to the point in your career where you realise that networking makes your life easier and you start to enjoy it, then networking becomes much more attractive. Like if you think, if I network here, the chances of me getting a job are much faster and I'll probably get the job I want as opposed to leaving it to chance on career websites of companies like ours where it's very hard to stand out from the crowd. I think the network is one of the most valuable things that you can take away from the program.

What advice would you give to young women who are unsure of a career in STEM?

We're lucky here in Ireland, the opportunities are plentiful. You can follow whatever road you want to and just because you qualify in microbiology doesn't mean that you have to follow that. Skills are so transferable and it's not just about academic skills but also about on-the-job learning but careers in STEM are really certainly very rewarding.

Also, I think people underestimate how quickly they add value. Sometimes students come on placements to our sites from whatever STEM course they're doing and then at the end of August somebody says: "Oh no, so-and-so is leaving!" And everybody asks: "Where are they going?" Well, she's in third year, she has to go back and finish. So, we're always trying to tell people, you have no idea how quickly you add value.

Do you have any final advice for women in general?

Those of us involved in the WiSTEM^{2}D programme feel strongly that there is no point in just raising awareness about the lack of female representation in STEM because everyone already knows this. Instead, a piece of advice that I was given at the International Women's Forum a couple of years ago is to "be an actor, not an ally". That really struck home with me. I understood then that you have to get out and do something about the issues that you see: meet people, discuss ideas, get eyeball to eyeball with them. That's what women need to do. That's what will make the difference. That's the vision of the WiSTEM^{2}D programme.

*To find out more about the WiSTEM^{2}D initiative, visit the website at **www.jnj.com/wistem2d**.*

Declarations

This article is part of a collaboration between Johnson & Johnson and the TSMJ to promote the awareness of professional opportunities for women in STEM. Kristen Andersen and Ava Janes are staff writers on the editorial board of the TSMJ, and ere asked to contribute an article to Volume 22. Johnson & Johnson is also a sponsor of the TSMJ Volume 22.

INTERVIEW: DR IAN FRASER

CyberKnife and the Future of Cancer Treatment

by Ava Janes

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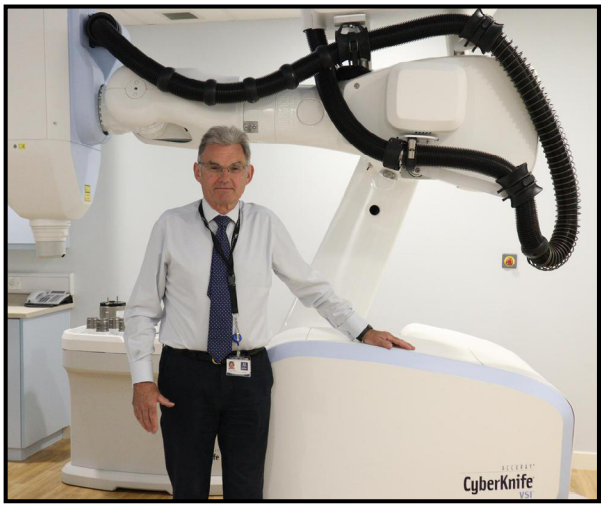
Dr. Ian Fraser stands next to the CyberKnife robotic radiosurgery system



Cancer is a disease that has wedged itself into the mind of society as one of a cruel and devastating nature. As the second leading cause of death worldwide, it comes as no surprise that advances have been made in recent years towards developing potential therapeutic options.

However, the most pressing issue today is no longer just the killing of cancer. Instead, the focus lies in extending life while simultaneously avoiding any impairment to that life. As oncologist Dr. Siddhartha Mukherjee so eloquently wrote in this 2010 book, "The Emperor of all Maladies: A Biography of Cancer", what current therapy truly demands is the use of a "fantastically nimble knife: sharp enough to kill cancer yet selective enough to spare the patient". It is with this in mind that we can consider the possibility that perhaps this knife exists in CyberKnife.

I spoke to Dr Ian Fraser, Consultant Radiation Oncologist at the Hermitage Medical Clinic in Lucan, where he is a member of Ireland's first and only CyberKnife team, and asked him to offer an introduction to CyberKnife and what he thinks about the future of cancer therapy in Ireland.

First of all, what is CyberKnife and how is it different from other cancer treatments?

CyberKnife is a linear accelerator mounted on a robot that targets tumours with radiation beams. What makes it different is that it targets the radiation very accurately, to 0.2 of a millimetre. Because it's non-coplanar, you are bathing the tumour in a field of radiation which can be extraordinarily accurately delivered. This prevents damage to normal healthy tissue. For prostate cancer, it allows a margin of 2 to 5 millimetres, where normally you have a margin of about 1 centimetre with a half a centimetre at the back. For intracranial diseases, we use up to 200 beams specifically to protect normal structures, because while radiation therapy is about what you want to hit, it's also about what you want to miss.

What cancers is CyberKnife licensed to treat and are there any risks associated with treatment?

Here in the Hermitage we focus on intracranial cancer. But it can also treat prostate and lung cancers due to its tracking ability which allows it to lock onto fiducials (gold seeds placed within the tumour) and so lock onto the tumour itself. This means that as the lungs or prostate move, CyberKnife tracks and targets only the tumour, unlike regular linear accelerators.

As for risks - there are always risks with radiation. Like in surgery, if you don't know where precisely the tumour is, you have the potential to miss. For example, if we have a prostate cancer where there is a breach of the capsule (outer layer of the prostate), we will not treat with CyberKnife because we use the capsule to define the borders of the targeted therapy. When the tumour has gone outside the capsule, we can't be certain where it is, and that's where your accuracy of 0.2 of a millimetre works against you.

CyberKnife is also expensive. The regular linear accelerator is going to cost you around €1.5–3 million. CyberKnife is €12 million. For the patient, it's around €20,000 for treatment, but is covered by health insurance. So it's a very expensive toy. But, if I was going to be treated for an intracranial, lung, or prostate disease, CyberKnife is what I'd want, because I think—and I've been in this field for a long time—I think that it's simply the best. It's the best I've ever seen.

What can you tell me about the others involved in the CyberKnife team?

The team is a three-cornered stool. You've got physicians, physicists, and radiotherapists who are all highly-educated in their specialised field and work together to create a plan that is checked and re-checked before proceeding. Not infrequently we will have to amend this plan multiple times until everyone is satisfied. All of this is for safety. Safety is paramount and we are always learning from experience. During treatment, the procedure is checked 40 times a second to make sure everything is going to plan. If something deviates even slightly, the robot stops automatically and we figure out what happened, why it happened, and the consequences so that we learn from and don't repeat any errors. You have a great system when team members are all happy to learn from an experience in order to keep improving treatment delivery.

Is there an experience that has particularly stood out to you from using CyberKnife?

There was a patient whose lungs were wood-hard from smoking. He had non-small cell lung cancer, and the surgeons said that there was no way they could operate on his lungs because if they did, the procedure would kill him. So he was referred for CyberKnife. He actually developed a pneumothorax and ended up in ICU after the fiducial was inserted. So his lungs really were in dreadful shape—completely fibrotic with hardly any movement. He was using his neck muscles to breathe. We treated him with CyberKnife, and the cancer disappeared. When he came back two years later with a second cancer in his other lung, we treated that too. He's had extra years of life and is still ticking along. If we hadn't had CyberKnife, we couldn't have treated him.

When the patient described his experience in an interview with the Sunday Independent, he said how he was treated for only five days, that he was lying on the bed and he felt absolutely nothing. He is so tremendously happy with himself, and his wife is now an advocate for CyberKnife. It's a wonderful thing to see people—who otherwise wouldn't have had a chance—end up in a much better place.

I can imagine then that CyberKnife would be a very popular option for patients. How satisfied are you with its accessibility, and who decides what patients get to avail of it?

I feel that it is not as widely available as it should be and that it would be much better if we could treat more public patients and had more open referrals from other hospitals around Ireland.

Currently, it doesn't even have a waiting list. This is for many reasons, one of which is that there are protocols to determine patient suitability. This is figured out through an MDT meeting which is made up of the surgeon, radiation oncologist, diagnostic neuroradiologists, physicists, and radiation therapists. That's five different groups of people who discuss the case and must all give the 'okay' in order for the treatment to go ahead. We have defined treatment protocols. If these protocols are not met, the treatment does not go ahead. If someone at any point along the treatment process says they are not comfortable with how appropriate it is, we stop and have a long look at the plan to see if this really is the best option for the patient. And if it isn't, the treatment doesn't happen.

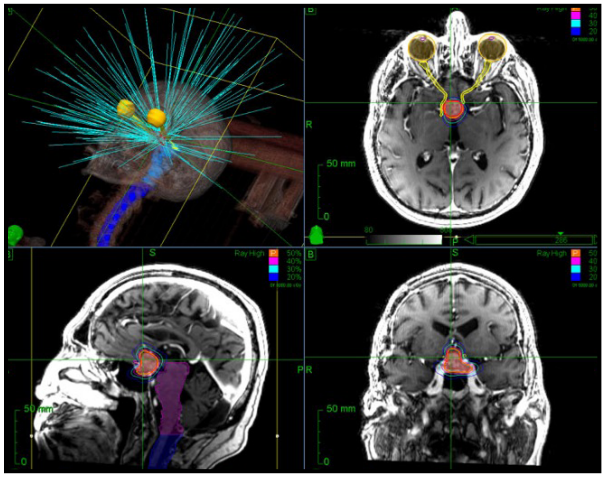
Where do you envision us being in 10 years' time concerning cancer treatment and what is the future of CyberKnife here in Ireland?

Oh, my god! Where am I even going to be in 10 years' time [laughs]? Well, when I started my career, the smallest tumour volume we could treat was 64 cubic centimetres. We're now down to 30 cubic millimetres. So, in 10 years' time, that'll be defined even better. The volume will be even smaller and therapy even more accurate.

The other thing that's coming in is artificial intelligence, which is going to identify your normal healthy structures—where your lungs are, where your spinal cord and oesophagus are—and then define the tumour treatment area. You'll still need a doctor, physicists, and therapists, but AI is going to move this entire process forward. It's going to change everything. Here in the Hermitage, we are hoping to shortly have artificial intelligence which we can use in our radiotherapy department.

Concerning the future of CyberKnife, I think the aim will be to secure another in Ireland and establish a network between them. The future of treating intracranial, prostate, and non-small cell lung cancer is definitely with short, sharp treatment administered from outside the body using something like CyberKnife, because it is extremely simple and equally as effective as surgery.

Targeting a pituitary adenoma with minimal dose to other critical structures such as the optic apparatus



Is there anything in this field that you think we should be talking about which we aren't?

Cancer is a multidisciplinary treatment area, so it's only going to flourish if everybody understands what the other members of the team have to offer. You've got to operate as a team. The purpose is to maximise the benefit for the patient. The timing of the different modalities may be the difference in outcome for the patient. It is so important that everyone respects the contribution of the others in the MDT. You see, teamwork is what medical care is all about. Teamwork is vital. A good team will always result in a better treatment than an exceptional individual ever will. Individualism is fantastic, but individualism has to be part of a team. And if you contribute to a team, that's far more satisfying for yourself and else everyone involved. ◂

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Declarations

Ava Janes is a staff writer on the editorial board of the TSMJ, and was asked to contribute an article to Volume 22. The author declares that the article was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

QUALITY IMPROVEMENT PROJECT

Improving the Quality of Medical Handover Through the ISBAR$_3$ Technique in Children's Health Ireland at Temple Street

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Abstract

Background: Medical handover is considered an important aspect of patient care to provide safe and quality care to patients. As the medical community moves away from 24-hour shifts, there is a greater need for a standardised handover to be implemented. Medical handover techniques are currently being criticised for their lack of structure, often leading to errors in patient care. Improvement in medical handover is crucial, as transfer in care can be associated with hospital mortality. We aimed to integrate interactive prompts and brief teaching sessions on the ISBAR$_3$ technique to improve the quality and standardisation of medical handover.

Methods: Plan-Do-Study-Act (PDSA) methodology was employed. Four cycles, each of a 3-day duration, were completed over a 4-week study period. Data collection and introduction of implementation measures were completed from Monday to Friday to increase staff awareness. The methodology of each cycle was developed from the outcomes of previous cycles and discussions with key stakeholders.

Results: The baseline data of this project revealed inconsistent and unreliable use of some aspects of the ISBAR$_3$ handover tool. The second cycle displayed an overall improvement in the engagement of ISBAR$_3$. The areas of *Identify*, *Situation*, *Background*, and *Assessment* averaged 100% utilisation across all days of phase 2. Outcomes of the third cycle revealed continuous engagement with ISBAR$_3$, inferring the beneficial use of multi-media prompts. Outcomes of the final cycle, focused on clinical handover adherence and standardise access to computer software, showed significant improvement in all areas of the medical handover.

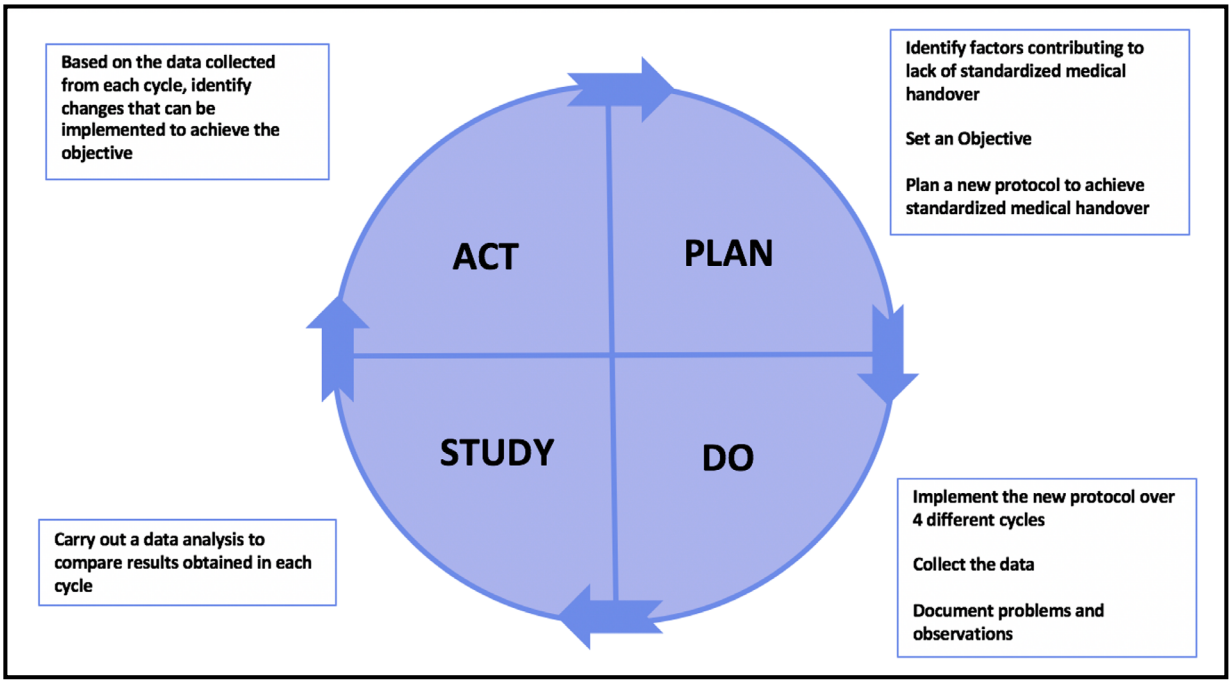
Conclusion: This PDSA–based quality improvement project demonstrates the speed at which a high-quality intervention can be rolled out in a high-pressure clinical environment. The 4-cycle PDSA model had a positive impact on the process measures of clinical handover in a tertiary paediatric centre.

Keywords: Medical Handover, Plan-Do-Study-Act (PDSA), Quality Improvement Project

Introduction

The HSE defines a medical handover as the transfer of responsibility and accountability for aspects of patient care to another professional or team on a temporary or permanent basis[1]. Teamwork, clinical expertise, and leadership are utilised in a structured manner by healthcare professionals to improve the quality and safety of patient care. Clinical handover is a high-risk time during the patient journey and is associated with hospital mortality[2]. Current criticism of handover includes poor communication, which is the leading cause of medical errors[3]. Exclusion of the patient can occur at many different points in the transfer of care during a patient's stay in hospital[4]. As full-time employment and 24-hour shifts become less common in medicine, there is an increased need for and reliance on efficient, standardised, and effective clinical handover[5]. Implementation of a handover programme has been shown to reduce medical errors by 23% and preventable adverse events by 30%[6]. The World Health Organisation advocates for the use of ISBAR$_3$ (*Identify, Situation, Background, Assessment, Recommendation, Risk, Readback*) as a handover tool due to its multidisciplinary nature and user-friendly technique[7]. This specific tool has also been suggested to improve individual and team communication in a timely manner[8]. Although, many studies have explored the importance of achieving a high-quality medical handover there are themes identified among the literature that highlight the gaps in the handover process. Some of the major themes identified among the literature included the lack of research on standardisation of electronic

Figure 1. **PDSA Model for Quality Improvement in Medical Handover**



documentation, minimal data on the handover process in the private hospital setting, and limited data on the structure and implementation of educational sessions regarding medical handover. More importantly, the role of patient interaction during the handover process remains an unclear and complex area in this field of study and requires further exploration. The aim of the project was to increase utilisation of the ISBAR$_3$ technique through a peer-led educational model using visual prompts, brief teaching sessions, technology modification, and stakeholder engagement in order to standardise the medical handover process.

Methods

A quality improvement framework was developed for clinical handover in the general paediatrics unit at Children's Health Ireland at Temple Street, which is a 154-bed tertiary paediatric hospital in Ireland. A Plan-Do-Study-Act (PDSA)[10] approach was adopted. This cyclical model provides a clear method for repetitious development of change by incorporating complex interventions of interdependent steps and key criteria[10]. Incorporating a PDSA cycle will provide structure for a quality improvement approach, such as the Model of Improvement (MFI). MFI is essential for creating a framework that incorporates developing, testing, and implementing changes that will ultimately lead to improvements[11]. Four cycles were completed over a 4-week study period from 9 December 2020–7 January 2021. Each PDSA cycle would take place for 3 days before moving onto the next cycle. Data was collected by a Specialist Registrar involved in the study and the implementation measures were introduced from Monday to Friday to increase staff awareness of the measures. The first cycle involved a *Plan* for the project, *Doing* a collection of baseline data on the quality and effectiveness of the clinical handover using process measures (**Figure 1**). The collection of baseline data on how often each handover task was completed, the distribution of handover information in group chats and task delegation, multi-media advertisements to raise awareness about medical handover, and the creation of dedicated login details for access to essential computer programs and printers were all part of the process measures. *Study* involved interpretation of this data and *Actions* that were implemented formed the foundation of the second cycle (**Figure 1**). The methodology of each cycle was developed based on findings of the previous cycle and discussions with key stakeholders (**Table 1**). Key stakeholders were paediatric medical Senior House Officers (SHO) or Registrars participating in clinical handover during the 4-week period of this study.

Results

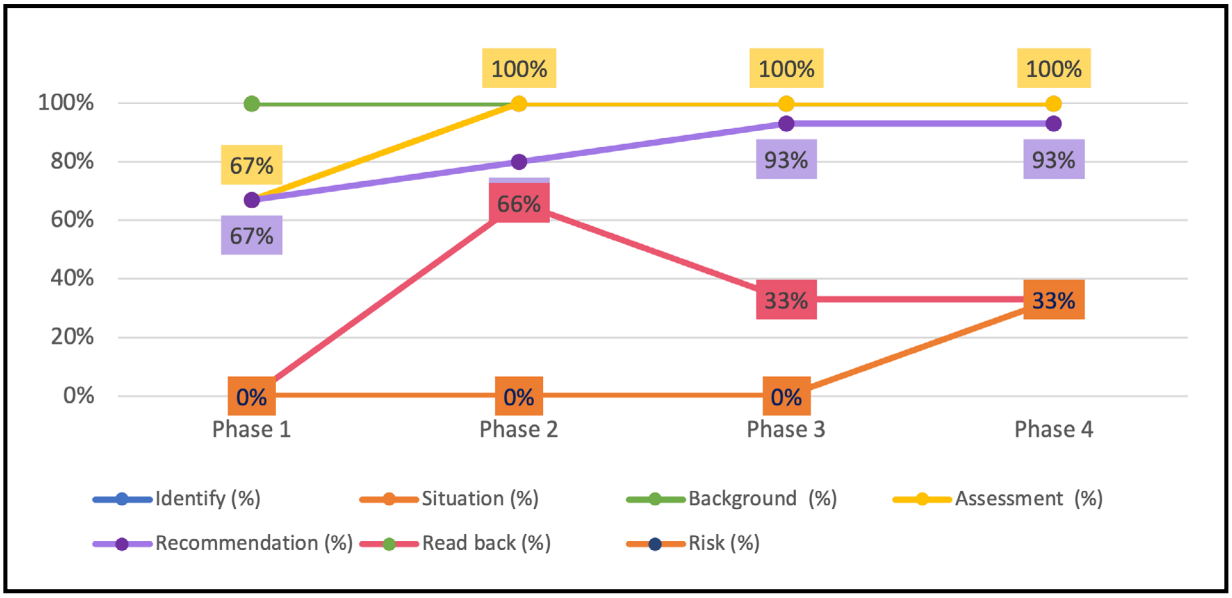
The baseline data of this project revealed inconsistent use of some aspects of the ISBAR$_3$ handover tool. When incorporating ISBAR$_3$, *Identify*, *Situation*, and *Background* were consistently achieved across all the 3 days of phase 1; however, *Assessment* and *Recommendation* were only achieved on day 1 and 2 (**Figure 2**). Additional baseline data showed insufficient engagement by team members in handover tasks, such as readback, risk, updates regarding the Watchers list, intensive care unit (ICU) discharges, medical consults, and Paediatric Early Warning Scores (PEWS)/arrests documentation. During phase 1, the radiology programme, National Integrated Medical Imaging System (NIMIS), was accessed on day 3 and lists were updated on day 1, but there was no use of printed handover lists. The data analysis from phase 1 highlighted areas of improvement that became the target for phase 2.

Table 1. **Details of Four PDSA Cycles Conducted by Research Team from 9 December 2020–7 January 2021**

	Plan	Do	Study	Act
PDSA 1: 9–11 December 2020	• Understand the current procedural protocol in place to develop key strategies for improving medical handover	• Collect baseline data on the quality and effectiveness of the current handover method used at that point in time	• Team attendance 100% • Readbacks, risk, watchers updated, ICU discharges, medical consults and Paediatric Early Warning Scores (PEWS)/arrests not documented • Lists not printed • Lists updated 1 out of 3 days • **Day 3 lacked assessment and recommendation following ISBAR$_3$ tool** • NIMIS accessed 1 out of 3 days	• Teams were not utilising every aspect of the ISBAR$_3$ tool • Key aspects of medical handover process were excluded
PDSA 2: 12–14 December 2020	• Address lack of awareness of the impact of handover and lack education regarding the ISBAR$_3$ structure • Increase efficiency of the handover with increased computer program use and pre-printing of lists	• Posters about medical handover reminders placed at congregation points • Reminder messages displayed on most frequently used computer monitors	• Team attendance 100% • Readback improved to 2 out of 3 days • Medical consults improved to 2 out of 3 days • 33% increase in lists printed • Lists updated 2 out 3 days • **Following ISBAR$_3$ tool; assessment improved 100% on day 3 and recommendation averaged 80%** • NIMIS accessed 3 out of 3 days	• Implementation of education sessions/ information showed an improvement in the uptake of ISBAR$_3$ protocol • Establishing clear roles for each team member showed benefit
PDSA 3: 15–17 December 2020	• Increase awareness of handover, to reinforce the structure of ISBAR$_3$, and to seek feedback from key stakeholders	• Posters about medical handover reminders placed at congregation points • Reminder messages displayed on most frequently used computer monitors	• Team attendance 100% • Readback decreased to 1 out of 3 days • Medical consults decreased to 0 out of 3 days • Lists printed 1 out of 3 days • Lists updated 3 out of 3 days • **Following ISBAR$_3$ tool; assessment 100% across all 3 days and average recommendation improved to 93%** • Documentation of PEWS improved to 1 out of 3 days • NIMIS accessed 3 out of 3 days	• Multi-media reminders proved to be effective in reinforcing the structure of ISBAR$_3$
PDSA 4: 5–7 January 2021	• Increase adherence with printing of the lists prior to clinical handover • Standardise access to computer programmes	• Creation of a dedicated computer login for clinical handover—access to printers and essential computer programmes	• Team attendance 100% • Readback maintained at 1 out of 3 days • Risk, watchers updated, ICU discharges documentation increased to 1 out of 3 days • Medical consults improved to 2 out of 3 days • Lists updated 3 out of 3 days • Lists printed 3 out of 3 days • **Following ISBAR$_3$ tool; assessment 100% across all 3 days and average recommendation improved to 93%** • Documentation of PEWS improved to 3 out of 3 days • NIMIS accessed 3 out of 3 days	• The addition of each previous cycle resulted in an overall positive outcome for the medical handover process • The results reveal that it is beneficial for teams to actively engage in each aspect of the ISBAR$_3$ handover tool to see an overall improvement

The second PDSA cycle involved distributing handover information in WhatsApp groups and completing an educational session with medical staff to emphasise handover importance and the ISBAR$_3$ structure. A selection of entertaining memes was used to capture attention and improve interaction between key stakeholders. Task delegation was also formalised in this cycle by displaying roles and tasks on evenly spaced chairs in the handover room. Tasks included opening the radiology and laboratory computer programmes at the beginning of handover, printing handover lists, and updating the lists. This step served to improve adherence to public health Coronavirus Disease 2019 (COVID-19) guidance, increase computer program use for more efficient handover, and address the issues highlighted from phase 1. Results of this cycle displayed an overall improvement in the engagement of ISBAR$_3$. The areas of *Identify, Situation, Background,* and *Assessment* averaged 100% utilisation across all days of phase 2. When analysing the area of *Recommendation*, the calculated average was 80% for the duration of phase 2. There were also improvements in the use of *Readback*, printed lists, updated lists, and NIMIS programme.

Figure 2. **Run Chart of Compliance With ISBAR$_3$ Elements Over 4 Phases**



For the third PDSA cycle, posters about medical handover were displayed in key congregation points throughout the hospital to increase awareness of handover, reinforce the structure of ISBAR$_3$, and obtain feedback from key stakeholders. Reminder messages were affixed to the most frequently accessed computer monitors to increase use of the online shared worklists and reduce reliance on verbal handover. Outcomes of this cycle revealed continuous engagement with ISBAR$_3$. The areas of *Identify*, *Situation*, *Background*, and *Assessment* continued to average 100% use across the duration of phase 3. The use of *Recommendation* increased to an average of 93%. There was consistent use of NIMIS (100%) and an increased uptake in PEWS/arrest documentation by a day (+33%). A reduction was seen in the use of *Readback*, the discussion of medical consults, and printing lists by a day (-33%). Although there was regression in a few of the handover tasks, there was an overall increase in use of ISBAR$_3$.

The fourth PDSA cycle involved creating a dedicated computer login for clinical handover that provided access to printers and essential computer programmes. This step aimed to increase adherence to printing of the lists prior to clinical handover and standardise access to computer programmes during clinical handover. The use of *Identify*, *Situation*, *Background*, and *Assessment* was consistent, while the use of *Recommendation* remained at an average of 93% during phase 4. The final phase of the PDSA cycle showed significant improvement in all areas of the medical handover that were analysed. Discussion about risks, watchers, and ICU discharges increased by 1 day (33%). Updated and printed lists were both fulfilled on all days. Discussion about medical consults increased by 2 days (66%), documentation of PEWS or arrests increased by 2 days (66%), and NIMIS access remained at 100%.

Discussion

Several previous studies have focused on the challenges that arise when conducting a medical handover[12-14,16-18]. Throughout our search, communication seemed to be the challenge to arise most often. As many institutions move away from 24-hour shifts, there is a greater need for structured medical handover with technical communication about patients, their conditions, and current ongoing needs of care. The quality of communication among medical professionals is essential for patient safety and optimal care.

Communication includes technical facts about medical needs, but also requires positive attitudes and professionalism to foster dynamic relationships among colleagues and ensure effective conversation[12]. In addition to communication, other barriers to achieving a structured medical handover included time management, delegation of responsibility, and administrative challenges. Understanding the challenges of a medical handover will provide insight on how to develop a protocol to improve the quality and structure of a sustainable medical handover.

Sarvestani et al. discussed time management as a barrier to effective handover practices[13]. Sarvestani et al. demonstrated that an average handover lasted for approximately 41 minutes, and that time was usually not managed appropriately[13]. It was found that prolonged verbal reports during a handover often led to the inability to prioritise the patients' needs[13]. With technological advancements and a move towards fully supported electronic databases, verbal communication can be lost during the process. A study conducted by Auroa et al. demonstrated that verbal communication is still very important when it comes to transmitting patient information[14]. They found that the replacing a telephone call with an electronic reporting system for reporting critical lab values resulted in 45% of emergency lab results going unchecked[14]. The researchers concluded that ineffective verbal communication during medical handovers is a common event regarding adverse events

in patient care[14]. It can be concluded that effective verbal communication during a medical handover is critical for improving safety and quality of patient care. The implementation of structured verbal communication and use of skills such as "read-backs" during handovers have been shown to reduce errors in patient care[15]. Further review of the literature demonstrated that handovers combining both verbal information and electronic data results in minimal data loss during the transmission of patient information[16].

Regarding medical handovers, delegation of responsibility is of utmost importance. There are often many professionals involved in providing care for one patient. When there is a lack of responsibility or clear leadership roles, complications tend to arise and lead to errors in patient care. Leadership is important to delegate tasks based each professional's knowledge, experience, and expertise. Inappropriate delegation of tasks during medical handovers can compromise patient care[17].

Complications in medical handovers can also arise when there are technical issues within administrative processes. Many institutions rely on electronic tools to record, review, and analyse patient information. Barriers to the use of electronic tools can cause poor communication, lead to non-cohesiveness, and prevent standardised data transfer during medical handovers[18].

Although it is critical to understand the barriers we face when conducting medical handovers, it is just as important to identify techniques and tools that are beneficial in creating a structured medical handover. Dr Ming-Keng Teoh of Medical Protection Society states that "good handovers provide continuity of care and can help to avoid errors" [19]. A good handover not only allows the exchange of information, but also the chance to ask questions and affirm the information received about the patient[17]. There are several steps that should be taken to perform a successful handover. There should be an assigned senior clinician to facilitate the session and encourage discussions between all other team members. Each session should be allotted an adequate timeframe based on the size of the institution and patient population. A good medical handover should take place in a focused environment free from interruptions and distractions. When appropriate, handover should involve health professionals from other specialties and disciplines for a multi-disciplinary approach[20].

Implementation of the $ISBAR_3$ framework is beneficial for assembling a medical handover[21]. The framework stands for Identification, Situation, Background, Assessment, Recommendation, Read-back, and Risk. This simple framework is logically constructed and simplified to allow its users to quickly recall its elements and conduct a comprehensive handover. The $ISBAR_3$ tool provides a focused approach to set expectations, ensure completeness of information, and reduce errors in patient care. There are many different methods when approaching a medical handover. Implementation of the $ISBAR_3$ technique has been shown to increase communication content, improve structure and consistency in the delivery of patient information, and allow recipients to feel prepared with essential information about their patients[22]. To achieve good quality handovers, it is important to deliver educational training sessions to medical staff on how to properly execute and utilise the $ISBAR_3$ method. An Australian study found that junior doctors valued handover education and desired more constructive feedback from senior doctors[9]. When the study was conducted, there was poor attendance at the educational sessions. Those who did attend the training sessions found it to be very beneficial. The researchers concluded that some of the reasons for poor attendance to the training sessions included a lack of awareness about the importance of medical handovers, competing clinical demands, and the challenges of implementing educational programs in a hospital setting. We found our results to be concurrent; the implementation of educational sessions among medical staff and updates via group chats were associated with better use of the $ISBAR_3$ structure and improvements in the medical handover process.

There are multiple barriers that can hinder the quality of medical handovers. However, with the introduction of improved communication techniques, educational programs for medical professionals, and the standardisation of a structured protocol, it is possible to improve the quality of handovers and optimise patient safety across healthcare institutions. In our project, only the morning handover (8.30am) was studied during this project for feasibility reasons.

This project does have limitations. We used a short time frame for each cycle. Ideally, more time allotted to each cycle would have been more beneficial to see a greater evolution of change but due to change over of Specialist Registrars the selected timeframe was only feasible. With frequent rotation changes among the teams at Temple Street, a short time frame for each cycle was decided on to allow for each cycle to completed and analysed as thoroughly as possible before moving onto the next cycle. Despite the short time frame of the cycles, significance in the data remained clear throughout the duration of the project.

In addition, this project was conducted during the COVID-19 pandemic. The pandemic caused an ever-evolving environment within the hospital, potentially leading to unpredictable changes in specific protocols regarding the health and safety among staff and patients. The methodology design of this project was developed during the pandemic with the hopes of incorporating techniques that will withstand diverse and challenging situations that may arise in the future of healthcare. We recognise the importance of evolving with the changes that the COVID-19 pandemic poses on the hospital setting and more specifically the medical handover process.

Conclusion

This PDSA–based quality improvement project demonstrated the speed at which a high-quality intervention can be rolled out in a high-pressure clinical environment. The 4-cycle PDSA model had a positive impact on the process measures of clinical handover in

a tertiary paediatric centre. The implementation of the ISBAR$_3$ technique will work to increase communication, improve structure and consistency in the delivery of patient information, and prepare recipients with essential patient information. Future studies may involve linking results from this project with outcome data, such as length of stay, time from medical consultation request to consultant review, and consultant satisfaction with incoming registrar's knowledge of cases.◂

Declarations

The authors declare that this quality improvement project report was conducted in the absence of any relationships—commercial, financial, or otherwise—that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW

Administering Shingles Vaccine Prior to the Initiation of Biologics Therapy: A Systematic Review

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Abstract

Background: Shingles, also known as herpes zoster, is a viral infection caused by the varicella-zoster virus. The classic feature is a painful dermatomal rash. Although the disease is often self-limiting, complications such as postherpetic neuralgia can cause long-lasting morbidity. Patients who are immunosuppressed are more susceptible to developing shingles. The purpose of this paper is to systematically review the evidence for prophylactic use of the shingles vaccine prior to initiating biological therapy.

Objectives: To evaluate the evidence for shingles vaccine prophylaxis prior to initiating biologics therapy.

Methods: We performed a comprehensive Boolean search of PubMed and EMBASE from January 2000 to October 2019 for the following terms: prophylaxis, prior, shingles vaccine, varicella-zoster, infliximab, biological therapy, and guidelines. Eligible studies met the following criteria: published in English since 2000, used any shingles vaccine type and dose; and involved both vaccine monotherapy and autoimmune disease biological therapy. Randomised controlled trials, meta-analyses, and systematic reviews were included. Duplicate studies were excluded, as well as non-English papers.

Results: 32 studies met the search criteria, of which 8 were selected for the literature review. All studies had generally differing conclusions as to whether shingles vaccination in autoimmune patients undertaking biologic therapy was safe and effective.

Conclusions: Patients with autoimmune diseases should be considered for the herpes zoster vaccine prior to initiating biological therapy. Our findings support the use of the live attenuated vaccine, *Zostavax*, or the non-live vaccine, *Shingrix*. However, further research is required to evaluate specific autoimmune conditions and specific biological agents with a view to the formulation of national clinical guidelines on the use of the herpes zoster vaccine in the immunocompromised.

Keywords: Shingles, Herpes zoster, Varicella-zoster virus, Vaccine prophylaxis, Biologics

Introduction

Herpes zoster (HZ), otherwise called shingles, is an infection of a nerve and surrounding skin caused by the varicella-zoster virus (VZV)[1]. Whilst occurring mostly during childhood, it can remain dormant and reactivate later in life. Characterised by a unilateral vesicular and painful rash, severe complications can also occur. These range from postherpetic neuralgia (PHN), long-term pain continuing after the rash has subsided, to potentially death[2].

Within the general population, shingles occurs approximately every 4 per 1000 person-years, though these rates are higher amongst elderly autoimmune patients, particularly those on immunosuppressive therapy[2]. This is worrying, given the increased use of immunosuppressive medications like biologics. Widely used for their minimal toxicity profile[3], higher efficacy, and target specificity; biological agents including tumour necrosis factor alpha (TNFα) inhibitors have become mainstream therapeutic options for autoimmune diseases[4]. Whilst directing their therapeutic effect by targeting abnormal immune activity, the mechanism of action can cause immunosuppression leading to VZV reactivation[5,6].

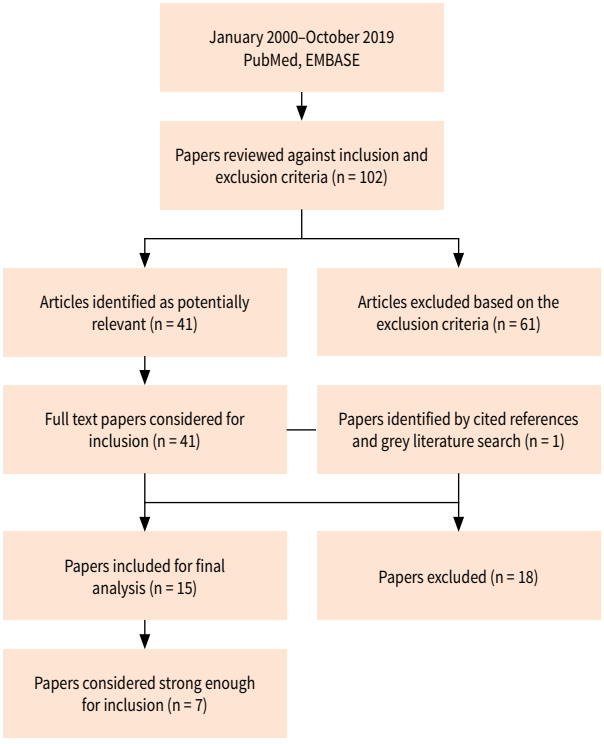
The use of a shingles vaccine is an avenue currently being explored to provide prophylaxis against VZV reactivation. Although the 2005 Shingles Prevention Study demonstrated the live-attenuated vaccine's efficacy and informs much of our current practice, HZ vaccination in immunocompromised cohorts remains poorly understood[7].

Thus, the objective of this systematic literature review is to evaluate the evidence surrounding prophylactic shingles vaccination in adult autoimmune patients prior to initiating biological therapy.

Methods

A literature search of PubMed and EMBASE databases was carried out. The databases were searched for titles and abstracts containing keywords to identify the risk of various infections among patients receiving biological

Figure 1. **PRISMA Chart Highlighting Inclusion of Articles for the Literature Review**



therapy for autoimmune diseases. The following Boolean search parameters were used: "Prophylaxis" OR "Primary Prevention" AND "Shingles Vaccine" OR "Varicella Zoster Vaccine" AND "Autoimmune Disease" AND "Adult Patients"' OR "Infliximab" OR "Biological Therapy" AND "Guidelines".

Search Strategy

The first live-attenuated vaccine for the prevention of HZ, *Zostavax*, was released by the Food and Drug Administration (FDA) in the USA in 2006[8]. However, the search was broadened to include data for when the first biological agent, Etanercept, was approved by the FDA in 1998 and started seeing clinical usage for rheumatoid arthritis (RA) in 2002[9]. This broadening of the time scale ensured we could account for the emergence of biological therapy in autoimmune diseases.

Initial results were recorded with the removal of duplicate results. Relevant articles were reviewed according to titles and abstracts for inclusion in the literature review.

Inclusion/Exclusion Criteria

Studies were included in the literature review if they were published in English, published from 2000-2022, and if studies involved (a) VZV vaccine monotherapy, (b) any patient over the age of 18 with autoimmune disease, and (c) any biologic therapy causing immunosuppression.

Studies were excluded if they remained unpublished or if the data was not specific to vaccination or biologics. This was supplemented by a grey literature search. The discrete number of papers retrieved, excluded, included, and analysed are displayed in a PRISMA diagram (**Figure 1**).

Results

Study Outcome

Study findings (as shown in **Tables 1–2**) were mixed, differing in whether patients with autoimmune disease on biologic therapies had a higher incidence of developing shingles. All, however, did not find a definitive link between HZ infection following biologic therapy. This led to mixed recommendations. Only one study recommended vaccination being acceptable with biologic therapy[10], with the rest either recommending vaccination with certain (conflicting) caveats or stopping short of recommending it.

Defining a stringent 'evidence-based conclusion' was difficult. Only seven studies were found, with many of them being reviews of current guidelines, which tended to homogenise biologics and autoimmune diseases and give non-clinically specific data. Primary research was lacking, and most examined populations were too small for a significant conclusion within their settings.

Only one study was deemed significantly relevant in study scope[11], but its findings were unclear. Another study demonstrated statistically significant VZV-specific immune markers following vaccination[12], though laboratory markers do not directly translate into being disease-free. Taking all this into account, any links between biologics and prophylactic vaccination remained probable at best.

Discussion

Biological Therapy

Most biologics reviewed were TNFα inhibitors; this makes sense, given that TNFα is key in many inflammatory diseases[13]. Aside from the etanercept study[14], all studies homogenised biologics under 'biological therapy' or failed to specify specific drugs under mono/dual therapy. Thus, except for finding that dual biologic-thiopurine therapy increased HZ risk[14], we could not gauge the different extent any biologics or therapy combination had on immunosuppression or opportunistic infection risk.

Reviewing external literature yielded mixed results. Whilst one study showed a higher HZ risk in non-TNFα biologics than other immunosuppressive therapies[15], an alternative study with IL-17 inhibitors found no HZ risk change in psoriasis patients[13]. Presumably important, it is also unclear what effect biologic dosage could have; one study mentioned 'low dose biologics' but did not evaluate whether the resulting small HZ risk was because of the low dose, or despite it[16].

It is also unclear if immunosuppressive therapy usage generally increased HZ risk. One study found no significant differences in RA patients for VZV-specific immune markers and cell-mediated immune responses following live VZV vaccination and subsequent tofacitinib treatment[17].

Demographics: Autoimmune Disease Cohorts

Used to treat over 80 different illnesses, most biologics are typically indicated for inflammatory bowel disease

Table 1. **Papers Deemed Fit for Inclusion in Final Analysis**

Reference	Objective	Design	Population	Study Population and Age	Intervention and Duration	Effect/Benefit	Recommendations	Other comments
Papadopoulou et al. (2013)	To compare existing recommendations on vaccination of adult patients with autoimmune rheumatic diseases (ARDs) in Europe, North America and Australia	Systematic Review	ARD patients in Europe, North America & Australia	N/A Age not explicitly mentioned; lowest age recommendations reviewed to were adults ≥ 50	Abatacept, rituximab, tocilizumab, others (but not specified). Duration of biologic therapy not mentioned either.	Not covered.	As of Feb 2014, EULAR and various European and Australian committees on immunisation practices recommend avoiding VZV vaccination in patients receiving any immunosuppressive therapy, due to a lack of literature on the subject.	General guidelines are not specific to the VZV vaccine. Paper notes that most recommendations are based on expert opinions.
Kopylov et al. (2012)	To determine the prevalence of seropositivity for VZV-IgG in immunomodulator-treated IBD patients (including anti-TNFs biologics)	Case-Control Study	IBD (CD & UC)	121; 86 of them were on anti-TNFs Study cohort mean age = 37 ±12.8	Infliximab, Adalimumab. Duration of therapy not mentioned; study only recorded whether biologics were used at time of serological testing.	Most (90.7%) patients using anti-TNF biologics were seropositive for the VZV IgG, suggesting that in this group, biologic therapy probably does not significantly interfere with VZV IgG production (thus, immunity). Negative history of VZV exposure was a poor predictor of VZV IgG seronegativity.	The authors recommend serological testing for HZV for all IBD patients regardless of exposure history prior to initiation of immunosuppressive therapy with subsequent vaccination of patients found to be seronegative. This questions the current European Crohn's and Colitis Organisation (ECCO) guidelines, which recommends VZV vaccine immunisation ≥3 weeks before immunomodulator therapy onset (preferably at IBD diagnosis), with a negative history of chickenpox, shingles, and VZV vaccination.	Prophylactic vaccination data not included, measured via self-questionnaire on prior exposure to VZV. This can include the VZV vaccine and/or history of VZV-related illnesses.
Furer et al. (2019)	To update the present EULAR recommendations for vaccination in patients with autoimmune inflammatory rheumatoid disease (AIIRD); including information on the incidence/prevalence of vaccine preventable infections and the efficacy, immunogenicity, and safety of vaccines provided to AIIRD patients undergoing immunosuppressive therapies	Systematic review	AIIRD patients (adults & paediatrics) on immunosuppressive therapy (glucocorticoids, conventional synthetic / biological / targeted synthetic DMARDs)	N/A	Includes, but not limited to: Infliximab, etanercept, adalimumab, certolizumab, golimumab abatacept, rituximab, secukinumab, ixekizumab, belimumab, anakinra, canakinumab. Duration of therapies not mentioned.	Not covered; see "Association between Vaccination for Herpes Zoster and Risk of Herpes Zoster Infection among Older Patients with Selected Immune-mediated Diseases"	EULAR recommends giving the live attenuated herpes zoster vaccine in mildly immunosuppressed AIIRD patients on a case-by-case basis and preferably only to those seropositive for VZV antibodies (to prevent primary varicella infection). EULAR notes that the newly licensed Shingrix vaccine which has been recommended for patients aged 50 and over (including immunosuppressed patients) may be the future preferred vaccine for AIIRD.	Findings were like the 2011 guidelines. All recommendations are still expert opinion. Also recommends that vaccines should be administered prior to planned immunosuppression; for B-cell specific therapy, ≥ 6 months after administration and 4 weeks before the next course.
Bye et al. (2016)	To identify 'at risk' IBD patients who may be targeted with a new adjuvant herpes zoster subunit vaccine	Retrospective cohort study	IBD (CD & UC)	N/A Mean age of those with VZV infection = 42 years (Range 21-81 years)	Anti-TNF biologic monotherapy and dual therapy, type unspecified. Time from initiating therapy to VZV infection ranged from 3 months to over 10 years	HZ infection is associated with increasing IBD severity and dual therapy (particularly with thiopurine). Of the 30 cases of HZ identified (25 CD, 5 UC)- none had previously received the HZ vaccine. Of this group, 10% were on anti-TNF monotherapy and 47% were on dual therapy (anti-TNF and thiopurine therapy [93%] or methotrexate [7%]). Age and length of immunosuppressive therapy do not seem to predict HZ infection.	Severe IBD patients and/or patients on dual-immunosuppressive therapy could benefit from immunisation with the new non-live, non-attenuated vaccine.	N/A

Abbreviations:

Table 2. **Papers Deemed Fit for Inclusion in Final Analysis (Cont.)**

Reference	Objective	Design	Population	Study Population and Age	Intervention and Duration	Effect/Benefit	Recommendations	Other comments
Cheetham et al. (2015)	To characterise the potential risk of disseminated VZV and herpes zoster post-administration of the zoster vaccine in patients who were currently receiving immunosuppressant medications	Retrospective cohort study	Not explicit; i.) Unclear what the (individual) indication was for patients using etanercept, ii.) Split participants into groups who had "inflammatory and immune-mediated conditions", which were broken down further by systems; autoimmune diseases may or may not have featured	145 (on etanercept); study looked at a total of 14,554 patients on various immunosuppression therapy (only etanercept was the relevant featured biologic therapy) N/A	Etanercept	No cases of disseminated VZV were identified with either current or remote usage of immunosuppressant drugs, including etanercept, in the 42-day window post-vaccination. Twenty-five cases of herpes zoster occurred during the 42-day window in the current-user group vs. 17 cases in the remote-user group; overall, this led to the conclusion that during the 42-day period, there is a modest increase in HZ risk in the group undergoing current immunosuppression vs. those with remote exposure. There is no specific discussion surrounding etanercept, so little conclusion can be drawn.	The findings support current recommendations that patients should withhold their immunosuppressant drugs for 4 weeks before zoster vaccine immunization. This is a general recommendation and is not/does not seem to be etanercept-specific.	N/A
Zhang et al. (2012)	To examine the link between HZ vaccination and HZ incidence within and beyond 42 days after vaccination in patients with selected autoimmune diseases in the context of biologics and other autoimmune therapies	Retrospective cohort study	RA, psoriasis, psoriatic arthritis, ankylosing spondylitis (AS), and/or IBD 463,541 patients; 18,683 received the vaccination	463,541 patients; 18,683 received the vaccination All >60y/o; mean age = 74 ± 8 years	Anti-TNF biologics (adalimumab, etanercept, infliximab, certolizumab, and golimumab) & non-TNF biologics (abatacept and rituximab)	No cases of varicella infection were documented within the 42 days post-vaccination and starting biologic therapy. Vaccination was associated with a decrease in VZV risk by 40% over a median 2-year follow-up period.	Unclear; questions current recommendations contraindicating the HZV vaccine in autoimmune patients receiving biological therapy.	Study concludes by suggesting the need for an RCT specifically addressing this topic.
Eberhardson et al. (2017)	To demonstrate the immunogenicity and safety of ZVIN in patients with RA, SLE, IBD, AS, MS, PsO, and other autoimmune diseases receiving immunosuppressive therapy who are receiving either biologic or non-biologic immunosuppressive therapy	Randomised control trial	AS, IBD (CD and UC), cerebral sarcoidosis, MS, psoriasis, psoriatic arthropathy, RA, SLE	354 for total study; 170 on biologics Adults ≥18	Not explicitly mentioned	This was not directly covered. The study indirectly measured (potential) HZV infection by measuring VZV-specific immune response markers. To this end, the inactivated VZV vaccine (ZVIN) was well tolerated and showed statistically significant VZV-specific immune responses approximately 28 days after the last dosage regime. Overall, the frequency of adverse events also decreased with subsequent vaccine doses.	The results may provide relevant information for this patient population who may benefit from the prevention of HZV and HZV-related complications. This is assuming further phase 3 studies confirming the efficacy, immunogenicity, and safety of the ZVIN vaccine are conducted.	Indirect measurement of immunosuppression by measuring gpELISA and IFN-γ ELISPOT responses in patient levels. However, although it meets the threshold this does not mean the vaccine is safe for usage.

(IBD), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE)[12,18]. This made reviewing the nuances in biologic immunosuppression of individual diseases difficult.

Despite this, most varicella-zosters vaccination in immunocompromised patients research pertained to IBD. Current European Crohn's and Colitis Organisation (ECCO) guidelines recommend VZV immunisation at least three weeks prior to commencing immunomodulatory therapy[9]. Despite some conflict on vaccine timing, all studies agreed that all IBD patients should undergo VZV-IgG serological testing prior to vaccination and that prophylactic vaccination does have a protective role, especially in seronegative patients.

For autoimmune rheumatic disease, the evidence is less clear. Our literature for these groups were all systematic reviews with no concrete data and recommended against vaccination[19], or only in mildly immunosuppressed patients[20]. If looking at vaccination without biologics, one study found that despite a higher absolute shingles incidence rate of 50% compared to healthy populations, the zoster vaccine was still protective[21]. Whilst HZ vaccination is likely useful for autoimmune rheumatic patients, its safety remains unclear when factoring in biologic therapy.

Demographics: Age

Amongst different age groups, current data recommends the *Shingrix* vaccine in adults over 50 years of age, including immunocompromised patients[16]. However, National Health Service (NHS) guidelines in the UK prohibit vaccination in patients older than 80 years of age[3], given data showing *Zostavax*'s efficacy wanes with age[21]; this is supported by another study demonstrating only 38% efficacy in immunocompetent patients over 70 years of age[22]. Presumably, this pertains to patients undergoing biologic therapies too, suggesting vaccination benefits do not outweigh the risks in older patients.

Timeline Indications

Timing of administration is important, given that the current *Zostavax* vaccine is live, and biologics suppress the immune response. Amongst those supporting vaccination, there is no consensus on when to start and/or stop biologics following vaccination. Recommendations on when biologics should begin post-vaccination range from three weeks to three months[9,11]; some instead recommend a case-by-case approach[23]. Other literature simply deferred to national guidelines on general vaccination procedures in immunocompromised patients[16].

There was even less literature on when to stop biologics if vaccinating later. This is problematic, as many patients have an ongoing disease, but no prior VZV exposure. The only paper that explicitly mentioned this recommended following current guidelines on varicella-zoster vaccination i.e., withholding immunosuppressant drugs for four weeks prior[13]. However, there was no reference made to stopping immunosuppressant medication prior to vaccination when recommencing treatment for IgG-seronegative VZV patients[9].

Current NHS guidelines state that patients receiving the live vaccination should wait for an established immune response before beginning immunosuppressive therapy[3]. This is supported by the Center for Disease Control (CDC) in the USA[24], which notes that waiting four weeks should be sufficient for viral live vaccines. However, they recommend against delaying therapy if this would worsen the underlying condition, as most live vaccines are attenuated; this should only occur following specialist consultation on a case-by-case basis[25].

Long-term, *Zostavax*'s efficacy wanes over time[26]. Different studies show different extents of change, but specific to autoimmune patients on biologics, it is most probable that *Zostavax* is protective for at least two years[10].

Live vs Non-live

The current VZV vaccine, a live attenuated vaccine known as *Zostavax*, has shown efficacy in immunocompromised patients by providing 70-90% immunity persisting for at least 10 years[9]. The European Alliance of Associations for Rheumatology vaccination recommendations for autoimmune inflammatory rheumatoid disease (AIIRD) patients have shown vaccine efficacy after 42 days on biologic disease-modifying antirheumatic drugs with no HZ incidence increase[16]. Interestingly, trials have shown a potential reduction of HZ risk by up to 70% in adults over 50 years of age, with lower HZ incidence after 2 years, regardless of immunosuppressive medications[16]. Current clinical practice considerations are based primarily on *Zostavax*. However, giving live-attenuated vaccines to immunosuppressed patients, especially those on low-dose biologics, remains controversial[12].

A newer non-live recombinant vaccine, *Shingrix*, is currently recommended for adults over 50 regardless of previous VZV vaccination and immune status. Whilst *Shingrix* is currently undergoing clinical trials and is not recommended for immunosuppressed patients[27], it is promising. If *Shingrix* was deemed effective, it would likely see larger usage in 'at-risk' patients. Additionally, it would be less likely to be contraindicated with concurrent biologic therapy.

Pharmacoeconomics

When evaluating the role of prophylactic vaccination, consideration can be given to cost-effectiveness. One US study found *Zostavax*'s cost-effectiveness ratio per QALY (Quality-Adjusted Life Year) gained between $\$25,379 - \$27,609$[28]. Incidentally, this is within the Irish healthcare system's incremental cost-effectiveness ratio of $€20,000 - €45,000$[29]. This suggests that prophylactic vaccination is economically viable, implying a role to play in clinical practice assuming safety can be definitively established.

Limitations

This review's conclusion was limited by the few available studies; most existing literature reviewed either HZ infections and autoimmune suppression (mainly with non-biologic therapy), or prophylactic vaccination in autoimmune patients, without combining all three. This made it harder to summarise our findings. In making our judgement, we had to extrapolate indirect

literature on this subject.

One possibility for improvement would be to expand the criteria, such as including data prior to the year 2000 as well as studies on paediatric patients. Studying prophylactic vaccinations of other opportunistic diseases in similar autoimmune cohorts could also reveal more about the general safety and efficacy of vaccination prior to biologic therapy. Although not specific, this could yield a clearer understanding of the vaccination-biologics interaction, which could help inform us, given the limited findings we have.

Conclusion

We believe there is a definite role for HZ vaccination in prophylaxis against shingles in autoimmune patients undergoing biologic therapy. Although some suggest otherwise, we recommend erring on caution and following national vaccination guidelines as to when and how to vaccinate; case-by-case exceptions ought to be considered too. However, further research is required, particularly regarding specific autoimmune conditions and biologic agents as well as *Shingrix*, to improve the formulation of clinical guidelines on the use of the HZ vaccine in the immunocompromised[30].◂

Declarations

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW

Should Antibiotic Treatment or Surgery be First-Line for Acute Uncomplicated Appendicitis? A Systematic Review

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Abstract

Background: Acute appendicitis is the sudden inflammation of the vermiform appendix. It is the most common abdominal emergency. Appendicectomy, performed open or laparoscopically, has been the mainstay in the treatment of uncomplicated appendicitis. This technique has numerous advantages, namely the impossibility of recurrence. The use of antibiotic-only treatment for acute appendicitis has associated benefits and risks. Procedure specific complications of appendicectomy such as wound infections and incisional hernias can be avoided. This treatment option is gaining popularity amongst patients due to these potential benefits.

Aim: To determine whether appendicectomy or antibiotic treatment is superior as first-line treatment for acute uncomplicated appendicitis.

Methods: Several databases were searched to identify published literature relevant to this field of study. The databases used were Cochrane Library, Medline, and PubMed. Articles that reported on trials utilising antibiotics or surgery for the treatment of acute uncomplicated appendicitis were selected and further screened to ensure that they were randomised controlled trials, 'English full-text articles' that were published in peer-reviewed journals from the years 2010-2021. Other types of research studies such as case reports and meta-analyses alongside studies that involved participants aged 16 or younger were excluded.

Results: The initial search identified a total of 124 studies. Of these studies, 47 duplicates were excluded and the remaining 77 underwent title and abstract screening. From this screening, 20 studies were identified for a full-text study, which led to the inclusion of 10 papers for this review. On review of these studies, all 10 of these random controlled trials compared the outcomes between antibiotics and surgical intervention for the treatment of acute uncomplicated appendicitis.

Conclusions: There is insufficient evidence to suggest that antibiotic therapy should replace appendicectomy as first-line treatment for acute uncomplicated appendicitis. However, while antibiotic therapy failed to meet the criteria for superiority compared with appendicectomy in several major studies, consideration should be given to the other advantages of antibiotic therapy, especially in resource-poor countries, where it can be used to free up hospital beds for emergencies that warrant greater care and intervention.

Keywords: Acute uncomplicated appendicitis, Appendicectomy, Antibiotic therapy

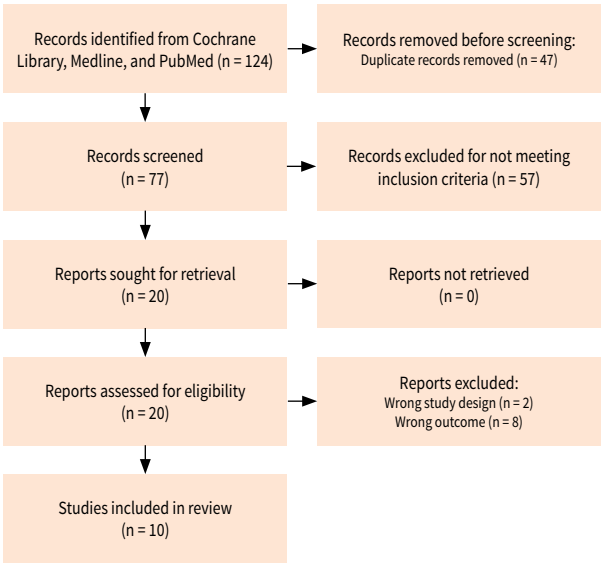
Introduction

Appendicitis is the sudden inflammation of the vermiform appendix. It is the most common abdominal emergency, accounting for an estimated 17.7 million cases and over 33,400 deaths in 2019[1]. The incidence of appendicitis, although stable in most western countries, is suggested to be rising rapidly in newly industrialised countries, underscoring the importance of developing novel treatments[2].

Appendicectomy, performed open or laparoscopically, has long been the mainstay in the treatment of uncomplicated acute appendicitis. First performed in the late 19th century, this technique is described to have numerous advantages, namely the impossibility of recurrence[3]. It is considered to be a relatively safe procedure with a mortality rate of 0.8 per 1000 for acute uncomplicated appendicitis[4]. However, the incidence of postoperative complications such as wound infections and the formation of intra-abdominal masses have been reported in as high as 40% of all appendicectomy patients[5]. Furthermore, surgical intervention may not be feasible due to patient co-morbidities, or a patient's preferences given the assumption of higher associated costs and longer duration of absence from work[6].

The use of antibiotics-only treatment for acute appendicitis was first described by Harrison in 1953 and

Figure 1. **PRISMA Chart Highlighting Inclusion/Exclusion of Articles at Different Stages of the Review**



has associated benefits and risks[7]. Procedure specific complications of appendicectomy such as wound infections or incisional hernias can be avoided, with the potential trade-offs being higher rates of recurrence and associated readmission for appendicectomy[8]. Given the potential benefits, it is no surprise that this treatment option is gaining popularity amongst patients, with a 2021 survey finding that 49.2% of patients preferred antibiotic-only treatment for acute uncomplicated appendicitis[9]. Through critical analysis of several existing studies, this systematic review will contribute further insight into the outcomes of antibiotic treatment for uncomplicated acute appendicitis in comparison to surgery and draw firmer conclusions for their use. Its implications may also have potentially life-saving role in resource poor countries.

Methods

Several databases, including Cochrane Library, Medline, and PubMed, were used because of their relevance to this field of study. The search terms used in each database were as follows: (antibiotics) AND (surgery OR appendicectomy) AND (acute uncomplicated appendicitis).

In this systematic review, we only included randomised controlled trials (RCTs) that investigated the effects of antibiotic treatment or surgery for first-line treatment of acute uncomplicated appendicitis. Other types of research studies such as case reports and meta-analyses alongside studies that involved participants aged 16 or younger were excluded. Only 'English full-text articles' published in peer-reviewed journals from the years 2010-2021 were included.

In total, 124 papers were obtained through the initial search and imported into Covidence for a thorough screening process comprising three major components. Every article in each component was screened by two independent reviewers to ensure eligibility according to the predetermined criteria. Any disagreements on an article were resolved by a third independent reviewer.

Results

The initial search identified a total of 124 studies. Of these studies, 47 duplicates were excluded and the remaining 77 underwent a title and abstract screening. From this screening, 20 studies were identified for a full-text analysis, which led to the inclusion of 10 papers for this review. On review of these studies, we identified 10 RCTs which met our inclusion criteria. The remaining articles were excluded as they were either not published yet, followed the wrong patient population or were the wrong study design. **Figure 1** details the number of studies that were included/excluded at each stage of the review.

We selected RCTs because they are the highest quality of evidence. Nevertheless, we recognise that all studies have a risk of bias. Regarding the 10 studies that were included within our review, they are all RCTs that compared the outcomes between antibiotics and surgical intervention for the treatment of acute uncomplicated appendicitis. **Tables 1–2** summarises the key data in each study.

Discussion

This review compared antibiotic treatment and appendicectomy for acute uncomplicated appendicitis by examining the recurrence rate (only relevant in the antibiotics group), length of stay, quality of life, complication rate, acceptance of each treatment, and cost.

Advantages of Antibiotics vs. Surgery

Antibiotics treatment had several major advantages, most notably significantly lower overall complication rates compared to appendicectomy[6,8,12].

Appendicectomy does involve a risk of postoperative complications in approximately 2-23% of patients, with 3% of patients developing adhesions related to the appendicectomy leading to hospital readmission in the following 10 years[14]. Salminen et al. described complications like surgical site infection, incisional hernias, abdominal or incisional pain, or obstructive symptoms in 24.4% of the surgical group and 6.5% in the antibiotics group within 5 years[10]. Thus, in terms of the complication rate, antibiotics may be superior to appendicectomies. In the Antibiotic Therapy versus Appendectomy for the treatment of Uncomplicated Acute Appendicitis (APPAC) trial, the commonest cause of morbidity in the appendicectomy group was related to wound infections.

Due to significant investments of time, cost, and training involved, laparoscopic appendicectomies are more common in areas that are able to afford these investments. This study suggests antibiotics may be more useful in resource-limited areas[10]. Antibiotic treatment was also associated with significantly lower total costs, in terms of overall social costs and sick leave (3.6 days shorter)[10,11,13], and even after adjusting for age and sex[13].

According to Prechal et al. there is a high level of acceptance of antibiotic treatment among acute

Table 1. **Studies included in the review**

Reference	Study Design	Number of Participants	Primary Outcome(s)	Secondary Outcome(s)	Results (Group A = Cohort receiving surgery Group B = Cohort receiving antibiotics)
(2018)[16]	RCT	45	The primary outcome was the success rate (resolution of symptoms within 2 weeks and no need for further treatments).	Secondary outcomes were complication rate; negative appendectomy rate (only in surgical arm); and long-term outcomes within a year as recurrence.	In group A, all participants obtained the primary outcome (success), however there were negative secondary outcomes which were noted for five patients; two of which presented with negative appendectomies and the remaining three with wound infections. On the contrary, within group B, the treatment failed for 16.8% of the patients. Furthermore, one of the patients experienced relapse at 30 days.
(2020)[12]	RCT	130	Outcomes such as hospital stay, complications, recurrence within one year and patient's satisfaction were examined.	Outcomes such as hospital stay, complications, recurrence within one year and patient's satisfaction were examined.	Regarding hospital stay, Group A had an average stay of 2.02 +/- 0.85 days, versus 6.28 +/- 2.44 days in group B. Furthermore in regards to recurrence within 1 year, group A was found to be 1.54% versus group B which was 27.69%. Additionally, in group A, 96.92% of patients were satisfied, compared to 67.64% patients in group B. However, regarding complications, group B had a 3.08% complication rate when compared to 15.38% in group A.
(2017)[17]	RCT	227	Outcomes that were examined included duration of pain (in hours), duration of hospital stay, conversion to surgery, duration of days for absence from work, and negative appendectomies.	N/A	The duration of pain and analgesic consumption was much higher in group B in comparison to group A for the first 2 days after surgery. However, the intensity of pain started to decrease after 2 days in group A and 4 days in group B. There were no noted differences in the 1 month follow up. Furthermore, the duration of hospital stay was longer for group B than group A. Additionally, the mean cost therapy was more expensive in group B when compared to group A. On the other hand, group A experienced much more infections than group B.
(2021)[11]	RCT	186	The primary end-point for the trial evaluated the success rate of antibiotic treatment only for acute uncomplicated appendicitis at 1-year follow-up. In the operative arm, the primary endpoint was defined as successful appendectomy, which was expected to be 100%.	Secondary end-points included a comparison of quality of life, cost and length of stay between the 2 study groups.	There was a significantly better EQ-VAS quality of life score in group A compared with group B at 3 months, 94.3 vs 91.0, and at 12 months 94.5 vs 90.4. The accumulated 12-month sickness days was 3.6 days shorter for the group B when compared to group A, 5.3 vs 8.9 days. The mean length of stay in hospital for both groups was not significantly different, 2.3 vs 2.8 days. However, the mean total cost was significantly higher for group A in comparison to group B, €4,816 vs €3,077.
(2017)[15]	RCT	124	The primary endpoint was treatment success, defined as no secondary appendectomy during follow-up and no recurrent appendicitis treated conservatively (primary antibiotic group), or successful appendectomy, defined as performed appendectomy (primary appendectomy group).	Secondary endpoints were duration of hospitalization, pain intensity (measured on a numeric rating scale, NRS), incidence and type of complications (according to the Clavien-Dindo classification), and duration of absence from work (only in the primary antibiotic group).	Treatment success at 1 year was 77.1% in group B and 100% for Group A. The initial hospital stay was significantly shorter in group B compared to group A, with a mean of 3.6 vs. 4.8 days. After 1 year, the cumulative hospital stay was not different between groups.

Table 2. **Studies included in the review (Cont.)**

Reference	Study Design	Number of Participants	Primary Outcome(s)	Secondary Outcome(s)	Results (Group A = Cohort receiving surgery Group B = Cohort receiving antibiotics)
(2015)[8]	RCT	530	The primary end point for patients in the antibiotic group was resolution of acute appendicitis, resulting in discharge from the hospital without the need for surgical intervention and no recurrent appendicitis during a minimum follow-up of 1 year (treatment efficacy). Treatment success in the appendectomy group was defined as a patient successfully undergoing an appendectomy.	Secondary end points included overall post intervention complications, late recurrence (after 1 year) of acute appendicitis after conservative treatment, length of hospital stay and the amount of sick leave used by the patient, post intervention pain scores (VAS score range, 0-10; a score of 0 indicates no pain and 10 indicates the worst possible pain), and the use of pain medication. Post Intervention complications included clinical wound infection (surgical site infection) occurring within 30 days after the operative procedure as diagnosed by a surgeon or with a positive bacterial culture, 19 other general postoperative complications (eg, pneumonia), adverse effects of the antibiotic treatment (eg, diarrhea), incisional hernia, possible adhesion-related problems (eg, bowel obstruction), and persistent abdominal or incisional pain.	In Group A here was a success rate of 99.6%, however in group B 27.3% were forced to undergo appendectomy within 1 year of initial presentation for appendicitis.
(2017)[18]	RCT	530	The primary endpoint in the antibiotic group was resolution of acute appendicitis, resulting in discharge from the hospital without the need for surgical intervention and absence of recurrent appendicitis during 1 year. In the operative group, treatment success was defined as successful appendectomy.	Secondary outcomes included overall post intervention complications, late recurrence (after 1 year) of acute appendicitis following conservative treatment, length of hospital stay and duration of sick leave, post intervention pain scores and use of pain medication. The present study focuses on all secondary outcomes with an effect on the overall societal costs in the context of evaluating the economic effects of both randomized treatment options with a 1-year fellow-up.	In group A, the overall societal costs were 1.6 times higher than those in group B. Additionally, those in group A were prescribed significantly more sick leave than those in group B, 17.0 versus 9.2 days respectively. When the age and sex of the patient as well as the hospital were controlled for simultaneously, the operative treatment generated significantly more costs in all models.
(2018)[10]	RCT	530	N/A	Pre-specified secondary end points reported at 5-year follow-up included late (after 1 year) appendicitis recurrence after antibiotic treatment, complications, length of hospital stay, and sick leave.	The cumulative incidence of appendicitis recurrence was 34.0% at 3 years, and 37.1% at 5 years. Of the 85 patients in group B who subsequently underwent appendectomy for recurrent appendicitis, 76 had uncomplicated appendicitis, 2 had complicated appendicitis, and 7 did not have appendicitis. At 5 years, the overall complication rate was 24.4% in group B. There was no difference between groups for length of hospital stay, but there was a significant difference in sick leave (11 days more for group A).
(2020)[13]	RCT	530	N/A	Post-hoc secondary end points of post-intervention QOL (EQ-5D-5L) and patient satisfaction and treatment preference were evaluated.	The quality of life between both groups was similar. Patients in group A were more satisfied in the treatment than patients in group B (68% very satisfied, 21% satisfied, 6% indifferent, 4% unsatisfied, and 1% very unsatisfied in group A and 53% very satisfied, 21% satisfied, 13% indifferent, 7% unsatisfied, and 6% very unsatisfied in group B). There was no difference in patient satisfaction after successful antibiotic treatment compared with appendectomy.
(2011)[14]	RCT	243	The primary binary endpoint was the occurrence of peritonitis within 30 days of initial treatment. Appendectomy done within 30 days of treatment initiation in the antibiotic group was not a primary endpoint if complicated appendicitis with peritonitis was not identified at surgery.	Secondary endpoints were the number of days with a post intervention visual-analogue-scale pain score >_ 4 (on a 0-10 scale), 15 lengths of hospital stay and absence from work (total days including any additional hospital stays), incidence of complications other than peritonitis within 1 year (postoperative wound abscess, incisional hernia, adhesive occlusion), and recurrence of appendicitis after antibiotic treatment (appendectomy done between 30 days and 1 year of follow-up, with a confirmed diagnosis of appendicitis).	30-day post-intervention peritonitis was significantly more frequent in group B than group B, 8 vs 2% respectively.

uncomplicated appendicitis patients and only 1 patient in this study opted for surgical treatment after evidence-based disclosure of the advantages and disadvantages of both treatments[15]. Additionally, studies exist that show that uncomplicated appendicitis could resolve in the first few days of antibiotic treatment, questioning the need for invasive surgery in this cohort of patients[10].

Disadvantages of Antibiotics vs. Surgery

The major downside of antibiotic treatment that is circumvented with appendicectomy is the possibility of appendicitis recurrence, as evidenced by many studies[8,10,11]. The rate for secondary appendicectomy post-antibiotic treatment was 27.3% within 1 year and was 39.1% within 5 years in the APPAC trial[10]. Antibiotics were also associated with longer hospital stays[8,12,13], though possibly due to predefined protocols in place to ensure patient safety.

In the 2011 RCT by Vons et al. comparing amoxicillin plus clavulanic acid with appendicectomy, antibiotic treatment failed to meet the criteria for non-inferiority to emergency appendicectomy for acute uncomplicated appendicitis due to significantly higher rates of 30-day post-intervention peritonitis in the antibiotics group (8%) compared to the appendicectomy group (2%)[14]. However, this may be due to many reasons, including errors during inclusion and randomisation, difficulty in differentiating between complicated and uncomplicated appendicitis even with multiple-detector CT scans, and antibiotic resistance among the causative bacteria1[4]. Importantly, the presence of appendicoliths was associated with significantly increased risk of complicated appendicitis and failure of antibiotic treatment, and on the exclusion of the subgroup of patients with appendicoliths (which was not in their exclusion criteria), results showed no significant difference in 30-day post-intervention peritonitis rates between the antibiotics and surgery groups[14].

Furthermore, Sippola et al. concluded that long-term patient quality of life was similar for both interventions, but patients who had antibiotic therapy and later had appendicectomy were less satisfied and 33% of these patients would not choose antibiotics as their primary treatment again[13].

Thus antibiotic therapy may be inferior to appendicectomy as first-line treatment of acute uncomplicated appendicitis in terms of appendicitis remission, post-intervention peritonitis rates and long-term patient satisfaction.

Strengths, Limitations and Biases

A strength of this review is the qualitative approach in analysing existing literature due to the heterogeneity between the studies in terms of their procedures, methods, criteria, outcomes, and so on.

However, there are several limitations in the studies reviewed. There was difficulty in recruiting patients in several studies[8,16], possibly due to open appendicectomy being the mainstay of treatment[8], which potentially reduced the power of the studies and made them inadequate to support the primary and secondary outcomes. Additionally, given that acute appendicitis, especially if complicated, is considered a medical emergency, this might have posed difficulties during the research process[16].

Another limitation is the possible bias that may be introduced if all patients with suspected complicated appendicitis underwent primary appendicectomy, such as in the study by Prechal 2019[15]. Also, there was difficulty in performing a randomised double-blinded placebo-controlled trial in some studies like the APPAC trial, where they were unable to blind participants, clinicians, and research assessors[8].

Furthermore, the choice of antibiotics differed between studies, some of which may not be the most appropriate for the patient. Amoxicillin and clavulanic acid used in the trial by Vons et al.[14] only provide limited coverage for E. coli, a major part of gut flora, and the efficacy of antibiotics may also be undermined by the rising incidences of resistant bacteria[8].

Conclusion

Antibiotic therapy as a first-line treatment option over appendicectomy in acute uncomplicated appendicitis has many tangible benefits for patients and the healthcare system. It also has some disadvantages compared to appendicectomy. The advantages include shorter initial hospital stays and significantly lower total costs, in terms of overall societal cost and sick leave. Antibiotic therapy was also associated with significantly lower rates of complications post-intervention. However, antibiotic therapy was also associated with a higher rate of recurrence and significantly higher rates of peritonitis post-intervention. Although antibiotic treatment failed to meet the criteria for noninferiority compared with appendicectomy in several major studies[8], consideration should still be given to the other advantages of antibiotic use, especially in resource-poor countries, to free up hospital beds for emergencies that warrant greater care and intervention, and in the cohort of patients with uncomplicated appendicitis who may not require surgical intervention as much as those with complicated appendicitis.

Further studies may be warranted to identify the best antibiotic regimens in the treatment of acute uncomplicated appendicitis, as well as further stratification of patients to be channelled through different treatment regimens for optimal outcomes. Depending on their presentation, some patient cohorts may not need invasive interventions like appendicectomies, some may benefit from different antibiotic combinations, and some may derive the greatest benefit from surgical intervention.◂

Declarations

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Liz Birdie Ong Shi Yun is a section editor with the TSMJ. This article was anonymised following submission and subsequently reviewed and accepted by an independent team of editors and peer reviewers as per the TSMJ's peer review and article acceptance protocol.

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LITERATURE REVIEW

Comparative Investigation of the Reasons Propagating Maternal Mortality in Sweden, India and Rwanda

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Abstract

Background: Haemorrhage, sepsis, and hypertensive disorders have been identified as the leading causes of maternal mortality worldwide. The majority of maternal deaths occur in developing countries and the majority are preventable. Despite the advent of technologies and scientific progress that have significantly reduced maternal mortality globally, developing countries disproportionately represent the majority of maternal deaths. Identifying and comparing countries with different maternal mortality rates is important because it provides an opportunity to reduce maternal death by understanding *why* and *how* we can learn from countries that perform well to inform and prioritize health policies, programmes and funding.

Objectives: First, to identify the leading causes of maternal mortality in Sweden, India and Rwanda. Second, to identify the factors contributing to maternal death and the strategies used by said countries to address and/or decrease maternal mortality. Third, to identify strategies that could be adopted to reduce maternal death.

Methods: International databases such as the World Health Organisation, World Bank, Population Reference Bureau, World Poverty Clock and the National Eclampsia Registry were used to identify key metrics. A scoping review was conducted in databases (PubMed Medline, Embase, Pubmed, Cochrane Library and Scopus) on quantitative and qualitative studies conducted in Sweden, Rwanda and India after 2000. We also searched for articles in search engines (Google Scholar and Google).

Results: The research highlights that socioeconomic and demographic barriers contribute to the higher rates of maternal mortality seen in developing countries. The implementation of standardised guidelines for the use of drugs, investment in community-led care and the implementation of a midwifery model could play a key role in addressing maternal mortality in developing countries.

Conclusion: It is understood that a multitude of factors contribute to maternal mortality. These perpetuating reasons are often closely interlinked in a complex relationship with the country's socioeconomic and political conditions. Therefore, in order to decrease maternal mortality rates in developing countries especially, the focus needs to be diverted towards bridging the gap between the urban and rural populations, and equipping mothers with accessible, affordable, and high-quality healthcare.

Keywords: Maternal Mortality, Sweden, India, Rwanda

Introduction

Maternal mortality is defined by the World Health Organisation (WHO) as the "annual number of female deaths from any cause related to or aggravated by pregnancy or its management (excluding accidental or incidental causes) during pregnancy and childbirth or within 42 days of termination of pregnancy" [1]. The three major causes of maternal mortality are 1) haemorrhage, such as from postpartum haemorrhage (PPH), 2) sepsis and 3) hypertensive disorders, such as gestational hypertension, preeclampsia (PEC), and eclampsia (EC). PPH refers to excessive bleeding after giving birth while maternal sepsis can develop during pregnancy or after labour due to an infection. Eclampsia refers to one or more seizures and/or an unexplained coma before, during and after birth, and is considered to be a complication of severe preeclampsia[2].

Sweden

According to the 2013 State of World Population report, Sweden has a maternal mortality rate (MMR) of 4 per 100,000, making it one of the lowest in the world[3]. The Swedish National Board of Health and Welfare's statistical database indicates that from 2010–2019, there were only an average of 0.075 deaths related to pregnancy, childbirth, or puerperium per 100,000 women per year, equivalent to an average of 3.7 total deaths per year[4]. While the 2019 data reported only 4 deaths related to

pregnancy, childbirth, and puerperium, there were still 54 deaths that year related to perinatal conditions, and these numbers could be higher as cases may have been underreported by hospitals or unaccounted for if they did not occur under obstetric care[5]. The large decline in Sweden's maternal mortality rates since the early 1900s has been largely attributed to the introduction of midwives and changes in reproductive health policy[6].

An external review conducted between 2007–2017 found that the leading causes of maternal death in Sweden were PEC, sepsis, and PPH[7]. Over the 11 year span, 10 women died from PEC and 8 died from infections. 7 of the 10 women that died from PEC died from intracranial haemorrhage (a severe and life-threatening complication of PEC). The review found that most maternal deaths due to PEC were preventable if diagnosed and treated earlier with antihypertensive medications[7]. The report recommended that Swedish healthcare providers closely monitor patients' blood pressure and immediately treat a systolic blood pressure greater than 160 mmHg with antihypertensives[7]. It is important to note that obstetric bleeding contributes to approximately 15% of the direct causes of maternal mortality in Sweden[7].

Antenatal Care

Created in 2013, the Swedish Pregnancy Register—formed through merging other maternal health registers—tracks and assesses the population, and is used to inform recommendations for perinatal care[8]. Sweden recommends that antenatal visits begin at 9 weeks gestation and receive a minimum of 8 antenatal visits throughout the course of their pregnancy[8]. All pregnant women are offered a second trimester ultrasound scan and a follow-up visit 8–12 weeks postpartum[8]. The second trimester ultrasound scan is significant because it can identify conditions such as placenta previa and vasa previa, which can lead to torrential obstetric haemorrhage, a major cause of maternal mortality in developing nations that lack healthcare resources[9].

Midwife Care

The role of midwives in women's care grew in Sweden in the 19th century, drastically reducing its maternal mortality rate[6]. The midwife licensure in Sweden is highly regulated and a practitioner must first graduate from a midwife educational program that requires 90 advanced-level credits[10]. Upon successful completion of this program, the Swedish National Board of Health and Welfare grants a license to practice[10]. A midwife must show competency in the field of reproductive, perinatal, and sexual health by demonstrating knowledge and skills within several competency areas[10]. The competency skills listed by the Swedish Association of Midwives include tending to the patient's "psychological, physical, and emotional needs of the patient seeking healthcare" by coordinating patient care with other members of the healthcare team; handling healthcare-technical activities/equipment; participating in research to enhance healthcare quality; promoting healthy choices from a lifestyle perspective and a reproductive and sexual health perspective; and managing normal and complicated pregnancy, labour, childbirth, and the postnatal period independently, including vacuum-assisted or forceps-assisted birth[10]. A midwife is also licensed to prescribe contraception and provide care for spontaneous or induced abortions regardless of circumstances[10]. This is important because it reduces maternal death due to unsafe abortions and improves accessibility and acceptability of healthcare services.

Sexual and Reproductive Rights

Sweden's welfare model and national response to sexual reproductive and health rights aims to address the societal and social inequities underpinning poor public health outcomes[11]. This open, non-judgemental approach improves healthcare outcomes by focusing on the rights of individuals to make decisions regarding their own sexual and reproductive health and to access services that support that[11]. Portugal implemented a similar strategy in 1970 when its maternal mortality rate was around 47.7 per 100,000 live births[12]. The policy reforms that were implemented improved the quality and accessibility of antenatal and obstetric care, and included sexual health education, access to safe abortion, and free contraception[12]. The implementation contributed to a subsequent decrease in maternal mortality to 6.9 per 100,000 live births by 2016[12]. Improving access to sexual and reproductive health services is integral to improving maternal mortality rates.

The Swedish government announced in 2005 that women's sexual and reproductive rights would be prioritized as a means of addressing maternal mortality, neonatal care, gender equality, sex education, right to contraception, safe abortion practices and HIV/AIDS initiatives[6]. Protection of women's sexual and reproductive rights in Sweden has contributed to overall maternal well-being. The country has built antenatal, paediatric, and school health services that have displayed positive health outcomes in young individuals[6]. The efforts of these programs have generated notable improvement in the health of both new mothers and their babies in Sweden, significantly contributing to the low maternal mortality rates seen in the country[6].

India

India's mortality rate is 113 per 100,000—on the spectrum of maternal mortality rates, India is considered to have a moderate MMR and its reduction remains a challenge[13]. Although India has made considerable progress in enhancing its reproductive care, the MMR does not yet satisfy the United Nations Millennium Development Goal threshold of 109 deaths per 100,000 live births[13]. Although conditions are improving and rates of haemorrhage, sepsis, and preeclampsia are decreasing, a wide range of unaddressed socioeconomic and cultural factors remain large contributors to the country's MMR.

Sepsis

The high rates of maternal death due to sepsis highlight the socioeconomic framework that maternal mortality operates within. A by-product of poverty is the lack of safe and hygienic settings and practices to carry

out deliveries and abortions which contributes to the precipitation of life-threatening sepsis. A study carried out at Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi from January to June 2016 observed 33 women with severe maternal sepsis[14]. During the study period, there were 14,550 admissions to the Obstetrics and Gynaecology Department, 366 (2.5%) of which were due to puerperal sepsis. Although this would seem relatively manageable in a high-resource setting, ultimately only 73% of these women were admitted into an intensive care unit (ICU) while 18% did not receive ICU care due to a lack of resources[14]. As a result, 85% of the 336 women with puerperal sepsis died[14]. The study identified that the considerable delay in diagnosis by the physician was the main contributing factor associated with severe sepsis[14]. On further observation by the research team, it was discovered that most of the women were admitted with no prior supervision, having delivered at home or in outside hospitals, hailing mostly from lower socioeconomic backgrounds[14]. Given that many of these women came from underprivileged backgrounds, this study highlights the impact of poverty on maternal mortality. As reported by the Population Reference Bureau, the lack of knowledge about obstetric complications, the lack of adequate transport connecting rural areas to urban centres, and the lack of access to adequate healthcare in rural settings perpetuates the high maternal mortality rates highlighted by the study above[15].

Poverty

A statement published by the WHO in 2016 highlighted the dire reality of women living in poverty in India, reporting that nearly 5 women die every hour in India from complications related to childbirth[16, 17]. It was reported that PPH accounts for 19.9% of maternal deaths, estimated to represent 78,000 to 117,000 maternal deaths in India[16, 17]. In the North-East state of Manipur, it has been reported that out of the 94 maternal deaths per 102,525 live births during the years 2000–2010, 53.19% died due to haemorrhage, accounting for about 21.27% of total deaths[18]. Rates of maternal mortality throughout the country are unequally distributed, ranging from as high as 300 per 100,000 live births in the state of Assam to as low as 61 per 100,000 live births in Kerala, a comparatively more affluent state[16, 17]. Assam has the highest MMR of all India's states, with three-quarters of these deaths occurring amongst tea plantation workers[19]. These workers lack access to basic services such as schools, healthcare, safe drinking water, and latrines[19]. Additionally, many of these tea gardens are far from hospitals making maternal healthcare inaccessible, a factor which drives unsafe home deliveries[19]. Therefore, in order to reduce the MMR and treat easily preventable causes of death such as PPH, the country needs to bridge internal socioeconomic gaps present within regions of India.

Eclampsia

Eclampsia is estimated to contribute to 5% of maternal deaths in India, with an average incidence of 1.9%[20]. The rates of maternal mortality have been declining for several reasons, such as the administration of magnesium sulphate postnatally to women who are at risk of developing eclamptic seizures and the improved management of their care in ICU and tertiary health care facilities[21]. However, there has been no decrease in the incidence of eclampsia over the decades and studies strongly suggest this is due to lost opportunities for prevention[21,20]. A cross-sectional study on the prevalence of eclampsia in India has shown a 20-fold difference in eclampsia rates between the states with the lowest and highest prevalence[22].

Antenatal care has been identified as the single most important factor for reducing maternal mortality in India[20], yet studies reviewing cases of maternal mortality in tertiary hospitals show that a majority of women (57.6–92.3%) have not attended an antenatal visit[23–25]. According to the Federation of Obstetric and Gynaecological Societies of India's National Eclampsia Registry (NER), of those that do register for antenatal care, a majority do so late in the course of pregnancy, with only 12.54% booking in the first trimester. Since 76.78% of eclampsia occurs antenatally[20], early identification and management of women at high risk of eclampsia is necessary for its prevention. Two other major factors contributing to high mortality rates secondary to eclampsia are 1) limited access to healthcare services and 2) magnesium sulphate scarcity. A majority of rural patients take 1–4 hours to access hospital care from the first convulsive episode and 40.5% of patients present after having 1–4 convulsions[20]. This highlights the need for better healthcare access and improved primary care management of eclampsia, including the administration of magnesium sulphate. Although the WHO recommends that magnesium sulphate "should be available in all health-care facilities throughout the healthcare system"[26], NER data shows that only 44% of women with eclampsia received magnesium sulphate prior to hospital admission and this can in part be explained by poor supply; some states have reported up to 61% of secondary and tertiary facilities with no magnesium sulphate stock[27]. In addition, there is a lack of standardized guidelines and training on magnesium sulphate administration resulting in variable and inadequate eclampsia treatment[28,29]. In order to tackle the persistently high incidence of eclampsia in India, there is a need for standardization of pre-eclampsia and eclampsia care as well as improvement in care access, training and focus on reducing socioeconomic inequalities that predispose to maternal mortality.

A considerable amount of the Indian population is below the poverty line with 90% of the population living in rural and semi-urban communities where health facilities are not accessible[30]. It is important to note that most health services in India are concentrated in urban medical centres and it is difficult for the rural population to utilize urban health care due to financial barriers. Therefore, the majority of abortions are performed by unqualified, untrained practitioners and home deliveries without medical support are also common, factors which significantly increase the risk of maternal

mortality[30]. Additionally, many women at the grassroots level remain uninformed about the use of contraception and safe reproductive practices. The lack of awareness of safe medical practices therefore plays a prominent role in propagating maternal mortality rates.

Reduction in Maternal Mortality

Despite all obstacles, India has nonetheless managed to achieve success in reducing maternal mortality. In a statement for the WHO, Dr Poonam Khetrapal Singh, WHO Regional Director for South-East Asia, commended India's effort to increase access to quality maternal health services, stating that since 2005, essential maternal health services have doubled[31]. Furthermore, Dr Singh stated: "State-subsidized demand-side financing like the Janani Shishu Suraksha Karyakram [which organizes free transport and no-expense delivery for women delivering in public health institutions] ... has largely closed the urban-rural divide traditionally seen in institutional births"[31]. Additionally, India has placed emphasis on addressing social determinants of maternal health—such as education—with now more than 68% of women being able to read and write[31]. All these steps have enabled women to take control of their reproductive rights and make decisions in favour of their health while bridging the gap between urban and rural areas, enabling equality and better access to healthcare.

Rwanda

In comparison to Sweden and India, Rwanda has been recognized to have one of the highest maternal death rates in the world. About 70% of recorded deaths are due to direct causes[32]. The majority of studies in Rwanda report data from the University Teaching Hospital of Kigali (CHUK), Rwanda's largest healthcare centre.

Sepsis

Sepsis and severe systemic infection are commonly reported as the leading cause of maternal death in Rwandan hospitals, and over one-quarter of these deaths are considered preventable[33]. Between 2012–2013, 77% of patients with postpartum infection suffered severe morbidity and mortality[34]. Inconsistent prophylactic antibiotic use prior to operative obstetric procedures likely contributes to these findings. In a rural hospital in Rwanda, it was found that less than half of all women who became septic following caesarean section received prophylactic antibiotics intraoperatively[34]. Facility-specific factors are also likely to play a role in the development of sepsis in these women. For instance, healthcare workers providing care in Rwandan hospitals may lack sufficient education to provide quality care. A 2011 survey of obstetric care providers in the Bugesera District demonstrated that a majority of providers felt they lacked appropriate knowledge, skills, and confidence in safe motherhood practices, and many failed knowledge assessments of general obstetric knowledge[35]. The lack of infrastructure and resources in healthcare facilities in Rwanda may also prevent safe obstetric practices in Rwandan hospitals as well. It has been found that less than one-third of healthcare facilities had year-round water access, and only 58% had functioning latrines[36]. This lack of access to water and sanitation has significant implications for infection control and infection-related mortality.

Postpartum Haemorrhage

Between 20–39% of maternal mortality cases in Rwanda are due to postpartum bleeding[37,38]. While the cause is multifactorial, both the recent genocide—which greatly limited resources—and an increasing population play a large role[39]. A significant proportion of the population deliver in tertiary care centres with rural skilled birth attendants. In postpartum simulations, these workers scored poorly, thereby reflecting gaps in their capabilities[40,41]. This likely perpetuates the high postpartum mortality rate. The WHO recommends that uterotonic drugs should be used in the third stage of labour by skilled birth attendants[42]. However, current guidelines in Rwanda only allow for oxytocin to be used in district hospitals rather than in rural health centres because of the specific storage and administration requirements[43]. When surveyed, most community health care workers felt that the lack of care and resources, such as lack of prenatal care and access to ambulances to district hospitals, were compounded by poverty, and that these factors played a part in the high rates of postpartum haemorrhage[32].

Pre-eclampsia and Eclampsia

PEC is one of the leading causes of maternal mortality in Rwanda, although the exact rates of PEC and EC are unknown[44,45]. There are several causes that contribute to the high rates of PEC such as undiagnosed chronic hypertension, lack of education, obesity, and complications associated with transport to a referral hospital. Three solutions highlighted in the literature to address PEC include the administration of antiplatelet agents (e.g. low-dose aspirin), addressing food security, and screening for chronic hypertension. A systematic review of 16 reviews found that antiplatelet therapy is associated with a 17% reduction in PEC, an 8% decrease in preterm (<34 weeks) births and a 14% reduction for all types of perinatal deaths (foetal, neonatal, and infant death)[46]. Antiplatelet agents should be given to pregnant women at a high risk of PEC[47]. Calcium plays a key role in reducing the risk of gestational hypertension and PEC, and as such, the WHO recommends daily calcium supplementation in pregnant women[48]. A systematic review found that the daily administration of 1–2 grams of calcium significantly reduced the risk of pre-eclampsia by 55% and 64% in women with an adequate and low dietary intake of calcium respectively[46]. In addition, addressing chronic hypertension is also important. A systematic review and meta-analysis of 55 studies from the United States found that pregnant women with chronic hypertension had a 25.9% higher incidence of superimposed preeclampsia[49]. Several studies in Rwanda have found a high prevalence of undiagnosed chronic hypertension in women of reproductive age[45,50]. Blood pressure (BP) screening is the cornerstone of a preeclampsia diagnosis. A cost-effective device that

can be used by minimally-trained members of the community could ensure that pregnant women get regular BP monitoring for the detection of hypertensive disorders of pregnancy. The semi-automated Microlife BP 3AS1-2 sphygmomanometer is one such device that has been validated to be accurate for use in pregnancy and pre-eclampsia in a low-resource setting[51].

Reduction in Maternal Mortaltiy

Rwanda has maintained the 7.5% reduction in MMR per year required to meet the Sustainable Development Goal introduced by the United Nations in 2015, which aims for the reduction of MMR to 70 or less by the year 2030[39,52]. This could be attributed to the collaborative efforts of the Rwandan government as well as international and local non-government organizations. For example, the United Nations Population Fund (UNFPA) has instituted a maternal mortality reduction programme in Rwanda to increase high-quality training and enhance local mobilization resources[53]. The Rwandan Ministry of Health has also partnered with UNICEF to generate a mobile health tool (mHealth) to track and monitor pregnant women for the early detection of complications[54]. A local organization has designed and implemented an emergency obstetric care package in district hospitals, which has reduced case fatality rates by 30-50%[55]. The Rwandan government has also instituted policies promoting safe obstetric practices nationwide, including incentives for larger proportions of women delivering within healthcare facilities[56]. Importantly, community participation is encouraged through the election of three community health workers per village, insurance for maternal healthcare services has become more financially accessible for mothers, and a national monitoring campaign has also been implemented to allow the country to better allocate healthcare resources in each community[56].

Rwanda's maternal mortality rates have been excessive for years, and although there has been some improvement, there are still relatively high rates of maternal mortality. Identifying the barriers to reducing maternal mortality rates is the first step in improvement. Potential barriers identified that can be addressed include education provided to rural health care professionals, provision of essential medications, training for the use and storage of these medications, improvements in hospital infrastructure, and a recognition of socioeconomic factors that prevent women from accessing the appropriate care in a timely manner.

Comparison

Globalization has enabled the rapid spread of technology and science; human civilization has advanced more in the past hundred years than in all the preceding years combined[57]. Globalization has many advantages but the absence of protective global measures has led to massive inequalities between nations[58]. The disparity in maternal deaths between developed and developing countries is one of the most significant divides of our time. The majority of maternal deaths occur in the developing world and are preventable in part due to the advent of technologies such as ultrasound sonography[57].

The most recent information from the World Bank estimates that 38.2% of the population in Rwanda lives under the poverty line, and—according to the World Poverty Clock—5% of India's population lives below the poverty line[59,60]. There is an unequivocal two-way link between health and poverty; illness impairs learning ability and quality of life which has a negative impact on productivity which perpetuates the cycle of poverty. Poor people are exposed to more environmental risks such as pollution, natural disasters, violence and poor sanitation which compounds over time[58]. Poor people are less informed about healthy lifestyles and have limited access to healthcare.

Maternal mortality and perinatal mortality are sensitive indicators and reflect the strength of the healthcare system. In 2020, Sweden spent $6,028 US dollars (USD) per capita on healthcare compared to $56.6 and $57.5 USD per capita spent by India and Rwanda respectively[61]. Sweden's healthcare model offers publicly funded antenatal and postnatal care by qualified midwives at a community-based level to ensure equal access and prevent unnecessary deaths[6]. In India, antenatal care is provided free of cost at public health centres, but with the caveat that private health care providers play a central role in delivering antenatal care which leaves many living in poverty disenfranchised. In rural India and Rwanda there is a lack of access to healthcare, so incorporating and/or expanding the midwifery model and investing in community-led care would be practical and beneficial.

Access to healthcare in rural areas is another key factor contributing to high maternal mortality rates in Rwanda and the implementation of community-led care could play a role in addressing the gap in accessibility. Community-level interventions such as educational programs play a key role in under-resourced settings as they are cost-effective and require minimal training[62]. Local groups for women who are not healthcare workers could coordinate several meetings per month after receiving basic training in maternal health, including—but not limited to—PEC and EC prevention, danger signs, and regular blood pressure monitoring using semi-automated blood pressure devices[62]. A systematic review of similar educational programs implemented in other under-resourced countries such as India, Bangladesh, Malawi and Nepal found that educational programs are associated with a 37% reduction in maternal mortality and a 23% reduction in neonatal mortality[62].

Limitations

The authors acknowledge that this study is subject to limitations. Firstly, our account is only as reliable as the primary investigations included, which varied in methods, data quality, and definitions used. We are also limited by publication bias, although every effort was made to minimize this. There was a relative scarcity of Rwandan quantitative peer-reviewed literature that met our inclusion criteria, and usable studies were mainly conducted at a single tertiary hospital, which may limit

the generalisability of our findings. The inclusionary criteria used were broad and non-specific.

Conclusion

It is understood that a multitude of factors contribute to regional differences in maternal mortality. These perpetuating reasons are often closely interlinked in a complex relationship with the country's socioeconomic and political conditions. Therefore, to decrease maternal mortality rates in developing countries especially, the focus needs to be diverted towards bridging the gap between the urban and rural populations and equipping mothers with accessible, affordable and high-quality healthcare. ◄

Declarations

The authors declare that this research was conducted in the absence of any relationships—commercial, financial, or otherwise—that could be construed as a potential conflict of interest.

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LITERATURE REVIEW

Defining the Role of Th17 Lineage Cells in People with COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) is a pandemic disease which has created a serious public health threat worldwide and causes pneumonia due to infection of the host with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There remains a key gap in the understanding of what decides the outcome between an appropriate immune response and immunopathology in COVID-19. Th17 lineage cells are a distinct population of CD4+ T helper cells which mediate protection against bacteria and fungi. Th17 cells are dysregulated in patients with severe COVID-19 and are significant contributors to the systemic cytokine storm experienced by critical patients. Th17 cells have been described to mediate damage in the lungs of COVID-19 patients by encouraging the recruitment of neutrophils, contributing to acute respiratory distress syndrome and cytokine storms, causing pulmonary fibrosis, disrupting normal alveolar architecture and oxygenation processes and ultimately leading to systemic organ damage and death. Th17 cells have also been reported to contribute to immune dysfunction in conditions associated with increased risk of disease severity in COVID-19. There is a gap in our knowledge surrounding Th17-mediated protective immunity versus aberrant uncontrolled Th17-mediated pathology in the lung. This review aims to investigate and define the mechanisms of Th17 cells in COVID-19 pathogenesis by comparing the features of Th17 cells in a healthy immune response of the lung with the severe disease state in critical COVID-19.

Keywords: Th17 Cells, COVID-19, SARS-CoV-2

Introduction to Th17 Cells

Th17 lineage cells are a distinct population of CD4+ T-helper (Th) cells which mediate protection against bacteria and fungi[1]. Th17 cells produce proinflammatory cytokines interleukin (IL)-17A, IL-17F, IL-22, IL-26, tumour necrosis factor-α (TNFα), chemokine ligand 20 (CCL20) and granulocyte macrophage colony-stimulating factor (GM-CSF)[2]. These proinflammatory cytokines operate on various target cells and consequently are involved in several inflammatory diseases for example autoimmunity, chronic inflammation and infectious diseases[3]. Th17 cells support B cell function and recruit other cells, such as neutrophils, to the site of inflammation[4]. In certain contexts of inflammation, Th17 lineage cells exhibit plasticity and can produce the Th1 cytokine IFN-γ[5]. This unconventional polyfunctionality has a role in mediating inappropriate inflammation during autoimmunity but may also be critical to mediating protection against infectious diseases[6].

Induction and Differentiation of Th17 Cells

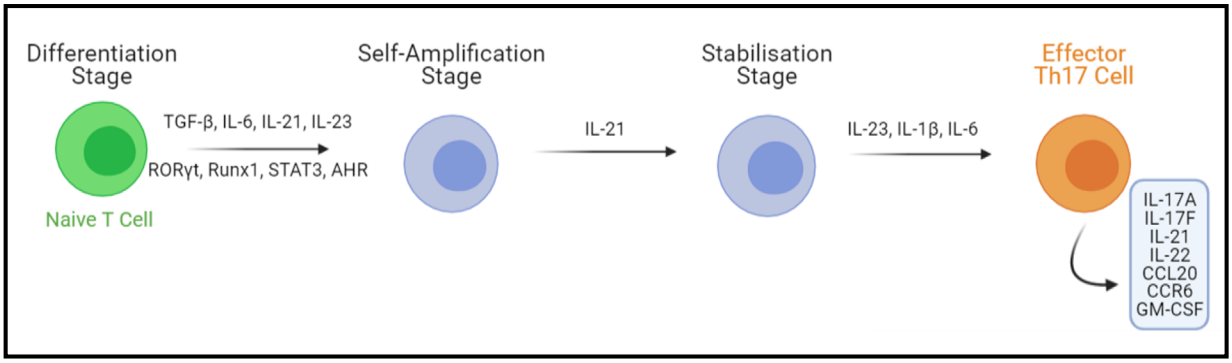
IL-6, IL-21, IL-23 and TGF-β drive Th17 cell differentiation (**Figure 1**). The master regulator of this differentiation process is the transcription factor retinoic acid receptor orphan receptor gamma-T (RORγt).

There are three stages involved in the differentiation of Th17 cells: the differentiation stage driven by TGF-β, the self-amplification stage driven by IL-21, and the stabilisation stage driven by IL-23. When TGF-β is low and IL-6 is present, this results in the differentiation of Th17, IL-21 generation and the stimulation of IL-23R. RORγt is activated through the downstream signalling of TGF-β and IL-6 and therefore stimulates the generation of IL-17A and IL-17F. Downstream signalling of IL-6, IL-21 and IL-23 leads to STAT3 activation which also contributes to Th17 cell differentiation by promoting RORγt. Runx1 is also involved in the process of Th17 differentiation as RORγt can trigger Runx1 and enhances differentiation. Transcription factor aryl hydrocarbon receptor (AHR) obstructs the negative regulators of Th17 differentiation, STAT1 and STAT5. IL-21 drives the self-amplification process and engages with TGF-β to amplify the differentiation process. The stabilisation phase is driven by IL-23 generated from antigen presenting cells and serves to enhance and sustain Th17 cell populations. Downstream signalling of IL-6 and IL-21 triggers IL-23R to be expressed on the surface of Th17 cells. IL-23 in combination with IL-1β is capable of stimulating T-bet+ RORγt+ Th17 cells without the involvement of TGF-β. Finally, effector Th17 cells produce IL-17A, IL-17F, IL-21, IL-22, CCL20, CCR6[1].

Th17 Cell Receptors and Signalling in Epithelial Cells and Fibroblasts of the Lungs

Th17 effector cytokines signal through the multimeric IL-17 receptor (IL-17R) which consists of IL-17RA and IL-17RC. IL-17R has a broad cellular distribution. In the airways, these receptors can be identified on epithelial

Figure 1. **Differentiation of Th17 cells**



cells and fibroblasts. IL-17 can mediate beneficial or detrimental effects in the lungs[7]. Mucosal epithelial cells of the lungs express IL-17 and IL-22 receptors indicating the important homeostatic role of these cytokines[8,9].

Basal airway cells contain IL-17Rs and induction of IL-17 by bronchial epithelial cells promotes a chemokine gradient which attracts an infiltration of pro-inflammatory immune cells such as neutrophils into the lungs[8,10].

Epithelial cells may contribute to lung fibrosis via IL-17, by encouraging the generation and secretion of collagen, leading to epithelial-mesenchymal transition. Autophagy in epithelial cells can be inhibited through IL-17 signalling[11]. This may contribute to lung fibrosis as autophagy regulates fibrosis[12]. However, IL-22 produced by Th17 cells can induce autophagy in epithelial cells and promote defence. IL-22 can also dampen inflammation and stimulate epithelial repair in response to injury mediated by pathogens[9,13]. Overall Th17 effector cytokines have complex interactions with epithelial cells mediating both beneficial or detrimental outcomes in the lungs.

Lung fibroblasts can shift to a profibrotic state as a result of IL-17 signalling and trigger TGF-β and collagen proteins which contributes to fibrosis[14]. IL-17 regulates the infiltration of granulocytes as well as the production of extracellular matrix from lung fibroblasts[14].

The Role of Th17 Cells in the Lungs

IL-17A plays an important role in lung immunity through initiating and driving disease or conversely ameliorating the infection process. Th17 cells are involved in neutrophil activation and triggering a cascade of immune mechanisms to eliminate pathogens and therefore are integral to host defence. However, this Th17-mediated immune response can drive a dysregulated inflammatory response and cause damage to the delicate lung tissue. Therefore, the regulation of Th17 cells in the host appears to be critical in determining disease outcome[15].

T_{RM} Cells in the Lungs from Th17 Cell Lineages

There is increasing evidence surrounding the key role of tissue resident memory T cells (T_{RM}) in various pathogenic infections[16,17] and the presence of tissue-localised T cells have been demonstrated to have specific importance in mediating lung immunity[18,19]. Investigation of T_{RM} cells in the context of human organ transplantation has displayed the importance of these cells in human lung tissue and discovered that long-term persistence of these cells was associated with reduced incidence of rejection[20]. These published studies indicate the importance of this cell population in lung immunity. Long lived T_{RM} 17 cells have displayed important protective effects against bacterial infection[21]. There is a paucity of human data surrounding the role of T_{RM} cells in health and disease and the emerging concepts regarding tissue-specific protective immunity continues to be investigated.

IL-17A tracking-fate mouse models identified that Th17 cells and its effector cytokine IL-17A give rise to the production of lung CD4 T_{RM} cells[21]. This study displayed that Th17 lineage cells capable of producing IL-10 develop into T_{RM} cells in the lungs. IL-10 producing Th17 cells encourage differentiation of macrophages into the 'anti-inflammatory' macrophage phenotype also referred to as M2 macrophages[22]. M2 macrophages are associated with immunosuppression, tissue remodelling, wound healing and fibrosis[22,23]. Th17 cells capable of producing IFN-γ but not IL-10[24], are associated with encouraging the differentiation of macrophages into M1 phenotype which have potent pro-inflammatory activities[22]. The tissue and the environment where Th17 cells are located determines whether these cells will contribute to excessive immunopathology or mediate protective effects. The cytokine milieu is a critical determining factor in this process. IL-1β inhibits IL-10 production in differentiating and in memory Th17 cells and inhibition of IL-1β result in increased IL-10 production[24]. IL-1β drives production of IFN-γ producing Th17 cells[24] and IL-27 and TGF-β drive IL-10 producing Th17 cells[25].

Coronavirus disease 2019 (COVID-19)

COVID-19 is a pandemic disease which causes a pneumonia due to infection of the host with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). By December 2021, there had been over 271 million cases of COVID-19 reported and over 5 million deaths[26]. Angiotensin-converting enzyme 2 (ACE2), the primary receptor for SARS-CoV-2[27], is abundantly expressed in epithelial cells of the lungs and therefore the lungs are the major organs impacted in COVID-19 infection[28].

SARS-CoV-2 infection is initiated by the virus binding to the ACE-2 receptor in the lungs which results in viral replication (**Figure 2**). Proinflammatory cytokines IL-1β and TNF-α are triggered as a result of alveolar macrophages undergoing apoptosis and pyroptosis. The production of these cytokines triggers a loss of renin-angiotensin system (RAS) due to downregulation of ACE2. The cytokines also initiate the production of Th17 cells which further contribute to production of pro-inflammatory cytokines and encourage the attraction of additional immune cells into the site of infection. Vascular permeability and leakage are increased as a result of proinflammatory cytokine signalling[29].

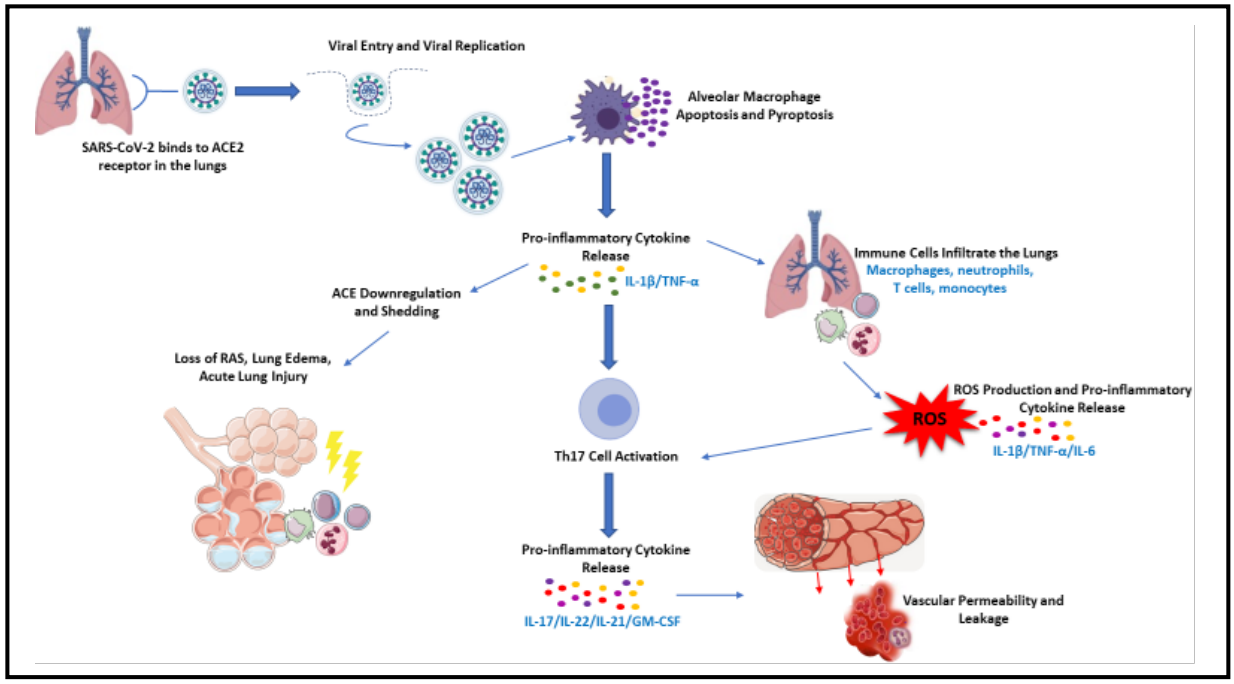
Pathogenesis and Clinical Manifestation of COVID-19 Infection

Multiple clinical symptoms have been reported in people infected with SARS-CoV-2, with most patients experiencing mild to moderate symptoms. Approximately 15% of patients can develop severe manifestations of the disease in the form of pneumonia and approximately 5% of patients may develop acute respiratory distress syndrome (ARDS) or multiple organ failure[30]. ARDS in COVID-19 infection causes diffused alveolar injury and damage to the lungs of infected patients. Patients experience breathing issues due to interstitial widening and oedema in the lungs[31]. Increased vascular permeability induces endothelial cells to become inflamed and therefore the vascular barrier of the lungs is impaired. The action of the virus binding to the ACE2 receptor induces this permeability and encourages infiltration of immune cells such as neutrophils and macrophages which in turn promotes the generation of inflammatory cytokines[32]. The production of these cytokines contributes to the inflammatory environment and drives the invasion of additional inflammatory cells into the site of infection. This severe proinflammatory immune response primarily affects the lungs but can progress to multiorgan dysfunction and cause extensive tissue damage and death[33].

Role of Th17 Cells in COVID-19 Disease

A cytokine storm drives disease severity and ARDS associated with COVID-19 (**Figure 3**). This cytokine storm is associated with increased levels of IL-1β, IL-2, IL-7, IL-8, IL-9, IL-10, IL-17, G-CSF, GM-CSF, IFNγ, TNFα, IP10, MCP1, MIP1A and MIP1B[34]. Patients who require ICU treatment are observed to have elevated concentrations of IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A, and TNFα in serum in comparison to patients who do not require ICU treatment[34]. Many of these cytokines involved in this cytokine storm are implicated in Th17 cell activation and function. Following activation of Th17 cells, they also further contribute to the cytokine storm and pro-inflammatory environment by producing their effector cytokines IL-17, GM-CSF, IL-21 and IL-22. GM-CSF contributes to inflammation by encouraging granulopoiesis and neutrophil infiltration. IL-17 encourages the production of IL-1β, IL-6 and TNFα which are responsible for systemic inflammation and fever. IL-17 also induces chemokines KC, MIP2A, IL-8, IP10, MIP3A which are involved in enlisting additional immune cells for defence. Matrix metalloproteinases are also

Figure 2. **Viral Replication of COVID-19 in the Host and Immunopathogenesis Promoting Respiratory Infection (Adapted from Asrani and Hassan[29])**



induced by IL-17 signalling and can contribute to tissue remodelling and injury[34]. Moreover, IL-22 is proposed to be involved in the potentially fatal oedema experienced by patients as it has a role in enhancing the production of mucins, fibrinogen, anti-apoptotic proteins, serum amyloid A and LPS binding protein[34,35].

Patients with severe COVID-19 have a vast amount of CCR6+ Th17 cells in their peripheral blood, which substantiates the role of Th17 cells in the cytokine storm[36]. In addition to this, De Biasi et al. showed T cells skew towards a Th17 phenotype in COVID-19 patients[37]. A comparison between COVID-19 ICU patients and healthy controls demonstrated that the ratio of Th17/Treg cells was significantly increased in infected patients and in those who died from COVID-19 infection compared with controls[38]. Several other studies have implicated Th17 cells in exacerbating critical COVID-19 disease, causing a skewed response towards Th17 cells which results in failing to control the virus and ultimately identifies the link between impaired adaptive immune responses and the pathology of severe COVID-19 disease[39-41].

Zhao et al. identified that following viral clearance, clonally expanded tissue-resident memory-like Th17 cells ($T_{RM}17$ cells) were observed in the lungs[42]. These $T_{RM}17$ cells were identified to have a cytokine expression of IL-17A and GM-CSF defining these cells as potentially pathogenic. Interactome analysis indicated that macrophages and CD8+ T cells resident in the lung co-operate with these $T_{RM}17$ cells and correlate with lung injury and disease pathogenesis. In addition to this, high concentrations of IL-17A and GM-CSF were reported in serum of patients with severe COVID-19. Overall, this study indicates $T_{RM}17$ cells are a possible driver of hyperinflammation[42].

The complex role of Th17 cells in COVID-19 disease has also been portrayed through the investigation of clinically recovered COVID-19 patients. Yang et al. has reported that severe COVID-19 disease has a dramatic effect on lymphocytes and immune dysfunction for weeks following clinical recovery[43]. Significant reduction and repression were recorded in the levels and functions of Th1, Th2 and Th17 cells after 11 weeks of clinical recovery, suggesting long-lasting immune dysfunction as a result of severe disease[43].

Immunotyping the features of asymptomatic COVID-19 disease in comparison symptomatic disease has offered interesting insight to the protective versus pathologic contribution of Th17 cells in COVID-19. Li et al. reported that severe patients develop a non-protective immune phenotype associated with aberrant Th17 cells and reduced Tregs which was associated with increasing neutrophils and monocytes into the lungs to mediate damage[44]. However, Li et al. also identified that asymptomatic patients established an enhanced effective and protective immunophenotype which was associated with averting uncontrolled immune responses and was characterised by decreased Th17 and Tregs[44]. The reduced levels of Th17 cells and Tregs suggest their role is balancing immune responses by decreasing the Th17/Treg axis and regulating excessive immune responses which can lead to damage[44]. Chan et al. also reported a protective role of Th17 cells in asymptomatic disease[45]. However, in their study it was reported that asymptomatic patients established higher levels of virus-specific Th17 responses and weaker and sufficient neutralising antibodies. These activities suggest a role for Th17 cells in anti-viral mechanisms and contributing to controlling balancing the immune response in disease and reducing the adverse inflammatory damage experience in severe COVID-19 disease[45].

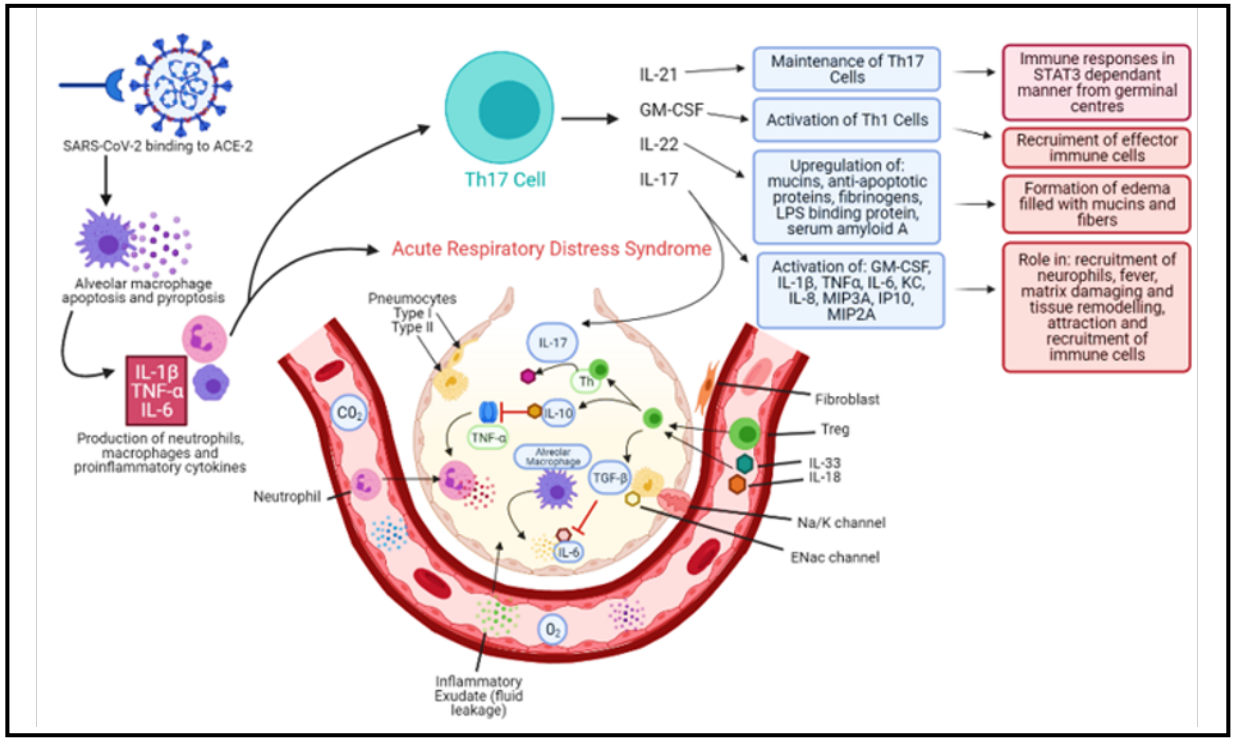
SARS-CoV-2 binds to the ACE-2 receptor in the lungs where the virus is endocytosed and interacts with alveolar macrophages stimulating an innate immune response. IL-1β, TNF-α and IL-6 are produced as a result of apoptosis and pyroptosis of macrophages. The production of these proinflammatory cytokines results in the production and recruitment of neutrophils, macrophages and additional pro-inflammatory cytokines into the site of infection. The production of these proinflammatory cytokines and inflammatory cells promotes the production of Th17 cells, as well as triggering a cytokine storm and contributing to the manifestation of ARDS[29]. Once the integrity of the epithelial cells in the alveolus become impaired, homeostasis is disrupted as epithelial sodium and sodium/potassium channels can no longer function appropriately. This leads to a breakdown in permeability of capillaries and the emittance of fluids. Th17 cells secrete IL-17 to trigger TNF-α which plays a role in damaging epithelial cells and stimulates degranulation via activation of neutrophils. Tregs in the alveolar microenvironment also contribute to ARDS by stimulating TGF-β and this contributes to fibrosis and epithelial injury[46]. The activation of Th17 cells also contributes to the cytokine storm through the production of effector cytokines IL-22, IL-21, GM-CSF and IL-17 which recruit a variety of pro-inflammatory cytokines into the environment which further mediate damage and pathology[29].

Role of Th17 Cells in Risk Factors Associated with Disease Severity in COVID-19 Infection

Age, sex, obesity, hypertension, diabetes, and chronic kidney disease (CKD) are associated with increased disease severity and increased signalling of Th17 cells and their effector cytokine IL-17A which can contribute to disease pathogenesis. Of the patients admitted to hospital with severe COVID-19, 60-80% were male[47]. Differentiation of Th17 cells can occur as a result of oestrogen deficit and decreased Treg cell frequency[48]. Oestrogen can downregulate the production of Th17 cells by obstructing RORγt signalling[49]. In murine studies of Coxsackievirus B3 infection, males display increased levels of Th17 cells compared to females and can be reduced via IL-17A neutralising antibodies[50]. These studies suggest that Th17 cells are repressed in females compared with males, proposing the potential that Th17 cells may be associated with the risk of severe COVID-19 in men[47].

Murine studies display that obesity increases polarisation of T cells towards a Th17 phenotype as a result of elevated IL-6 signalling[51]. Obese women have been reported to have greater concentrations

Figure 3. **The Role of Th17 Cells in Mediating Cytokine Storm and Acute Respiratory Distress Syndrome (Figure adapted from Asrani et al.[29] and Khadke et al.[46])**



of circulating IL-17A in comparison to lean women[52]. COVID-19 patients with BMI 27.0±2.5 present with worsened disease outcomes in comparison to patients with BMI 22.0±1.3[53]. An additional study investigating the relationship between BMI and COVID-19 displayed that 15.18% of patients who participated in this study were non-survivors and 88.2% of these patients had a BMI greater than 25[54]. These studies suggest that obesity can drive disease severity in COVID-19 which is associated with elevated levels of Th17 cells and IL-17 signalling. Dysfunctional and enhanced Th17 activities have been identified in patients with both type-I and type-II diabetes[55] suggesting that increased Th17 cells contribute to the complications of diabetes and may be a risk factor for severity in COVID-19. Similarly, CKD is a risk factor associated with COVID-19 severity and this condition is linked to dysfunctional Th17 cell activity[56,57]. Furthermore, murine models of hypertension have displayed that Th17 cells and IL-17A is increased during angiotensin II signalling. Studies on hypertensive diabetic patients, showed that there are high levels of IL-17A in their serum in comparison to healthy controls[58] and diabetic patients who are not hypertensive[59].

Finally, ageing is associated with dysregulated Th17 cell signalling. Peripheral blood mononuclear cells (PBMCs) of healthy older people contain increased Th17 cells and the effector cytokine IL-17A in comparison to control groups which are middle-aged and young[60] and the ratio of Th17/Tregs is also observed to polarise towards a Th17 phenotype in older individuals[61]. This predisposition of older individuals to have increased activity of Th17 cells may contribute towards an elevated risk of COVID-19 severity.

Conclusion

Many studies have outlined the protective role of Th17 cells against a diverse range of pathogens in the lungs by promoting infiltration of neutrophils and monocytes into the lungs. In addition to this, IL-17A regulates inflammatory responses in the tissues and host protection by triggering the induction of pro-inflammatory cytokines, chemokines, and antimicrobial peptides from various cells of the airways. These mechanisms are crucial for supporting successful protection against invading pathogens[62].

However, Th17 cells also mediate tissue pathology in various diseases and therefore responses of Th17 cells in the lung can be both protective and pathogenic. A critical balance is required to suppress the pathogenic mechanisms of Th17 cells and their effector cytokines in settings of inappropriate inflammation, but at the same time preserving their role in mediating early pathogen defence in the lungs is essential[2]. A more extensive understanding of the role of Th17 cells in lung inflammation may offer insight into therapeutic targets, which could block the pathological features of the Th17 response while maintaining the integrity of lung tissue and host defence.

There remains a key gap in the understanding of what decides the outcome between an appropriate immune response and immunopathology[63]. Th17 cells are dysregulated in patients with severe COVID-19 and are

significant contributors to the systemic cytokine storm experienced by critical patients, mediating damage in the lungs, contributing to ARDS and, causing pulmonary fibrosis disrupting normal alveolar architecture and normal oxygenation process, and ultimately leading to systemic organ damage and death[64]. Th17 cells have also been reported to contribute to immune dysfunction in other conditions associated with increased risk of disease severity in COVID-19[47]. Therefore, these mechanisms of Th17 immunopathology undoubtedly are worthy of future research. Defining the role of Th17 cells in the lungs will offer important information which can be applicable to a diverse range of respiratory diseases and inform future vaccine design and candidate therapeutics.◀

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Declarations

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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