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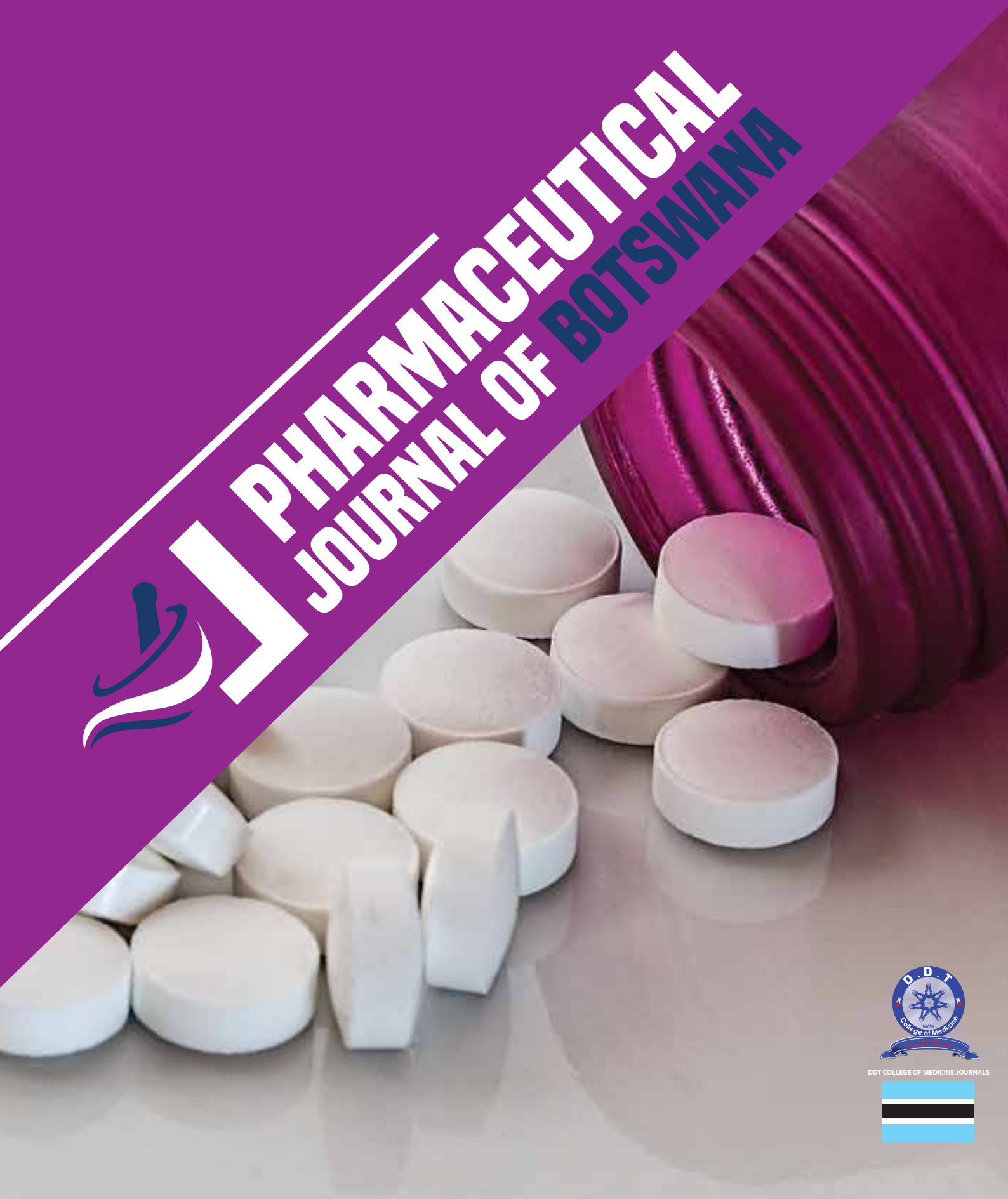

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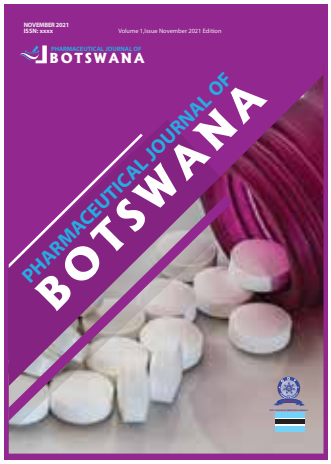

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Dr Tumelo Tlhoiwe
VICE CHANCELLOR

Vice Chancellor's Message To DDT academics Family and the Nation at large During this COVID-19 Pandemic

The whole world has been affected by Coronavirus, economies have shrunk, loved ones lost but our good lord has sustained us. I encourage everyone to consider research as a priority in order to come up with solutions to fight this pandemic.

The struggle you are in today is developing the strength you need for tomorrow. Being challenged in life is inevitable, but you have the choice to decide how you will react to the situation. Especially now, in this time of covid-19 crisis and uncertainty, change the changeable and accept the unchangeable. We may not be able to see it in the moment, but everything happens for a reason. Use this time to make a difference in your life or in the lives of someone else. Work on all areas of personal growth, spend quality time with family, and focus on goals for the future.

Train yourself to find a blessing in everything, Someone once said these words to me, which have stayed in my mind throughout my life. I truly believe that we are not put into a situation that we cannot conquer. Seeing the light in the midst of darkness is a lesson we all should learn, not only during this difficult time, but all the time. Stay focused on the good and making it better. It can only go up from here.

It's tough to see the light in times of darkness. My advice for all researchers and students is to continue to be positive and never give up hope. It's when we start to lose hope that we begin to struggle mentally. Lend a listening ear to everyone; sometimes all someone needs is a person willing to listen. We all need to come together in this time and continue to check on loved ones, friends, teammates, roommates, and classmates. You never know the impact of what a simple 5 minute phone call could do for someone. Spread that love each and every day.

"Life throws you curves but you learn to swerve." No one is ever really prepared for God's greater plans, but we figure it out, taking it one day at a time. During my time at university, there were some unfortunate events, but we always came together as a community to get it through it as one. Now more than ever, we need to take care of each other. Luckily we live in a world we can talk with friends and family virtually. Take care of yourself and your loved ones. We'll all look back on this time and remember the ones who helped us through this challenging time.

"Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less."

"A life lived in fear is a life half lived."

VC

Dr Derrick D. Tlhoiwe
CHANCELLOR

Chancellor's Message

To all academic fraternity of DDT College of medicine and beyond, I would like to thank every one of you for your contribution in building Our University college. Thank you for believing in our vision.

DDT continues with its vision as the top medical university in Botswana and draws inspiration from the government of Botswana which has encouraged every citizen to migrate from a minerals-led to a knowledge-based economy, DDT aspires to bring knowledge to Batswana by engaging in state of the art research work and bring solutions to challenging health problems such as the covid-19 pandemic.

Yes our journey has not been smooth, we all understand, "The size of your success is measured by the strength of your desire; the size of your dream; and how you handle disappointment along the way." Disappointments are just God's way to saying 'I've got something better'. Be patient, live life, have faith." We shall overcome every barrier ahead of us for ours is a noble task of improving the lives of Batswana.

I encourage everyone of you to commit to research work, Desire to face the challenge in solving the unsolved problems, concern over practical problems initiates research; Desire to get intellectual joy of doing some creative work; Desire to be of service to society; Desire to get respectability due to your creativity and innovation.

Covid-19 has ravaged many economies, I therefore encourage everyone of you to dedicate considerable amount of time in coming up with solutions to curb this pandemic.

DDT will set aside substantial amount of resources to go into each faculty research work. Your commitment to research will also build your promotion ladder to senior lecturer, assistant professor to full professor.

Last but not the least, I encourage you once again to remember that, The road to success and the road to failure are almost exactly the same it depends on the one you want embrace, Success is not final; failure is not fatal: Opportunities don't happen. You create them , It is the courage to continue that counts. It is better to fail in originality than to succeed in imitation. There are two types of people who will tell you that you cannot make a difference in this world: those who are afraid to try and those who are afraid you will succeed.

Chancellor

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ANALYSIS OF COVID-19 FIRST GENERATION VACCINES DESIGN VIRAL PLATFORMS USED.

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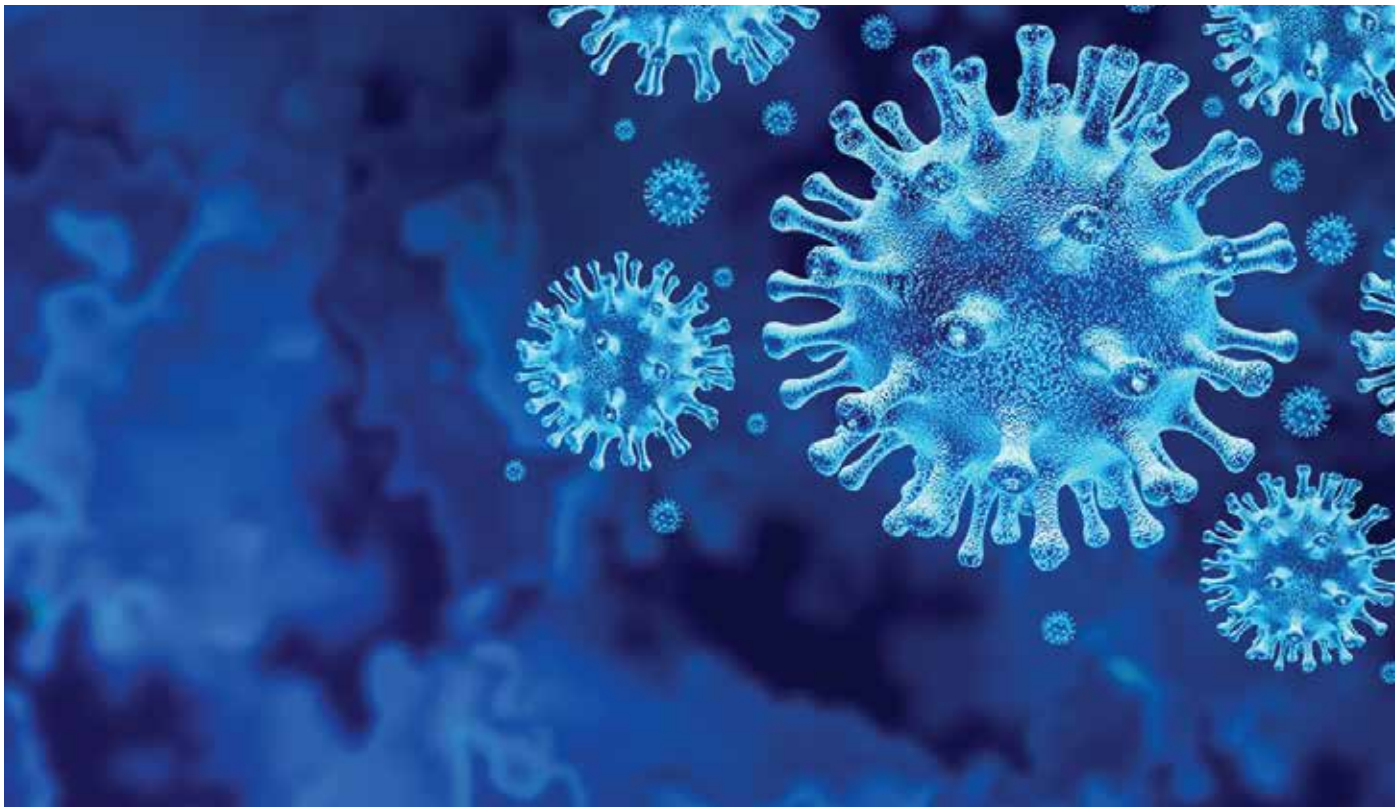


Abstract:

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or Coronavirus was initially detected in Wuhan, China in December 2019 and has subsequently resulted in the COVID-19 pandemic. The disease presents asymptomatically in some of individuals yet also causes symptoms ranging from those associated with influenza and pneumonia, acute respiratory distress syndrome (ARDS) and even death. The world is currently relying on physical (social) distancing, hygiene and repurposed medicines; however, it is predicted that an effective vaccine will be necessary to ensure comprehensive protection against COVID-19. There has been a global effort to develop an effective vaccine against SARS-CoV-2 with approximately 300 vaccines in clinical trials, and over 200 more in different stages of development. This review provides insight in respect of vaccines, which are in clinical use as of December 2020 and focusses on the Pfizer/ BioN-Tech/Fosun, Moderna mRNA-1273 and AstraZene-ca/Oxford AZD1222 vaccines.

Keywords: Coronavirus; Vaccines; AstraZeneca; Moderna (mRNA-1273); Pfizer, Johnson and Johnson, Gamaleya, Sinopharm, Viral Vector, Sputnik.

1.Introduction

In December 2019 a Coronavirus (COVID-19) outbreak was identified in Wuhan, China which subsequently spread across the globe. The COVID-19 pandemic has been attributed to the acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and exhibits a range of the clinical symptoms some of which are similar to influenza, include acute respiratory distress syndrome (ARDS) and pneumonia in addition to presenting with asymptomatic patients and all may ultimately result in mortality [1]. Initially the pandemic was perceived to be simple to manage with interventions such as physical (social) distancing, use of masks, adequate use of other personal protective approaches including hand sanitizer and face mask use however, at the same time and it was anticipated that the use of existing and new antiviral drugs, and effective vaccines would reduce mortality rates of COVID-19. Perhaps the initial naïve perception that the development of herd immunity through natural development of immunity through infection was the contributor to significant loss of life due to death [1]. By way of example, in Sweden, the authorities presumed that if 60% of the total population had been infected the resultant herd immunity would be adequate to

The comparison of number of infections eliminated by use of the vaccine in the other group was carried out by analysing the difference between r2 and r1 and in this case, it was established that the AstraZeneca vaccine was 73% effective and facilitates removal of 73% of cases which would otherwise occur.

protect the population [1,2].

However, this presumption failed, and a significant number of the Swedish population have since lost their lives due to COVID infection [2]. Consequently, the development of an efficient vaccine has been perceived as the only practical way to ultimately establish herd immunity on the globe. Researchers across the globe have been developing a vaccine for COVID-19 resulting in many vaccine candidates e in different stages of development of which some are in Phase 1 clinical trials [3].

The development of a safe and effective vaccine requires pre-clinical and clinical trials be conducted to minimize the potential of severe adverse effects when used on a large scale [3]. This review will focus on the current vaccines in which a summary of the biological and immune responses observed from previous COVID-19 infections and SARSCoV-2 is provided. In addition, this review describes exploratory and pre-clinical stages of SARS-CoV-2 vaccine development and a discussion regarding the target platform for designing an effective and safe COVID-19 vaccine with relevant clinical trial data. Furthermore, the ethical concerns surrounding the development and production of these vaccines is considered.

2. Immunogenicity to SARS-CoV-2

Recovery following SARS-CoV-2 infection requires a strong immune response and individuals infected with COVID-19 exhibit a strong immune response to the virus which also facilitates their convalescence [4,5]. Current evidence suggests that helper T cells in COVID-19 infected individuals recognise e spike proteins on the SARS-CoV-2 viral architecture. Consequently, T cells play a significant role in elimination of SARS-CoV-2 from the human body [5]. Moreover, the structure of SARS-CoV-2 includes a major trimeric glycoprotein envelope or S-protein located on the surface of the virus facilitating binding to host cells making it a primary target for the development of a successful vaccine.

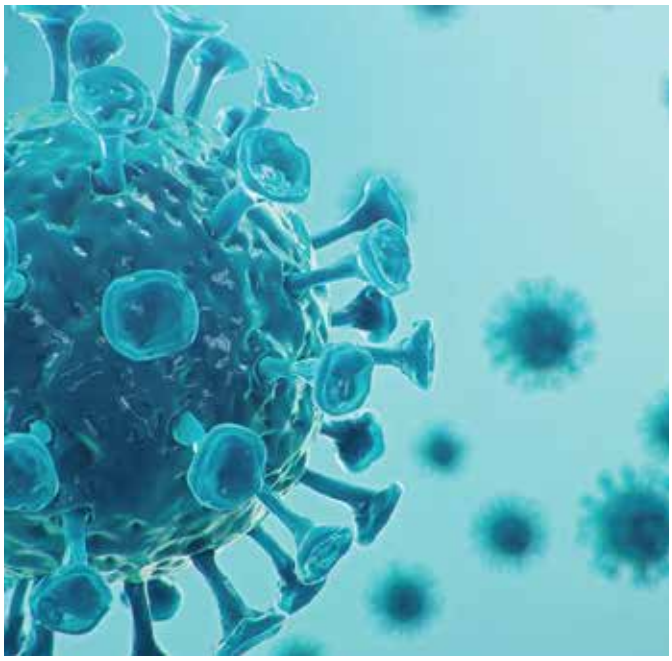
The AstraZeneca COVID-19 (AZD1222) coronavirus vaccine has been developed from a version of the common cold adenovirus [6]. The vaccine contains ChAdOx1, which includes the genetic sequence of the SARS-CoV-2 surface spike (S) protein.The S-protein located on the surface of SARS-CoV-2 is essential for the SARS-CoV-2 virus to infect host cells [6]. Most of the vaccines currently in clinical use have been developed using lipid nano particle-encapsulated mRNA, adenovirus 5 vector that expresses S-protein DNA, nucleoside modified RNA (modRNA) uridine containing Mrna (saRNA), electroporation of DNA plasmid encoding S protein, inactivated virus following viral propagation in cells with a SARS-CoV-2 clinical strain, lentiviral vector dendritic cells modification (LV-DCs and antigen-specific cytotoxic T lymphocytes (CTL) approaches and are schematically represented in Figure 1, the SARS-CoV-2 spike protein binds to ACE2 receptors in order to enter and infect human cells.

The production of a vaccine using spike protein may prime the immune system to attack the coronavirus in subsequent infections.

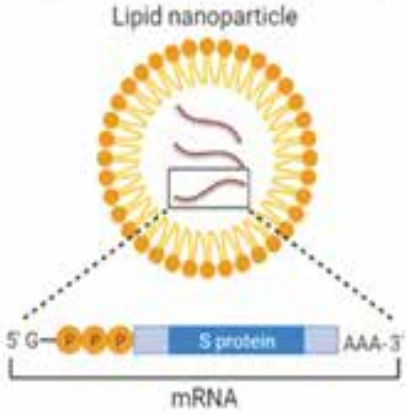
The spike protein is a major surface protein on the CoV virion and is the primary target for neutralising antibodies [7]. The S-protein undergoes dramatic structural re-arrangement when fusing the virus to the cell membrane of the host for viral genome delivery into the target cell. The 2 proline substitutions (2P) on the apex of the central helix stabilises the MERS-CoV, SARS-CoV and HCoV-HKU1 S protein [7].

The release of the SARS-CoV-2 sequence into the hose cell immediately triggers the manufacture of mRNA which expresses the prefusion-stabilised SARS-CoV-2 spike material (fig. 1) [8]. The mRNA-1273 induces potent neutralising antibodies and CD8 T-cell responses and provides protection against SARS-coV-2 [8]. Therefore mRNA-1273 detects and encodes the SARS-CoV-2 prefusion-stabilised spike protein.

BNT162b2 is lipid-nanoparticle formulation containing 5 nucleoside-modified RNA (modRNA) 6 which facilitates encoding of the full-length spike of SARS-CoV-2 [9]. The encoding is modified by two proline mutations for locking into the prefusion confirmation. The doses of BNT162b2 used result in high SARS-CoV-2 neutralising antibody levels in addition to responses from antigen-specific CD8+ and Th1-type CD4+ T-cells as depicted in Figure

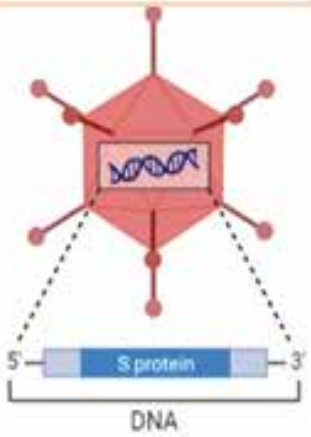


Moderna (mRNA-1273



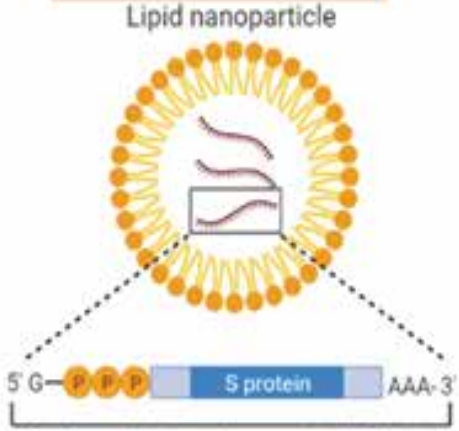
Platform: LNP-encapsulated mRNA encoding S protein.

AstraZeneca/Oxford's AZD 1222



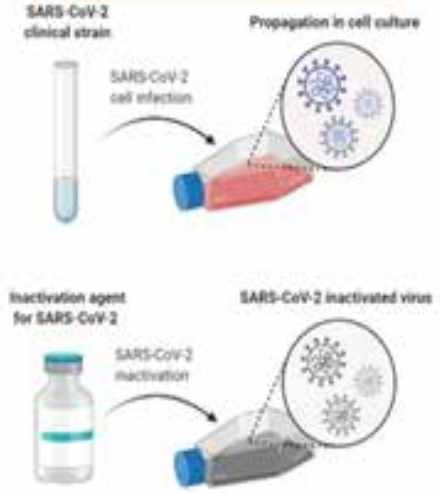
Platform: Adenovirus type 5 vector that expresses S protein.

Pfizer-BioNTech



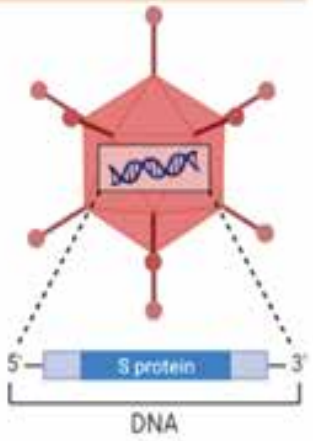
Platform: Nucleoside modified RNA (modRNA)
Uridine containing mRNA (uRNA)
Self-amplifying mRNA (saRNA)

Sinovac Biotech (Sinopharm)



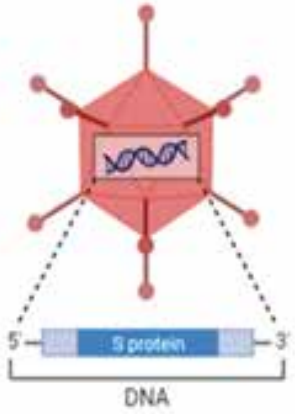
Platform: Inactivated virus vaccine produced from viral propagation in cells infected with a SARS-CoV-2 clinical strain.

Gamaleya (SputinK V)



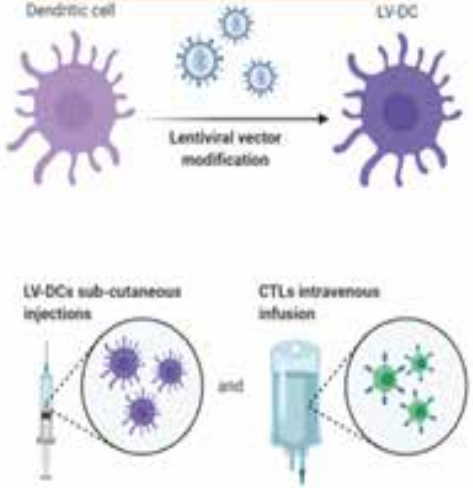
Platform: Adenovirus type 5 vector that expresses S protein.

Johnson and Johnson (Ad26.COV2.S)



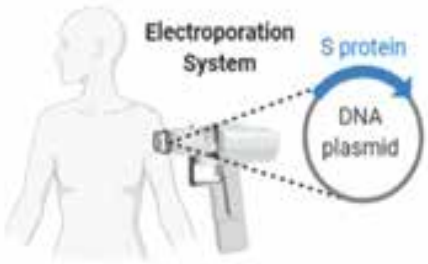
Platform: Genetically modified Adenovirus vector type 5 vector that expresses on S protein and uses double-stranded DNA.

Shenzhen Medical Institute (LV-SMENP-DC)



Platform: Lentiviral vector modification of dendritic cells (LV-DCs) and antigen-specific cytotoxic T lymphocytes (CTLs).

Inovio Pharma (INO-4800)



Platform: Electroporation of DNA plasmid encoding S protein.

3. Exploratory and Pre-Clinical Studies of SARS-CoV-2

Normally the development of new vaccines usually takes between 10 and 15 years whereas the development of a vaccine for COVID-19 over 12-24 months was astounding . The initial vaccine development phase or exploratory stage includes fundamental laboratory research augmented with computational modelling [11] to facilitate identification of natural or synthetic antigens which can be used as vaccine candidates. The second stage of the process includes pre-clinical studies in which cell or tissue culture and human model-based trials are used to establish the safety and immunogenicity of the test vaccine and/or an ability to provoke an immune response [12]. Initially safety, efficacy and immunogenicity are demonstrated in animal models after which clinical trials in small cohorts of human subjects are undertaken [12].

Due to the urgent need to develop prophylactic approaches against COVID-19, several vaccine candidates progressed to the clinical trial stage of development prior to demonstrating efficacy in animal models and provided the idea of pre-clinical research data were used to evaluate the Moderna mRNA vaccine candidate [13]. Vabret et al., the immunisation of mice with mRNA encoding alleviated perfusion and mediates CD8+ T cell response, whilst exhibiting dose-dependent neutralisation SARS-CoV-2 spike trimers by antibodies [14]. Two doses of the mRNA provided in a prime-boost combination to the mice prevented nasal mucosa and lung infections, after challenging SARS-CoV-2 infected mice, however, the trial did not show enhancement of immunopathology in animals receiving sub-protective doses [14].

4. Technology for COVID-19 Vaccine Design

There are many technologies being considered for COVID-19 vaccine development, including DNA, RNA, non-replicating viral vectors and inactivated vaccines [15]. DNA and RNA based vaccines were not developed aggressively nor licenced for human use previously therefore DNA and RNA based vaccines may not be an advantage during a pandemic situation [15]. However, in the light of available evidence DNA and RNA platforms do not require bioreactor culture techniques for production of an inactivated vaccine, and are easily developed in a laboratory as they are based on the genetic sequence of the virus [16]. For this reason DNA and RNA based vaccines for Covid management are under investigation [16]. In contrast non-replicating viral vaccines have been proven safe and effective and can be manufactured on a large scale [17]. As there is an urgent need for a COVID-19 vaccine in the current pandemic situation several DNA, RNA and non-replicating vaccines have been investigated using DNA and RNA platforms.

4.1 RNA Based Vaccines

4.1.1 Moderna mRNA-1273

Moderna is a US-based company that has developed a mRNA-based vaccine referred to as mRNA-1273 [18]. This vaccine codes for the production of spike proteins and administration of the vaccine results in immune cells present in the lymph nodes performing processing of mRNA, resulting in the marking of the protein in humans. The protein is subsequently recognised and marked for destruction. [18]. The Moderna vaccine forms part of the Operation Warp Speed initiative for accelerating the production of a usable vaccine. The preliminary Phase I trial data released by Moderna revealed that the vaccine, tested on mice by immunising them with the doses of 0.01, 0.1

or 1 µg, demonstrated a high pseudovirus NAb response with the 1 µg dose [13]. Moreover, the pseudovirus NAb response was also observed in mice who expressed a mutated form of the spike protein viz., D614G. The 1 µg dose demonstrated a robust and cytotoxic response by T-cells, and balanced responses of Th1/Th2 [13]. The mice did not exhibit increased pathology following administration of the 1 µg dose of vaccine. The Nab levels in mice in response to the 1 µg dose were comparable to that of a 100 µg dose in human subjects with the result that a 100 µg dose was considered necessary for carrying large scale efficacy trials.

4.1.2 BioNTech BNT162

The collaboration between the German company BioNTech and American company Pfizer resulted in the development of an mRNA-based vaccine for encoding the RBD domain of the SARS-CoV-2. The BNT162 product incorporates modified mRNA and includes a trimerisation domain derived from T4 fibritin [19]. For the phase I trial 45 healthy volunteers who were separated into groups to receive 10 µg, 30 µg, and 100 µg doses, were recruited and 9 participants received a placebo dose [19]. On the basis of the interim data, the participants demonstrated an increased level of IgG, which increased and remained elevated for 14 days following the second dose [19]. Individuals who received the 100 µg dose did not exhibit an increase for one day after vaccination, and exhibited peak IgG levels at 21 days following the initial dose [19]. The individuals who received the 100 µg dose did not receive the second booster dose and based on this information no difference between the health outcomes of individuals who received doses of 30 µg and 100 µg were observed [19].

4.2 Non-Replicating Viral Vectors Vaccines

The University of Oxford in partnership with AstraZeneca, a British pharmaceutical company, developed a viral vaccine, previously referred to as ChAdOx1. The pre-clinical trials for this vaccine were undertaken in a porcine model with a large antibody response observed [20]. A randomised controlled trial with 1077 healthy individuals was performed in the UK with participants receiving either 5 × 1010 vaccine particles or the meningococ

cal vaccine MenACWY [21]. The participants were further subdivided and categorised on the basis of paracetamol prophylaxis as this was used as a to reduce adverse events. The production of a recombinant adenovirus for ChAdOx1 nCoV-19 was undertaken and administered at a dose of 5 × 1010 viral particles dose by intramuscular injection [21]. Local and systematic events were fewer in individuals in the paracetamol group when compared to those individuals who received no prophylaxis [21]. However, liver enzyme upregulation through paracetamol use was not considered in this evaluation.

4.3 DNA-Based Vaccines

The American company Inovio developed the DNA-based INO-4800 vaccine. which is injected into the dermis after which electroporation is applied to ensure uptake into cells. The participants were divided into two groups who were administered a high (2mg) or low (1mg) dose [22]. The analysis of adverse events revealed that 28% of the individuals experienced Grade I adverse events after two months [22].

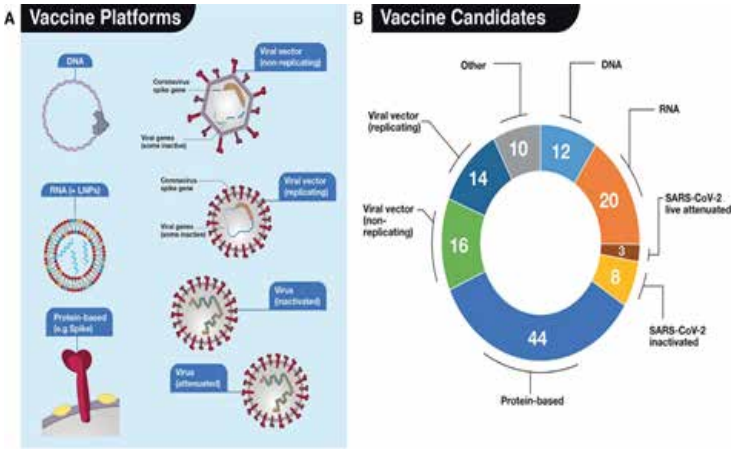


Figure 3: Vaccine platforms and candidates for SARS-CoV-2 and the COVID-19 (Adapted from Funk et al. [23])

5. Unpacking clinical trials data for SARS-CoV-2 vaccines currently under investigation

5.1 mRNA-1273

The primary endpoint for establishing the efficacy of the mRNA-1273 vaccine is the prevention of COVID-19 symptoms within at least 14-days following a second injection [24]. The efficacy levels of the mRNA-1273 were analysed and the consistency of the vaccine at the primary endpoint evaluated in subgroups for age, e health-related risk for severe disease, gender, race, and ethnic groups in addition to risk for COVID-19 [24]. A secondary endpoint was defined in terms of mRNA-1273 efficacy in preventing severe COVID-19, with reference to pre-defined criteria which included a respiration rate of > 30 breathes per minute, heart rate of > 125 beats per minute, oxygen saturation of 93% or lower less (the oxygen partial pressure to the oxygen reaction inspired ratio of < 300 mm Hg), acute respiratory distress syndrome and respiratory failure [24]. The criteria used included clinically significant neurologic, hepatic, renal dysfunction in addition to admission history to the intensive care unit. Some additional secondary endpoints included the efficacy of the vaccine to prevent COVID-19.Of interest solicited adverse events at the injection site were more frequent in the mRNA-1273 group compared to the placebo group [24]. Following the first dose, solicited adverse events totalled 84.2% in the mRNA-1273 and 19.8% in the control groups whereas, following the second dose the solicited adverse events were 88.6% in the mRNA-1273, and 18.8% in the control groups. The severity of injection site events in the mRNA-1273 group were reported as grade 1 and grade2 and observed more frequently in individuals who were SARS-CoV-2 positive at baseline when compared to subjects who were negative at the baseline [24].

The efficacy of mRNA-1273 vaccine was calculated by determining the difference in ratio of infected individuals in the control and vaccinated groups, respectively.

The number of individuals in the vaccine group was n1= 15000 and in the control group n2= 15000. In the vaccinated group, x1=11 individuals were infected by the virus, whereas in the control group x2=185 individuals were infected by the virus during the study [24]. The ratios of the infected individual within the vaccine group, 'r1' was 0.000733, whereas the ratios of the infected individual within the control group, 'r2' was 0.012333. The analysis of ratio of infection in the mRNA-1273, and placebo group revealed that a greater number of individuals were infected in the control group. Efficacy was determined by considering the difference in the ratios 'r1'and 'r2', which revealed that mRNA-1273, vaccine was 94% effective and facilitates removal of 94% of cases which would otherwise occur.

$$r1=x1/n1$$
$$r1=11/(15000\ )$$
$$r1=0.000733$$
$$r2=x2/n2$$
$$r2=185/15000$$
$$r2=0.012333$$
$$E=(r2-r1)/r2$$
$$E=(0.012333-0.000733)/0.012333$$
$$E=0.94$$
$$E=94\%$$

Where,

n1= Number of individuals in control group
n2= Number of individuals in vaccinated group
x1= Number of individuals in control group infected by virus
x2= Number of individuals in vaccinated group infected by virus
r1= Ratio of individuals in control group infected by virus to the total number of individuals in the control group
r2= Ratio of individuals in vaccinated group infected by virus to the total number of individuals in the vaccinated group
E= Difference in the ratios of infected individuals in the control and vaccinated groups.

5.2 BioNTech BNT162

The efficacy of the BNT162b2 vaccine by considering primary and secondary endpoints was reported by Polack et al. [9]. The primary endpoint was efficacy of BNT162b2 against confirmed cases of COVID-19 within at least 7 days onset following administration of the second dose and secondary endpoints included the efficacy of BNT162b2 against severe COVID-19 infection [9]. The effectiveness of the vaccine was estimated using,

Where,

IRR is the ratio of confirmed cases of COVID-19 illness per 1000 individuals.

Analysis of reactogenicity revealed that recipients of the BNT162b2 vaccines exhibited more local reactions and mild to moderate pain at the site of injection within seven days of treatment when compared to the placebo group [9]. Analysis of systemic reactogenicity revealed that events including headache and fatigue were experienced by 59% and 52% of the younger participant in the BNT162b2 group, whereas the event rate in the placebo group was comparatively lower after the first and second doses [9].

The number of individuals in the vaccine group was n1= 21720 and the control group n2= 21728. In the treatment group x1=8 individuals were infected by the virus, whereas, in the control group x2=162 individuals were infected by the virus [9]. The ratios of the infected individual within the vaccine group, 'r1' was 0.000368, whereas, the ratios of the infected individual within the control group, 'r2' was 0.007456. Analysis of the ratio of infection in the BNT162b2, and placebo groups revealed that a greater number of individuals were infected in the control group. In the analysis of data if the control group provides the rate of infection in the absence of using a vaccine, the number of infections eliminated by use of the vaccine in the other group is established by comparing the difference between r2 and r1 and in this case, it was found that the BNT162b2 vaccine was 95% effective and facilitates removal of 95% of cases which would otherwise occur

r1=x1/n1
r1=8/(21720)
r1=0.00036
r2=x2/n2
r2=162/21728
r2=0.007456
E=(r2-r1)/r2
r2=(0.007456-0.000368)/0.00
7456
E=0.95
E=95%

Where,
n1= Number of individuals in control group
n2= Number of individuals in vaccinated group
x1= Number of individuals in control group infected by virus
x2= Number of individuals in vaccinated group infected by virus
r1= Ratio of individuals in control group infected by virus to the total number of individuals in the control group
r2= Ratio of individuals in vaccinated group infected by virus to the total number of individuals in the vaccinated group
E= Difference in the ratios of infected individuals in the control and vaccinated groups.

5.3 AstraZeneca

According to the MHRA Information for Healthcare Professionals [25], the levels of protection following a single dose of the AstraZeneca vaccine were evaluated by exploratory data analysis by including participants who had received one dose of the vaccine [25]. Participant data were removed from the analysis performed as soon as possible following administration of the second dose, 12 weeks after the first dose [25].

Vaccine efficacy analysis revealed that 22 days post-dose, efficacy of the vaccine was 73% with 95% CI limits of 48.79 and 85.76 [25]. It was also observed that hospitalisation was reduced from 21 days after the first dose up to two weeks after the second dose. Consequently, it is likely that a single dose of the AstraZeneca vaccine will provide short-term protection against COVID-19 infection [25]. Protective immunity from the first dose was reported to last for up to 12 weeks. Exploratory analyses suggest that increased immunogenicity was highly correlated to a longer dose interval. In this exploratory trial the number of individuals in the vaccine group was n1= 7998 and the control, group n2= 7982 [25].

In the vaccinated group x1=12 individuals were infected by the virus following treatment whereas, in the control group, x2=44 individuals were infected by the virus. The ratio of infected individual within the vaccine group, 'r1' was 0.001500, whereas the ratio of the infected individual within the control group, 'r2' was 0.005512. Analysis of the ratio of infection with the AstraZeneca vaccine and placebo groups revealed that a greater number of individuals were infected in the control group.

r1=x1/n1
r1=12/(7998)
r1=0.001500
r2=x2/n2
r2=44/(7982)
r2=0.005512
E=(r2-r1)/r2
E=(0.005512-0.001500)/0.005
512

E=0.72786
E=73%

Where,
n1= Number of individuals in control group
n2= Number of individuals in vaccinated group
x1= Number of individuals in control group infected by virus
x2= Number of individuals in vaccinated group infected by virus
r1= Ratio of individuals in control group infected by virus to the total number of individuals in the control group
r2= Ratio of individuals in vaccinated group infected by virus to the total number of individuals in the vaccinated group
E= Difference in the ratios of infected individuals in the control and vaccinated groups.

6. Uncovering Clinical Data

6.1 Johnson and Johnson

The efficacy and safety of the Janssen COVID-19 candidate vaccine for protection against moderate to severe COVID-19 was evaluated in a phase 3 clinical trial by considering co-primary endpoints of 14 and 28 days after vaccination [26]. It was found that the Janssen candidate was 66% effective for the prevention of moderate to severe COVID-19 at 28 days after vaccination. A single dose of the Johnson & Johnson vaccine showed a 66% percent effectiveness at preventing moderate to severe disease from COVID-19 and 85% at preventing severe disease. However, there were variations in efficacy in regional clinical trials when evaluated for moderate to severe COVID-19 with a 72% effectiveness in the United States, 57% in South Africa and 66% in Latin America reported. The vaccine also exhibited good results when multiple variants of COVID-19, such as B.1.351 variant found in South Africa were tested.

Johnson and Johnson [27] reported that the onset of protection was also observed as early as the 14th day of infection. The Janssen COVID-19 vaccine provided complete protection against COVID-related hospitalisation and death 28 days after vaccination. The vaccine was reported to have a clear effect on the number of COVID-19 cases requiring extracorporeal membrane oxygenation (ECMO), mechanical ventilation, or other medical interventions.

6.2 Gamaleya

The Sputnik V vaccine developed by Gamaleya is based on a human adenoviral vector platform and makes use of adenovirus 26 (Ad26) and 5 (Ad5) as vectors to express the genetic sequence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein [28]. Logunov et al. [28] reported the interim results from a phase 3 clinical trial of the Sputnik V COVID-19 vaccine and the results revealed that the vaccine provided strong protection in all age groups that participated [29]. The efficacy of the vaccine established by monitoring confirmed cases of COVID-19 from 21 days after vaccine administration revealed 91.6% efficacy (95% CI 85•6–95•2) [29] and was equally effective in individuals in all age groups.

6.3 Sinopharm

Sinopharm, a pharmaceutical company based in the Republic of China, have developed an inactivated SARS CoV-2 vaccine, which has been administered to approximately 1 million individuals [30]. Additional phase 3 trials of the vaccine are currently being undertaken in Indonesia and Turkey [30]. In Brazil, the vaccine has been administered intramuscularly to participants in two different doses provided at an interval of 14 days [30]. The Sinopharm vaccine has been reported to be 79% effective [31] however, efficacy trials on the same product have p

roduced efficacy data of 50%, 65%, 78% and 91% [32].

7.Ethical Considerations Surrounding Vaccine Development and Production

A concerted application of science and technology is required to ensure that the research undertaken in respect of the COVID-19 outbreak includes risk assessment, management, vaccine development, and production whilst always promoting human rights. The development and production of an effective vaccine for dealing with the pandemic is y dependent on the outcomes of appropriately designed clinical and non-clinical trial outcomes performed in vitro, in animal and human subjects [33]. For this reason, there is a bioethical debate surrounding the trials conducted in respect of these vaccines developed during the pandemic. In respect of the COVID-19 situation, no vaccine has been proven to be effective for treatment of the disease and therefore an ethical dilemma when including healthy subjects for testing the efficacy of the vaccine exists [34]. The development and production of vaccines during pandemics is always likely to raise ethical concerns.

8. Challenges of Acquisition and Distribution of SARS-CoV-2 Vaccine in Middle- and Low-Income Developing Nations.

The rapid spread of the contagion crosses the globe and within less developed countries in Asia and Africa has resulted in a significant global health emergency. Countries require context-specific responses dependent on the prevailing situation such as number of COVID-19 cases ranging from none to a limited number or increased number of cases [32]. Decisive actions are required and effective physical (social) distancing, use of quarantine and/or lockdowns, implementation of widespread testing, contact tracing in a systematic manner are necessary to reduce the risk of further spread of the disease [32]. In combination with extensive testing the distribution of vaccines in low income developing counties is a significant challenge due to conflict, over population in rural and urban areas, and lack of accessibility to basic health services [30]. In developing countries, the most significant challenge includes the need for systematic decontamination measures and massive testing to reduce the risk of a devastating outbreak. The acquisition of COVID-19 vaccines requires an in-depth analysis of the changing epidemiology of the disease including the period of incubation between appearance and duration of symptoms [35].

The distribution of a vaccine is currently determined by considering an ability to develop and initiate testing and purchase vaccines [35]. A small number of multinational companies produce most of the vaccines globally and are also involved in negotiating with the private and public[36] sectors to sell their vaccines. In this respect developed countries of the

world attempt to purchase access to vaccine candidates well in advance whereas due to a lack of resources, developing countries are unlikely to have early access the vaccines [35]. Consequently there is likely to be inequitable access and an unethical allocation of vaccines, depending on the ability of countries to pay for vaccines and distributive justice is one of the fundamental considerations necessary when distributing vaccines during such a pandemic so as to ensure that the principles of distributive justice are met and the allocation of scarce resources are applied equally to all viz., local, national and global communities [35]. However, the limited supply of vaccines and the mass demand during pandemic situations is a challenge when aspiring to equal distribution of resources.

The lack of accessibility to vaccines and storage conditions required may result in failure to achieve desired clinical outcomes even if bulk distribution of vaccines to developing countries was successful [31]. The inadequate refrigerated cold chain network in many developing countries therefore poses a significant challenge. Consequently vaccine candidates for COVID-19 requires that require long term storage at -20 °C to -70°C are likely to result in the loss of vaccine particularly if inadequate refrigerated cold chain networks exist [32]. Therefore, the acquisition, distribution and successful clinical application of SARS-CoV-2 vaccine in low- and middle-income developing nations may be extremely challenging.

9. Conclusions

In light of the analysis and review of the vaccines that have been developed and approved for emergency use in many countries it is evident that grey areas exist and scientists are yet to establish conclusive solutions to ensure successful treatment strategies. Similar concerns are shared by the World Health Organization (WHO) in that assurance of long-term immunity or estimated time of immunity protection with the current vaccines are not yet known. In addition, there is no certainty of immune response or durability thereof. Evidence from the clinical trial data has revealed that the current vaccines have a e capability to protect some individuals against disease but are not conclusive in respect of an ability to prevent transmission and subsequent infection following exposure to the COVID-19 virus.

Furthermore, there is a dearth of evidence regarding the age-related use of these vaccines as, by way of example, the use of the vaccine in paediatric subjects has not yet been undertaken and efficacy established and as such these populations remain at risk to transmission and infection by the virus.

An additional concern relates to the availability of the sufficient vaccine doses to cater for entire communities and/or populations so as to ensure protection to a significant number and wide range of individuals, which may reduce confidence in the current intervention strategy and fight against COVID-19.

Consequently, it is recommended that adherence to COVID-19 protocols such as hand sanitization, physical distancing and wearing of masks is maintained despite the state of vaccination of an individual or population as the COVID-19 pandemic

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A meta-analysis of Environmental factors influencing the development and spread of antibiotic Resistance

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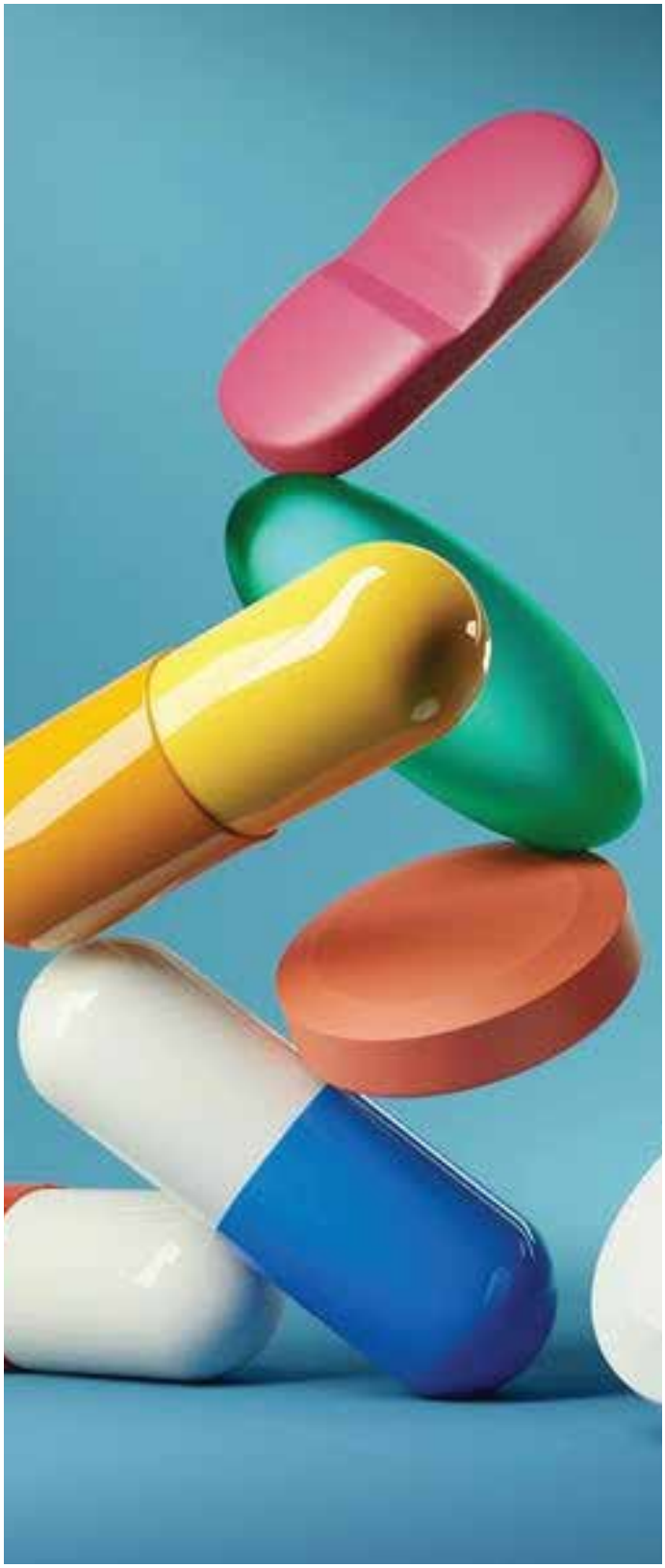

Abstract|

Antibiotics have massively improved the health of humans and animals since the antibiotic golden age up to date. Now the development of antibiotic resistance as a result of inappropriate drug use in medical and veterinary practice, food industries, agriculture and in communities is posing a global health problem. Most of the unused drugs, drug metabolites and residues enter the environment by several means thus affecting the natural ecosystems

They select the antibiotic-resistant mutants and facilitate the acquisition of antibiotic resistance determinants by the gene transfer elements that are progressively spreading among the environmental microbiota. Antibiotic resistance increases the cost of treatment, prolonged hospitalization due to resistant bacterial infections in addition to some individuals getting exposed to second and third-line drugs that are highly toxic thus increasing the adverse drug reactions in humans and economic loss in animals.
The aim of this research is to assess and analyse the environmental factors influencing the development and spread of antimicrobial resistance. To answer the aims and objectives of this study, a systematic review was adopted as an alternative suiting this study. Relevant data was taken from reliable sources and selected using prisma flowchart as a criteria for information inclusion and exclusion. Five reliable articles out of 60 articles were selected for data analysis.

The extensive use of antibiotics as well as inappropriate use has affected the environmental microbiota of the ecosystem, destruction of useful bacteria in the environment including the normal flora as well as increasing the selection of the pathogenic antibiotic resistant bacterial organisms that have led to their spread globally

Key words| Antibiotics, antibiotic resistance, environment microbiota

Background

Antimicrobial resistance highly contribute to a lot of deaths annually and this concerning issue has made WHO to seriously take it or recognize it as major health problem (WHO 2014). Recently, researchers have shown that normally, the struggle to eradicate antibiotic resistance growth has mainly happened in clinical, community and in recent years also agricultural sector (Bengtsson, P.J., et al 2018).

.According to Sahoo, C.K., et al 2010 antibiotic resistance is a serious crisis that troubles both current and future generations and pointed it out to be a situation necessitating urgent preventative measures to elude outbreak of untreatable infections. Lack of knowledge of how the environment can facilitate development and growth of antibiotic resistance unintentionally this it to be one of main drivers of antimicrobial resistance (Bengtsson, P.J., et al 2018).But the findings of study conducted by Hiltunen, Virta and Laine 2017 revealed that having knowledge about how environmental factors can drive antibiotic resistance may allow us to devise relevant/appropriate ways of how antimicrobial resistance occurrence can be reduced and managed. The impact of environmental influence on the use of antibiotics and resistance development in bacteria is primarily unknown and this force serious studies to be carried for this issue to be urgently addressed accordingly locally, regionally and internationally (Sahoo, C.K.,et al 2010).

.Farm animals has been pointed out to be the most to be exposed to large quantities of antibiotics and they act as reservoir of resistance genes while human production and use of antibiotics also in the farm or in clinic is also a recent addition to the natural and past process of antibiotic production and resistance development that happens on a global plate in the soil (Woolhouse, M., et al 2015).

HISTORY OF ANTIBIOTICS / ANTIMICROBIALS

According to Tomoo SAGA and Keizo YAMAGUCHI 2009 first antimicrobial in the world was salvarsan, a medication for syphilis that was produced by Ehrlich in 1910, in 1935 sulphonamides were synthesized by Domagk and other researchers, because this agents were synthetic they had limitations in terms of safety profile and efficacy. In 1928, Fleming discovered penicillin where he found that the growth of Staphylococcus aureus was inhibited in a zone surrounding a contaminated blue mold (a fungus from the Penicillium genus) in culture dish (Ventola, C.L.,P1, 2015) .Penicillin, which is is known to be having an outstanding safety and efficacy led in the era of antimicrobial chemotherapy by saving the lives of countless wounded soldiers in World War II and in two consequent years , new classes of antimicrobial agents were discovered and developed one after another, leading to a golden age of antimicrobial chemotherapy Tomoo SAGA and Keizo YAMAGUCHI 2009)
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In 1944, streptomycin, an aminoglycoside antibiotic, was discovered from the soil bacterium Streptomyces griseus and then chloramphenicol, tetracycline, macrolide, and glycopeptide (e.g., vancomycin) were discovered from soil bacteria (Rather, I.A., et al).

The development of bacteria resistant to frequently used antibiotics compromises operative treatment of infections resulting in the need for stronger drugs and more costly therapy (H. Wang., et al 2012). Also the WHO 2018 report revealed that around 2.4 million people could die in high-income countries between 2015 and 2050 without a sustained effort to contain antimicrobial resistance. Resistant bacteria dramatically reduce the possibilities of treating infectious diseases effectively and multiply the risks of complications and a fatal outcome for patients with infections of the blood.

Since Botswana is a middle developing nation there are still gaps in various sectors operating locally and in health sector a couple of environmental factors have shown to be one the most drivers of antimicrobial resistance. Human, plants and animals interface revealed that all this creatures depend on each other for survival. A full understanding of the ability of compensatory mutations to reduce the costs of resistance will help healthcare providers and the public as well to be aware of the danger/risk of inappropriate use of antimicrobials in the environment. (Melnyk, H,A., et al 2014).

Antimicrobials are used globally both in humans and in animals for the prevention and treatment of infectious diseases and in some countries, antimicrobial agents are used in animal farming as growth promoters, but antibiotic-resistant microbes are profoundly of paramount importance to human health even though the environmental reservoirs of resistance determinants are poorly understood (Heather K Allen., et al 2010).

Antimicrobial drug resistance globally has been of great concern. The the danger and extensive ramification that it present us with requires urgent global intervention. A number of research focusing on antimicrobial resistance has demonstrated significant transmission patterns and most of them have environmental implication. Appearance of these resistance microorganism demands robust intervention and police shift. In Botswana, there exists scanty data addressing this topic. Irrational use of antibiotics have been rampant. Use of antibiotics and other agents in the environment have influenced horizontal transfer of resistance factors. Its against this background that I chose to review this topic extensively.

RESEARCH AIM

The aim of this research is to assess and analyse the environmental factors influencing the development and spread of antimicrobial resistance

OBJECTIVES

1.To evaluate how environmental factors, influence development and widespread of antibiotic resistance.
2.To evaluate how misuse of antimicrobial agents by the public impact and contribute to global antibiotic resistance.

METHODOLOGY

In order to answer the aims and objectives of the research topic, data was systematically reviewed. The databases used for attaining the information included PubMed, Google scholar. The utilization of the multiple databases presented the opportunity to gain accurate and reliable information. PRISMA tool was also utilized for screening the research resources.

RESULTS

Several reputable sources of data were consulted and after removing duplicates 60 articles in total were identified through the systematic literature search. Articles were then screened and 30 of them were removed due to inconclusive results and findings. After full-text assessment for eligibility of the remaining 30 articles, a total of 20 articles were excluded because they had abstract only therefore remaining with 10 articles which were further screened. 5 journals were subsequently excluded due conflict of interest by authors. A total of 5 articles were included for the final analysis

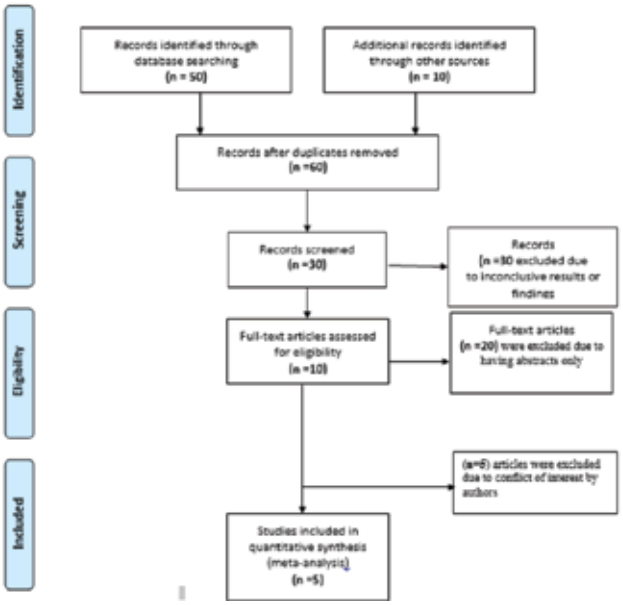
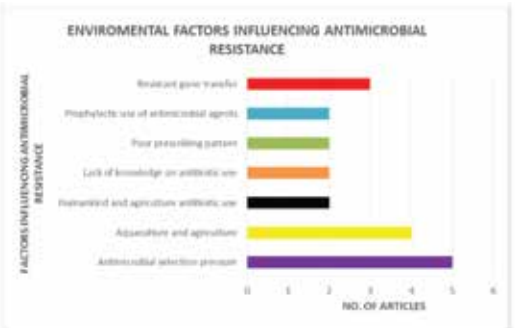


Fig 1.2| KEY RESULTS AND DISCUSSION



DATA ANALYSIS AND INTERPRETATION

Resistant Gene transfer

Researchers revealed that antibiotic resistance genes (ARGs) are developing contaminants putting the whole world under high risk and rigorous animal husbandry is assumed to be a main driver to the amplified environmental burden of ARGs (Zhu, Y.G.,et al 2013) . Also thesis review have shown that resistant gene transfer contribute by 60% to antibiotic resistance which is global crisis.

Prophylactic Use of Antimicrobial Agents

According to Callens, B., Persoons., et al 2012 93% of the group treatments were prophylactic whereas only 7% were methaphylactic and this study have shown that prophylactic group treatment was applied in 98% of the visited herds where broad spectrum antimicrobial agents were used. In Belgium, the guidelines for prudent use of antimicrobials are not yet implemented (Callens, B., Persoons. et al 2012). 40 % has been revealed by this review to be contributing as environmental factor influencing worldwide antibiotic resistance. But, Daneman, N., et al 2013 pointed out that the effect of decontamination on ICU-level antimicrobial resistance rates is understudied.

Poor Prescribing Pattern

Hicks, L.A., et al 2015 revealed that healthcare providers prescribed 262.5 million courses of antibiotics in 2011(842 prescriptions per 1000 persons and the prescribing rate was higher in the South census region (931 prescriptions per 1000 persons) in which most of them were prescribed irrationally therefore efforts to characterize antibiotic prescribing practices is necessary and in which understanding of the factors leading to high prescribing among key target populations will inform appropriate prescribing interventions. This thesis have shown that 40 % of environmental factors influencing antimicrobial resistance is contributed by poor prescribing pattern. Also the findings of study conducted by Abera, B., Kibret, M. and Mulu, W., 2014 the two most important factors mentioned for AMR development were patients' poor adherence to prescribed antimicrobials (86%) and overuse of antibiotics (80.5%).

Lack of Knowledge on Antibiotic Use

A couple of physicians and nurses lack up to-date knowledge on AMR and almost 47% of them have low knowledge regarding action, use, safety and resistance of antibiotics (Awad, A.I. and Aboud, E.A., 2015). 41% of prescribers had attitudes towards using and accessing antibiotic irrationally. This review have shown that 40 % of environmental factors influencing antibiotic use is contributed by lack of knowledge on antibiotic use.

Humankind and Agriculture Antibiotic Use

According to Graveland, H., et al 2010 human MRSA carriage was intensely linked with intensity of animal contact and with the number of MRSA positive animals on the farm. 40% of environmental factors influencing antibiotic resistance is contributed by use of humankind and Agriculture antibiotic use.

Aquaculture and Agriculture

According to Cabello, F.C., et al 2016 aquaculture uses hundreds of tonnes of antibiotics annually to prevent and treat bacterial infection and the passage of these antibiotics into the aquatic environment selects for resistant bacteria and resistance genes and he lamented that this encourages bacterial mutation, recombination, and horizontal gene transfer. This thesis revealed that 80 % of environmental factors influencing antibiotic resistance is contributed by aquaculture and Agriculture.

Antimicrobial Selection Pressure

According to Holmes, A.H., et al 2016 to fight the danger to human health and biosecurity from antibiotic resistance, an understanding of its mechanisms and factors is required. Antibiotic resistance selection is driven by antimicrobial exposure in health care, agriculture, and the environment and also onward transmission is affected by standards of infection control, sanitation, access to clean water, access to assured quality antimicrobials and diagnostics, travel, and migration.

CONCLUSION

It is now evident that antibiotic agents play a crucial role in our everyday lives as they are used in various sectors such as in the treatment of both human and animal bacterial diseases, by livestock farmers as feed additives to enhance growth of livestock animals, in food industries as preservatives and in commercial ethanol production to prevent bacterial contaminants of the fermentation plants, in horticulture to treat plant diseases as well as in tissue cultures. However, according to the study conducted by Godfrey S. Bbosa1, 2 and Norah Mwebaza 2013 there is a huge prevalence of irrational use antibiotics in the above aforementioned sectors above as this affected the environmental microbiota of the ecosystem, destruction of useful bacteria in the environment including the normal flora as well as increasing the selection of the pathogenic antibiotic resistant bacterial organisms that have led to their spread worldwide.

In conclusion, this study urge all environmental regulatory statutory bodies to revisit their policies and formulate well suiting ones to curb or professionally combat environmental factors influencing antibiotic resistance

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A SYSTEMATIC REVIEW OF THE EFFECTS OF IRRATIONAL USE OF ANTIBIOTICS

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Abstract |

An antibiotic is an agent that inhibits bacterial growth or kills bacteria/any substance produced by a microorganism that is lethal to the growth of other microbes. Although antibiotics play a crucial role in saving almost everyone against infections its inappropriate use can lead to fatal repercussions like the emergence of antibacterial resistance microorganisms

The aim of the study is to evaluate the effects of irrational use of antibiotics and its impact on antibiotic resistance which is a global crisis.

For the aims and objectives of this study to be answered, a systematic review approach was adopted and this methodology suitably applied well in our research design. Data was collected from academically reputable data bases and studies were selected using the PRISMA tool approach for inclusion and exclusion. Five articles were selected in the final analysis of the findings.

The major findings identified by this study connected several factors related to irrational antibiotic usage to be increasing antibiotic resistance. Among these include the spread of resistance facilitated by self-prescribing of antibiotics, poor regulatory monitoring, poor compliance to antibiotic prescribing, limited antibiotic options, lack of knowledge on antibiotic use, inappropriate antibiotic prescribing, counterfeit medicines, availability of antibiotics as OTC drugs and overprescribing of antibiotics.

In conclusion we can say that, irrational use of antibiotics is associated with increased antibiotic resistance and therefore there is an urgent need to improve/monitor antibiotic prescribing practice in primary healthcare delivery system locally in Botswana, regionally and globally

Background

The inappropriate and irrational use of antibiotics has contributed significantly to the development of antibiotic resistance and patients infected with resistant organisms have an increased risk of poor clinical outcomes, including death, and consume more healthcare resources.

According to the World Health Organization (WHO), resistance to the antibiotics is one of the major threats to human health today. Antibiotic resistance is defined as the resistance of microorganisms to antimicrobial agents and that happens when bacteria changes to protect itself from antibiotics.

Antibiotics are deemed to be among the most frequently sold drug classes in the developing countries (Buke et al., 2003). According to the findings of the study conducted by Metlay, J.P et al., 1998 the irrational use of antibiotics emanates from for example, negligence of physicians and the sale and pharmaceutical marketing of antibiotics without prescription in some countries.

Inappropriate use of antibiotics is a serious public health problem locally, regionally and

internationally hence gives the whole world an assignment to devise relevant measures to monitor antimicrobial agent's usage as misuse of this agents lead to the development of antimicrobial resistance (Wutzke, S.E.2005).

Based on the findings of Chopra, I. and Roberts, M., 2001 it is highly possible that a single antibiotic may not only select resistance to just one particular drug. This means resistance can occur with other drugs of similar structure and related compounds of the same class. For example, resistance to tetracycline may result resistance to oxytetracycline, chlortetracycline, doxycycline, and minocycline.

In 2014 World Health Organization (WHO) cautioned that the antibiotic resistance dilemma is reaching epic proportions and also MDR bacteria have been confirmed to be a significant danger to public health and national security by the IDSA and the Institute of Medicine, as well as the federal Interagency Task Force on Antimicrobial Resistance (Golkar, Z et al., 2014).

There is need for sensitization and education of healthcare sector and public on irrational use of antibiotics and their impact on antibiotic resistance and the ways to alleviate the problem, more especially in our country Botswana since limited studies have been conducted in this topic.

RESEARCH AIM

The aim of the study is to evaluate the effects of irrational use of antibiotics and its impact on antibiotic resistance which is a global crisis

GENERAL OBJECTIVE

The general objective of the research is to establish key factors that bring about the irrational use of antibiotics, and its effect on antibiotic resistance.

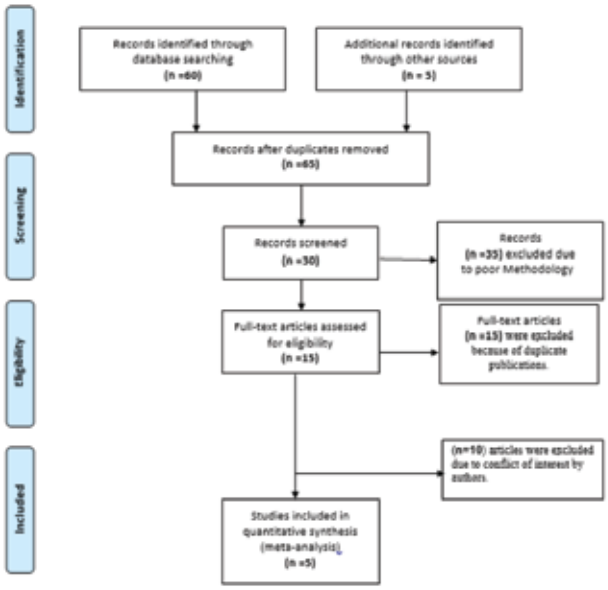
SPECIFIC OBJECTIVES

1. To explore actions that are being used to counteract the antibiotic resistance crisis globally.
2. To explore those actions being used in Botswana to address antibiotic resistance.
3. To determine possible implementations to alleviate the problem of antibiotic resistance

METHODOLOGY

In order to answer the aims and objectives of the research topic, secondary data was systematically reviewed. Data was collected from academically reputable data bases like PubMed and Google scholar the utilization of the multiple databases presented the opportunity to gain accurate and reliable information. Studies were selected using the PRISMA tool approach for inclusion and exclusion. Five articles were selected in the final analysis of the findings.

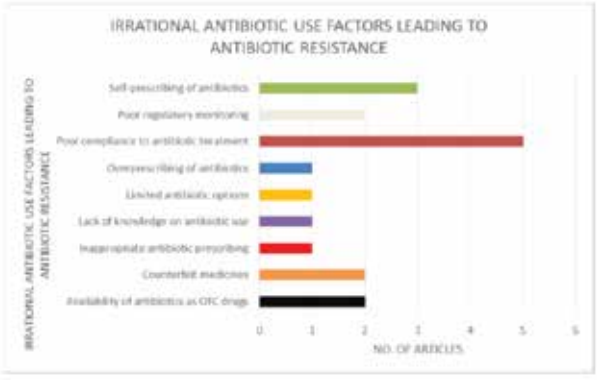
Figure 1 Prisma diagram, showing the criteria for selecting journals



RESULTS

Several reputable sources of data were consulted and after removing duplicates 65 articles in total were identified through the systematic literature search (see PRISMA flow diagram in figure 1). Articles were screened based on their year of publication and other Key aspects of PRISMA governed the research process. 35 had poor methodology and were excluded. After full-text assessment for eligibility of the remaining 30 articles, a total of 15 articles were excluded due to multiple publication hence remaining with a total of 15 articles which were further screened, and 10 journals were excluded due to conflict of interest by authors. A total of 5 articles were included for the final analysis.

Fig 1.2| KEY RESULTS AND DISCUSSION



DATA ANALYSIS AND INTERPRETATION

Availability of antibiotics as OTC drugs

According to Dameh, M., et al 2010 giving out antibiotics over-the-counter unnecessarily led to development of bacterial resistance something which necessitates urgent action to be taken. This review have revealed that 40% of irrational use of antibiotics is contributed by availability of antibiotics

over the counter. Also Toutain, P.L. et al 2013 indicated that in both human and veterinary medicine, it has been shown that overflowing the market with different generics and/or branded drugs has amplified overall antibiotic intake connecting with the development and spread of bacterial resistance to antibiotics. Therefore appropriate policy measures have to be set prohibiting the issue of giving out antibiotics an OTC medicines.

Self-prescribing of antibiotics

Self-medication is a world-wide phenomenon and capable drivers of antibiotic resistance globally and the results of such practices must always be highlighted to the public because inappropriate use of antimicrobials without medical regulation may result in a higher risk of incorrect, or undue therapy, missed diagnosis, delays in appropriate treatment, pathogen resistance and increased morbidity (Bennadi, D., et al 2013).According to Hernandez-Juyol, M., et al 2002 there is need to augment awareness and implement regulations to support judicious and safe practices. This thesis revealed that 17,6% of irrational antibiotic use and antibiotic resistance is contributed by self-medication. Self-medication is the use of antibiotics to treat or eradicate self-prescribed drug for chronic or recurrent condition (Alhomoud, F.,et al 2017).All this irrelevant or misuse of antibiotics increase the current global antimicrobial resistance.

Poor regulatory monitoring

According to Gould and Bal. et al 2013 poor infection control practices, inappropriate antibiotic use and the consistent dismissal of warnings against overuse of antibiotics normally lead development of antimicrobial resistance now putting the whole public locally, regionally and internationally under high risk of untreatable infections. This review have revealed that 11.8% of irrational or inappropriate use of antibiotics is influenced by poor monitoring of antibiotic usage and this gab gives all relevant healthcare sector to formulate and implement appropriate measures to address this issue accordingly. This concerning issue have also been supported by the findings of Centres for Disease Control and Prevention (CDC) which lamented that bacteria for develop resistant to antibiotic if has exposure to that agent frequently or over and over unnecessarily (CDC, 2013).

Lack of knowledge on antibiotic use

According to Napolitano, F., et al 2013 the irrational and inappropriate use of antibiotics in primary healthcare delivery system may results from a complex collaboration between several factors, such as practices of physicians, the patients' attitudes, beliefs, knowledge of antibiotic use, the self-medication etc. Therefore, regulating the antibiotic use needs a complex approach with knowledgeable and engaged health-care professionals, pharmacists, health authorities, and consumers. Review have revealed that 5.9% of irrational use of antibiotics in general is caused by lack of knowledge on rational use of this agents.

There is an urgent requirement of discovering newer antibiotics to fight the drug-resistant pathogens and to reduce the mortality linked with drug resistance and this need can only be fulfilled via (Gould and Bal, 2013; Spellbergand Gilbert, 2014).This need can be fulfilled through conduction of collective research work at local, regional and international level and making the public aware of risks and consequences of inappropriate/irrational use of antibiotics (French, 2010).Researchers have found that microbial resistance is so prevalent and fatally dangerous and currently becomes an international concern.

Inappropriate antibiotic prescribing

According to Krushna Chandra Sahoo., et al 2010, prescribing of any type of higher antibiotics unnecessarily or inappropriately was initially was one of the reasons for limited yielding of desired outcomes. This review have found that % of irrational use of antibiotics is contributed by inappropriate prescribing of antibiotics in primary healthcare facilities in this has being pointed out the major driver of global antimicrobial resistance. High patient load can cause improper diagnosis, leading to inappropriate management and incorrect use of antibiotic, therefore all relevant diagnostical and treatment guidelines have to be put in place to ensure that there is rational prescribing of antibiotics in healthcare settings (Krushna Chandra Sahoo., et al 2010).

Counterfeit medicines

According to Essack et al., 2011 counterfeiting of pharmaceuticals is highly challenging in all parts of world to the extent that one in five medicines sold is estimated to be counterfeit. Also findings of couple of studies revealed that majority of counterfeit medicines have been imported from India and Pakistan and reach pharmacies through illegal means to the extent that South African Medicines and Medical Devices Regulatory Authority (SAMMDRA) failed to curb this problem. Therefore, sales data may provide a misleading and inaccurate measure of the use of antibiotics because of counterfeiting.

Limited antibiotic options

Irrational use of antibiotics as prophylaxis, for a prolonged duration and use of broad-spectrum antibiotic can results in antibiotic resistance which in turn might lead to increased morbidity and mortality rates either locally, regionally or internationally (Bbosa, G.S. 2013).This review revealed that % of irrational use of antibiotics in clinical practice is contributed by limited choices or options of antibiotics in management of infections which in turn result in inappropriately use

of available, but now worsening antibiotic resistance issue unnecessarily.

Overprescribing of antibiotics

Study conducted in India revealed that antibiotics are prescribed at an incorrect dose, frequency, or duration, and this over prescription or overuse are seen in all healthcare settings like public and private hospitals, clinics and pharmacies (Kotwani, A. and Holloway, K., 2011). According to this thesis 5.56% of current irrational prescribing of antibiotics is contributed by overprescribing of antibiotics and this in turn results increased antimicrobial resistance and morbidity/mortality

Poor compliance to antibiotic treatment

According to Cetinkaya et al., 2010 various factors may heighten inappropriate antibiotics usage, which could be due to doctors' knowledge and experiences, diagnostic uncertainty, patients' expectations, lack of patient and health care professionals education, pharmaceutical marketing, antibiotic selling without a prescription as well as economic and political reasons. This thesis revealed that 29,4% of antibiotic resistance is contributed by poor compliance to antibiotic treatment. Misuse of antibiotics in eradication of viral infections is mutual and the prevalence of self-medication is alarmingly high (Sawair et al., 2009). Researchers have agreed that there is need to further search and hold the vital issue of antibiotics misuse is in both public use side and patient's side Arnold and Straus, 2005 also denoted that important approaches to control antibiotic resistance it may be through educational interventions directed at patients.

CONCLUSION

In conclusion we can say that, irrational use of antibiotics is associated with increased antibiotic resistance and therefore there is an urgent need to improve/monitor antibiotic prescribing practice in primary healthcare delivery system locally in Botswana, regionally and globally. Key factors like, self- prescription, lack of knowledge of antibiotic use (Rather IA, et all., 2017), over prescription by prescribers and the general lack of stout rules and regulations to govern the use of antibiotics, are some of those that need to be seriously addressed if any difference will be made. The key solution is awareness, sensitisation, locally, regionally and to the world, to educate all stake holders to educate each and every one affected in this crisis. Regulations by the necessary bodies have to be stern to facilitate the acceptable standards

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Clients Serviced

PHYSICOCHEMICAL CHARACTERISATION OF THREE BRANDS OF IBUPROFEN 400 mg TABLETS IN GABORONE, BOTSWANA

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Abstract|

Non-steroidal anti-inflammatory agents like ibuprofen are widely used in management of pain and inflammatory illnesses. Ibuprofen availability in different brands brings about a great challenge to health experts as it is indicated for different therapeutic purposes. The aim of the study was to evaluate physicochemical properties of commercially available three brands of ibuprofen 400 mg tablets in Gaborone, Botswana. The Ibuprofen tablets` brands were acquired from the community pharmacy and evaluated for organoleptic properties, uniformity of weight, friability, disintegration, hardness and assay by visual titration. The results of the three brands; Apo-ibuprofen, Ibunate and Ibufen were found to be 0.57 ± 0.004, 0.54 ± 0.004 and 0.88 ± 0.027 for uniformity of weight, friability of 0.04%, 0.03%, and 0.003%, disintegration time of 1.49 min, 5.39 min and 21.19 min, as well as hardness of 8.0 ± 0.61, 6.8 ± 0.76 and 5.6 ± 0.65, respectively.

For assay, 3 brands of Ibunate, Ibufen and Apo-ibuprofen gave percentage contents of 95.6 ± 5.0 %, 95.7 ± 2.2 % and 82.1 ± 3.9 %, respectively. In conclusion, the three brands met the international standards of BP 2018 for physical tests of uniformity of weight, friability, disintegration and manufacture`s specification for hardness. However, only Apo-ibuprofen failed the assay specification.

This variation in the strength of ibuprofen calls for the need to undertake the study in other medicines and that the study be extended to other parts of Botswana to ensure quality medicines. In addition, Apo-ibuprofen brand should undergo further scrutiny by Botswana Medicines Regulatory Authority (BoMRA) to ascertain this findings.

Key words| Ibuprofen, Physicochemical, Brand, Tablets, Characterisation.

Background

The spread of substandard and adulterated pharmaceutical merchandises is a global spectacle, which has been of great concern to many countries as stated by (Clarke, S., 2002). ISO 8402-1986 standard define quality in a totality of features and characteristic of a product or services that bears its ability to satisfy the stated or implied need and Uddin et al add to say quality is the result of intelligence efforts not an accident, this is of sensitive issue as pharmaceutical industry is concern (Dewan, S.M.R., 2013 et al). The lack of facilities for effective quality control analyses as an important element in quality surveillance and ineffectiveness of drug regulatory authorities is one of the factors that lead to substandard products in importing countries (Ebeshi, B.U., 2009 et al).

Non-steroidal anti-inflammatory drugs such as ibuprofen have been used over a decade in management of a multitude of pain, rheumatic diseases and may have a role in the treatment of conditions characterized by inflammatory processes (Klueglich, M., 2005 et al).
This drug belongs to class II in The Biopharmaceutical Classification System, which means that despite the good permeability, this drug has poor solubility (Grimling, B., 2015 et al). The history of ibuprofen is inextricable linked with the understanding of the concept and process of pathogenesis of inflammatory diseases which is believed to have begun over 40 year ago with the influence of the actions of the therapeutics used by that time (Rainsford, K.D., 2003). Dr. Stewart Adams was the principal initiator who led to the discovery ibuprofen. He has written quite a number of the pharmacological factors of the discovery of propionic acids (Rainsford, K.D., 2003).

Dr. Steward Adams who was a pharmacologist at the research department of the Boots Pure Drug Company Ltd at Nottingham, UK stated this with the aim to discover an analgesic drug possessing efficacy of great value over aspirin as stated by (Rainsford, K.D., 2003). Kim D state thus Dr. John Nicholson on the other hand grew to become the first individual to synthesize ibuprofen after he reviewed in depth the medicinal chemistry of the propionic acids and their chemical discovery technique underlying the development of ibuprofen (Rainsford, K.D., 2003). Ibuprofen is available as tablets in different names. Tablets are solid preparations each containing a single dose of one or more active substances and usually obtained by compressing uniform volumes of particles (Jayan, S.C., 2014 et al).

In this Modern era of today many companies manufacture the same medication in the same dosage forms which are tablets, capsules, syrup, etc. at different trade names also known as brand names, which put users of these medication at a greater dilemma of which brand is good for them, because the active content is the same in all the brands. Even if the active ingredient is the same the physicochemical characteristics of these dosage form play a greater central role in which they can end up giving the user the assumptions that the other tablet of the same active ingredient is more efficacious than the other.

The active ingredient of ibuprofen in spread evenly across the dosage form like any other drugs, so these content might decrease with time depending on the shelf life and stability. So measures need to be put to play to examine the physicochemical characteristics such as uniformity of weight, friability, hardness, disintegration, and percentage content which all of these play a mutual role towards the stability, the shelf life and the therapeutic effect of our product. Uniformity of weight ensure accuracy and consistence of dosage form within a batch. Friability is the tendency of a solid substance to break into smaller pieces under duress or contact which can end up decreasing the active content of our tablet. Hardness determine the breaking point and structural integrity of the tablet, so hardness of tablets have a great effect on the disintegration and dissolution of which in turn play a major role in the release of active ingredient, absorption, bioavailability and therapeutic effect. Quality of the product must be ensured according to compendia of drugs and this pharmacopoeias are called drugs standard (Uddin, M.S., 2015 et al).

Health care providers in the community pharmacy are facing problems of choosing which brand(s) of ibuprofen tablet (400 mg) is (are) appropriate for their patients as many brands are now available within the country's market and as believed by most consumers, a certain brand possesses more efficacy than other brands hence patients insist on demand of brands with perceived better efficacy. Herein, three brands of ibuprofen were analyzed in the laboratory to establish if they meet the BP specifications through the evaluation of their physicochemical characteristics.

RESEARCH AIM

The aim was to carry out a comparative study of 3 brands of ibuprofen through investigating their physicochemical characteristics.

HYPOTHESIS

It was hypothesized that there was variation in efficacy of different brands of ibuprofen due to variations in their physicochemical characteristics.

METHODOLOGY

Commercially available three brands (Apo-ibuprofen, Ibunate and Ibufen) of ibuprofen 400 mg tablets were purchased from pharmacy outlets (Gaborone, Botswana) and evaluated for physicochemical properties of uniformity of weight, friability, disintegration, hardness and assay. The tablets formulations were assessed as per the British Pharmacopoeia (BP), 2018 and unofficial standards as recommended by the manufacturers.

Fig 1: Physical test parameters' measurements for the 3 ibuprofen 400 mg tablets' brands

Table 1: Assay of 3 brands of ibuprofen by visual titration

Brand	Percentage content ±SD
Apo-ibuprofen	82.1 ±3.9
Ibunate	95.6 ±5.0
Ibufen	95.7 ±2.2

DATA ANALYSIS AND INTERPRETATION

1. UNIFORMITY OF WEIGHT

Uniformity of weight apply to dosage forms which are supplied in single dose forms because of their susceptibility to more variants than comparable preparations supplied in multi dose forms. It is necessary that entirely the drugs of a particular lot must be uniform in weight. Medicines are designed to contain a precise amount of drug in a detailed amount of a formula, the mass of the tablet being made is consistently measured to aid safeguard that a dosage contains the proper amount of drug. If there is any weight deviation, it must fall inside the prescribed limits. Looking at the average weight of the brands examined which are indicated in table 9 shows that the range of the average weight fall above 250 mg.

Therefore BP 2018 states that for tablets with average weight of greater that 250 mg, no more 2 individual mass should deviate from the average mass by ± 5% and no more than 1 individual mass should deviate by double the percentage of ± 5%, hence stated thus the result of uniformity in table 5, 6 and figure 4, signify that all the brands were successful within the specification, though 2 tablets from Ibufen were out of range with a percentage of a range of ±5 % as shown in figure 3. The pharmacopeia complied with respect to uniformity of Weight of all the brands examined. Although the tablet weight is not necessarily equal to the active ingredient of the tablet, a more that 5% increase reflects a bit on an increase of the active ingredient and noticing the average difference within the brand could result in raised suspicion on the general equivalence of the aforementioned brands. So this variation could be as a result of the amount of excipient included in the tablet formulation. It can also be due to errors arising during experimental measuring of the mass of these tablets. In addition, errors might also be due to the air flow around the weighing balance that impact the interpretation of weighing balance. All these errors will lead to imprecisions of measurement of mass.

2. FRIABILITY

Friability test was executed to assess the capability of the tablets to bear scrape in packing, handling and transporting. It was measured since tablet hardness is not a complete parameter of strength due to the tendency of some tablets capping on abrasion, losing their crown portions when compressed into very hard surfaces. This test is significant in a sense that the tablets can cap leading to a reduction in the active ingredient of the tablets because it is assumed that the active moiety is distributed equally across the dosage unit. Capping may reduce the active moiety which can lead to under dose. A minimal friability values for all the tablet brands was a suggestion of the ability of the tablet to withstand stress due to abrasive forces, without crumbling during shipping, packing, handling and dispensing. These values also reflect the hardness of the tablets. The Pharmacopoeia (BP 2018) states that the friability value of tablets should be less than 1%. Friability results of the three brands assessed complied with BP 2018. The three brands Apo-ibuprofen, Ibunate and Ibufen gave friability values of 0.04%, 0.03% and 0.003%, respectively as shown in table 6. These results indicated that the brands were of quality due to their ability to resist pressure exacted upon them. The three samples gave very small percentage value, implying that the difference between the initial weight before friability and the final weight after tablets where exposed to pressure could be due to external factors. The air flow around the weighing balance that impact the interpretation of weighing balance.. This factor could contribute to significant change in the sample mass read and affect the final result. Even though the brands passed the test when these results were compared to the results of the study conducted by Eraga, S.O., et al 2015, where they also assessed the friability of ibuprofen tablets, they indicated high percentages of friability than these results which can signify that these brands display good abilities to resist pressure from external forces during transportation, handling and dispensing.

3. DISINTEGRATION

This is defined as the state in which no residue of the dosage unit under test remains on the screen of the apparatus, therein symbolizing the time taken for the dosage unit to breakdown when it comes in contact with the gastric fluids. The process of disintegration does not imply complete dissolution of the tablet or the drug. It is used as a guide to the formulator to produce quality formulation and also to ensure uniformity of dosage forms with the batch and batch to batch uniformity because the manufacturing process and the type, amount of excipients such as binders are also known to impact the disintegration of the dosage unit. The disintegration time plays a major role in the dissolution time of the tablet, which will impact absorption, bioavailability and the therapeutic effect of the dosage unit and as such it can be the rate limiting step for absorption. The analysis of the results are specified in table 7. The British pharmacopeia 2018 stipulates that the disintegration for coated tablets is 60 minutes and disintegration for the indicated results of all the brands showed compliance with BP 2018 as illustrated in figure 4. Even though the tablets passed the test, the variation in disintegration time between the brands was noticed in Appendix 1, 2, 3 with Apo-ibuprofen and Ibunate giving a small disintegration times while Ibufen gave the high disintegration but within the acceptable limit. This implies that the brands would definitely have good absorption. However, this experiment could fail due to less amounts of disintegrates required to aid the breakdown of the tablets into primary powder when introduced to gastric fluids. A greater compaction force during manufacturing will lead to slow disintegration which then result in delayed onset of action of the drug.

Even if disintegration test permit for accurate measurement of the construction of fragments, granules, or aggregates from solid dosage forms, no information was obtained from these tests on the rate of dissolution of the active drug. In general, the disintegration test serves as a component in the overall quality control of tablet manufacture.

4. HARDNESS TEST

Tablet needs a certain amount of strength to withstand mechanical shocks of handling in manufacture, packaging and shipping. In addition, tablets must be capable to endure sensible abuse when in the hands of purchaser. Acceptable tablet hardness and resistance to crushing are necessary for customer acceptance. Although hardness is significant to resist external force, it also plays a major role in relation to disintegration and perhaps to more significance, towards drug dissolution release rate. Checking of tablet hardness is particularly significant for medication products that possess actual or potential bioavailability complications or those that are subtle to altered dissolution release profiles as a purpose of the compressive force. So, it is essential to check the hardness of tablets when they are being compressed and pressure adjusted accordingly on the tablet machine. Table 7, 9 and figure 4 displace the results of the hardness test conducted on the three brands. It indicates individual tablets hardness and average hardness for every brand.

The hardness was measured in kg/cm2 and were obtained through the use of Monsanto hardness tester. The results complies with the manufacturer`s specification which states that tablet hardness should be within a range of 5-10 kg/cm2. The mean ±SD% of the Apo-ibuprofen (8.0 ±0.61), Ibunate (6.8 ±0.76), Ibufen (5.6 ±0.65). These mean values imply that Apo-ibuprofen is harder than the other two samples whereas Ibufen recorded the least mean value. Though Ibufen recorded the least mean value this could have been due to the shape of the table. When using the Monsanto hardness test, shape plays a crucial role because the tablet under test must be held alone its oblong axis in between the two jaws of the tester by pushing forward the movable face inside through turning the plunger clockwise.

This means that pressure was already being exacted on the tablet at 0 kg/cm2. Ibufen had fine, soft, sharp sliding edges which disable the table to be held along its oblong axis hence required more pressure to be held along its oblong axis at 0 kg/cm2. When pressure was applied to test for its hardness it broke at lower kg/cm2 values than Apo-ibuprofen and Ibunate. Therefore this factor contributed to the lower mean value of Ibufen. Since hardness has an impact on disintegration time of tables it was expected to see Ibufen disintegrating faster than Apo-ibuprofen and Ibunate. It recorded a greater disintegration time than the other samples. However, this does not dispute the fact that hardness affects disintegration which in turn affects the dissolution rate, delaying drug absorption which reduced bioavailability resulting in minimal therapeutic effect. So the difference in the disintegration in the presence of the hardness of Apo-ibuprofen could be due to added disintegrants which aid in the breaking up of the tablet when exposed to gastric fluids.

5. ASSAY

Assay was used to examine the active content of Ibuprofen in the tablet. According to the British Pharmacopoeia (BP) 2018, in order to formulate an efficacious dosage unit the amount of the active content should be between 95- 105 % of the labelled ibuprofen, therefore any value that falls off the range was regarded as a failure. From the experiment as illustrated from table 10, the 2 brands of Ibunate and Ibufen gave a percentage content which was within the (BP) specifications as follows 95.6% and 95.7 %, respectively while Apo-ibuprofen showed a percentage content of 82.1% which fell out of the range of 95 %- 100 %, this implies that it did not comply with the specifications of the B.P 2018. These findings prove the variation of the active ingredients within the brands of ibuprofen 400 mg. The implication of the lower active content is that this brand may lead to under dose which gives reduced bioavailability and therapeutic effect of the dosage unit. Therefore, it is important that these physicochemical parameters of same strength units are examined from time to time to verify their compliance with international standards.

CONCLUSION

In conclusion, the three brands (Apo-ibuprofen, Ibunate and Ibufen) complied with the international standards of BP 2018 for physical tests of uniformity of weight, friability, disintegration and manufacture`s specification for hardness. However, of the three brands studied for assay (chemical test), only Apo-ibuprofen failed the specification. In order to ensure quality medicines, it is recommended that other medicines be subjected to the study and that the study be extended to other parts of Botswana. In addition, Apo-ibuprofen brand should undergo further scrutiny by Botswana Medicines Regulatory Authority (BoMRA) to ascertain this findings.

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THE ROLE OF COMMUNITY PHARAMCISTS : A SYSTEMATIC REVIEW

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Abstract|

The aim of this research is to assess the role of the pharmacists in primary healthcare system to improve patient quality of life. In order to answer the aims of this study, due to constraint of time and limited financial resources, a systematic review approach was adopted, and data was collected using a secondary data collection method. Data was collected from five (5) journals, already published by other authors. These articles were selected using the PRISMA tool approach. Recently, several development and emerging role of pharmacist have been recognized in the multidisciplinary provision of healthcare and the roles of the community pharmacist include dispensing, communicating, compounding, detecting, managing drug therapy and minor ailment management are the common roles of pharmacists. Furthermore developing care plan, compound sterile medication, dispensing and managing drug therapy were the most common role of a pharmacist in primary health care system. To conclude, the stated roles elucidate the fact that pharmacist duties are not based around dispensing area and the most common roles of a community pharmacist include teaching, dispensing, preparing compounded medication, providing medication information to Doctors and patients, supporting patient self-care therapy, managing drug therapy ,minor ailment management.

Key words| Pharmacist, Primary healthcare, Quality, Life, Community.

Background

Primary Health Care has been defined as activities which are basic on patient care, including planning and delivering care to each patient, monitoring the patient to understand the results of the care, modifying care when necessary and completing the follow up. In many parts of the world, primary health care is undergoing a paradigm shift that highlights new roles and responsibilities in the provision of patient care (Barnes, D., et al 1995). Community pharmacists are drug specialists working in medicinal services in urban areas, towns and towns crosswise around the world. They work from their own drug stores or out of neighbourhood medicinal services focuses and specialist's medical procedures.

One of the main agenda set by the World Health Organization (WHO) for the future of public health is to form accessible, multidisciplinary networks of public health professional who actively engage within communities and provide key public health services in order to ultimately improve the life expectancy of the population (James E et al 2014). This characteristic feature provides a platform for more proactive contribution in solving gaps in public health services and programs including health-promotion and a variety of preventive service.

Pharmacists, are as members of the primary health-care team are at point of interaction with the public, are becoming progressively involved in primary health care and their roles of pharmacists evolved to a wider scope of practice and the role of community pharmacists is expanding globally from merely dispensing medication to involving in different public health services and playing a key role in disease state management (Elvey, R., et al 2013) .

This includes the skill to prescribe for minor illnesses, renew/extend prescriptions, prescribe emergency drug therapy, change drug dosage/ formulation, recommend therapeutic substitutions, initiate prescription drug therapy, administer injections, and conduct, order, receive and interpret laboratory tests (Bishop, A.C.,et al 2015). An extended role for pharmacists for the purpose of improving patient care and drug therapy outcomes has been promoted by the World Health Organization (WHO) and the international Pharmaceutical Federation (FIP).

THE ROLE OF THE COMMUNITY PHARMACISTS

Pharmacy is among the oldest of the health professions (Bush P. J., et al 2009) and over the past four decades, the pharmacy profession in the health care system has made significant efforts to swing its focus from medication supply to patient care (Emmerton, L., et al 2005). Pharmacists' professional roles and duties have evolved historically from a focus on medication dispensing and compounding to include provision of patient information, education, and pharmaceutical care services (Noyce PR et al 2007). In the USA, the Omnibus Budget Reconciliation Act of 1990 expanded this role by instructing that pharmacists educate patients about their medications and this means Community pharmacists can offer accessibility, expertise in therapeutics, face to-face contact and skills in drug problems and adherence (Schatz, R., et al 2003).

Pharmacists have become ever more involved in broadening their role beyond the product oriented functions of dispensing and compounding of medications to the provision of cognitive pharmaceutical services, information, and pharmaceutical care (Bryant, L.J., et al 2009). Pharmacists in many of these roles are based in delivering patient-centred care through patient assessment; development of pharmacotherapy care plans; monitoring, adjusting, and initiating therapies; and patient education. Moreover Narrowed roles of pharmacists is compounding, dispensing and labelling prefabricated products. For patients with chronic conditions, pharmacists have an opportunity to monitor their patients' use of combined medications and pass along information about possible interactions. It appears that pharmacists are the member of primary health care system, (Eades, C.E., at el 2011), and the play different roles in different healthcare organization. Despite this differences there is a need to identify the common roles of community pharmacist in primary health care.

RESEARCH AIM

The aim of this research is to evaluate the role of the community pharmacists in primary healthcare system to improve patient quality of life.

OBJECTIVE

1. To review the literature and identify the key roles of community pharmacist
2. To review published literature and evaluate the most common roles of pharmacist primary health care system.

METHODOLOGY

In order to answer the aims and objectives of the research topic, secondary data was systematically reviewed. The databases used for attaining the information included PubMed, Google scholar. The utilization of the multiple databases presented the opportunity to gain accurate and reliable information that signified the primary aspects of the study. Also, the research study used the PRISMA tool for screening the research resources.

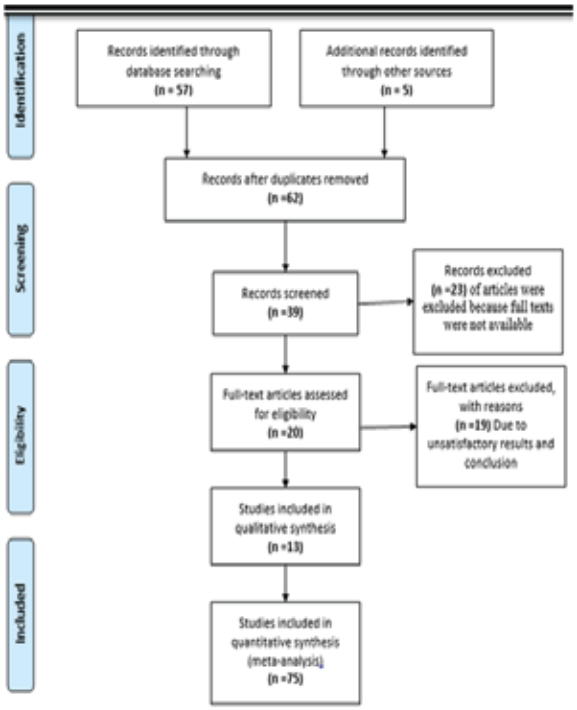

Figure 1.0: PRISMA Chart flow

RESULTS

Identified studies were uploaded into endnote (Thomas Reuters) and duplicates were removed. 2 reviewers vetted through the study based on the topic and abstracts that met the inclusion criteria. Studies selected after the first screening were further screened through a detailed full text browsing, to further exclude studies that had some of the exclusion criteria. Out of 62 studies identified, 23 were excluded due to full text not available . Out of the 29 selected, 19 were further excluded due to unsatisfactory results and conclusion. Out of the 20 selected, 15 were further excluded due to year of publication. Only 5 were finally used.

Figure 2.0: shows role of pharmacists

DATA ANALYSIS AND INTERPRETATION

1. Dispensing

Dispensing refers to the process of preparing and giving medicine to a named person on the basis of a prescription and it involves the correct interpretation of the wishes of a prescription (Goldfischer, J.D., et al 1986). This process may take place in a public or private clinic, health centre or community pharmacy settings but dispensing one of the vital element in primary health care system as a role of the pharmacist. Dispensing includes all the activities that occur between the times the prescription in presented and the time the medicine or other prescribed items area issued to the patient. On the reviewed approximately 90% journals stated dispensing as one of the common roles of community pharmacist. No matter where dispensing is done, errors should be avoided. Good dispensing practices ensure that an effective form of the correct medicine is delivered to the right patient, in the correct dosage and quantity, with clear instructions, and in a package that maintains the potency of the medicine.

2. PROVIDE MEDICATION INFORMATION TO PHYSICIANS AND PATIENTS

According to figure 2.0, providing medication information is one of the important roles of pharmacists. Interpersonal communication skills is one of an significant element for pharmacists to master, whether counselling patients, communicating with physicians, or interfacing with associates, pharmacists use their interpersonal communication skills daily.(Kerr, A., et al 2016.) Effective communication by pharmacists is essential to improve the use of medications by patients and ensure optimal therapeutic outcomes (McDonough, R.P. and Bennett, M.S., 2006). In addition to verbal communication, appropriately written recommendations to physicians to resolve drug therapy problems can be an effective strategy for drug therapy changes. Pharmacists can improve patient adherence to drug therapy through appropriate strategies, including patient counselling and education.

3. COLLABORATION WITH OTHER HEALTH CARE TEAM

The interprofessional collaboration with the multidisciplinary team of healthcare professionals has paved the path for various opportunities to provide patient centred pharmacist care through multifaceted interventions. Pharmacists are pharmacotherapy experts, and possess pivotal skills which qualify them for playing active roles in the process of designing and application of clinical pathway (Ismail, S., et al 2018). Collaborate with multidisciplinary pathway team to provide evidence-based, patient-centred therapeutic regimens in the form of order sets within clinical pathways to achieve the goals of the Department of Medicine and the institution.

Bring into line clinical pathways with formulary decisions by the pharmacy and therapeutics Committee, the use of formulary medications, facilitate the adherence to the approved restricted medications, integrate institutional drug use policies and measures to maximize patient safety and seek for optimum use of therapeutic regimens throughout.

4. PREVENTING MEDICATION PROBLEMS

Medication errors are any error in any step of the medication process prescribing, transcription, dispensing, administration and monitoring the medicine (Adverse drug event, Dispensing error)(Velo, G.P. and Minuz, P., 2009). This are 'an unintended event that harms the patient or carries a risk of harm, as a consequence of the action, or lack of action, of the health service. The main strategy to reduce dispensing errors is to implement a system oriented approach rather than a disciplinary approach targeted at an individual. The following is a list of strategies for minimizing dispensing errors.

Transcription / Prescription errors account for dispensing errors. These errors can be reduced by consistently using reliable methods to verify patient identity while entering the prescription into the computer.

Furthermore the pharmacist should confirm that the prescription is correct and complete, check all prescriptions, beware of look-alike, sound-alike drugs, be careful with zeros and abbreviations, must organize the workplace, reduce distraction when possible, take the time to store drugs properly and always provide thorough patient counselling. Completing this process will provide an opportunity for the patient to see the medication and ask questions if it looks different from what he or she has been taking

5. A TEACHER/ LECTURER

Teaching is one of the roles of community pharmacist but it's not of importance in primary health care. Teaching is a system of actions intended to induce learning," while learning can be defined as a change in performance potential with the intent of providing the learner with the capability to perform actions that he or she had not previously accomplished(Owens, P. and Gibbs, T., 2001). The practice of pharmacy is occurring in an information rich environment in which technology affords access to more information than ever before and dispensing technologies are making it easier for the pharmacist to be acknowledged for the knowledge they impart in facilitating positive patient outcomes(Robinson, E.T., 2004). This knowledge is often communicated to patients or other health professionals, and it is this transfer of knowledge that should be expanded for pharmacists to transition into the role of educators. By redefining the pharmacist as an educator, they are not required to have teaching certificates, however, that the basics of teaching and learning can be taught to pharmacists and pharmacy students similar to temporary an appreciation of their role as educators within the healthcare system.

6. MANUFACTURING / COMPOUNDING

Pharmaceutical manufacturing is the process used to formulate and create commercially available drugs. Unlike compounding, manufacturing creates drugs in pre-set formulas or doses on an industrial scale. Often, pharmaceutical manufacturing companies generate millions of doses or formulas per year. The large scale benefits society by providing quick and easy access to preformulated medications.

Compounding is the process a manipulating pharmacy uses to create custom medications from base ingredients for patients. This is done by mixing various pharmaceutical components to meet the needs of an individual patient.

7. MINOR AILMENT MANAGEMENT

A minor ailment is a less serious medical condition that does not require lab or blood tests. Examples include cold sores, mild eczema, oral thrush, heartburn, hay fever, skin rash, fungal skin infections and yeast infections (O'Loughlin J., et al 1999).

Pharmacists are highly trained, educated and trusted health care professionals. They are the medication experts. Their university curriculum includes training on the assessment and treatment of these minor ailments.

Unlike a doctor, pharmacists do not have the authority to prescribe controlled substances such as narcotics and other mood-modifying drugs. Pharmacists cannot prescribe drugs that can cause addiction or dependency and abuse. If the condition and treatment required is within pharmacists' prescribing limits, you may still receive treatment even if you do not have a doctor. Expanding the role of pharmacists to assess and treat minor ailments gives patients another choice for accessing health care services. Pharmacists will continue to refer patients with more serious conditions to their family physician or an emergency room.

8. CARE GIVER

Pharmacists' services have grown well beyond functions tied only to dispensing medications. Many pharmacists also provide such advanced patient-centred services as coordination of medications during care transitions, medication management, comprehensive medication reviews with ongoing medication monitoring, chronic disease management, disease education, prevention and wellness services, and patient education.(Allen B.E. & Suveges L.G. 1995)

The pharmacist as caregiver as one the roles of a pharmacist remains behind in place , though, when considering the fact that pharmacists could, be better than any other healthcare professional, when comes to addressing these medication issues as they have the most in-depth pharmacotherapy experience. As part of the care team, pharmacists can identify duplicative drugs or potential safety issues associated with drug interactions. Pharmacists are trained to develop and monitor rational, effective drug therapy regimens and this often results in decreasing the overall number of medications taken.

9. MANAGEMENT OF DRUG THERAPY

One of most common role of community pharmacist is managing drug therapy on the health care team, the pharmacist is the key member who provides ongoing drug therapy monitoring. This service optimizes therapeutic outcomes of patients, focuses its efforts on optimizing medication regimens for the highest risk patients, to elicit a change in drug therapy, to reduce incidence of adverse drug events from the medication. Pharmacists educate patients and their caregiver about potential adverse effects and work with patients to ensure adherence to the therapy to improve patients' outcome

CONCLUSION

To conclude, the stated roles elucidate the fact that pharmacist duties are not based around dispensing area and the most common roles of a pharmacist include teaching, dispensing, preparing compounded medication, providing medication information to Doctors and patients, supporting patient self-care therapy, managing drug therapy ,minor ailment management. And other roles of community pharmacist which are of importance but are not common include, participation in public health activities, developing care plan, referring patients and making changes to existing drug therapy. Community pharmacists are the most accessible of all health care workers and as such play a key role of health care services at all levels. Previously the pharmacist worldwide was seen as responsible primarily for manufacturing and supplying medicines, today the pharmacist's role has evolved towards a clinical orientation. The profession is still under continuous transition. With change in the health demands, pharmacists have a further role to play in patient care.

Pharmacists as members of the health care team should play a role in ensuring affordable access to quality essential medicines, dissemination of appropriate information to patients, the general public and other health professionals, and participating in health promotion and health education programs. The most common roles of pharmacist in primary health care system include compounding, managing drug therapy, providing drug information and collaboration with other health care team.

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EVALUATION OF FACTORS INFLUENCING TREATMENT DECISION IN HIV/TB COINFECTIONS

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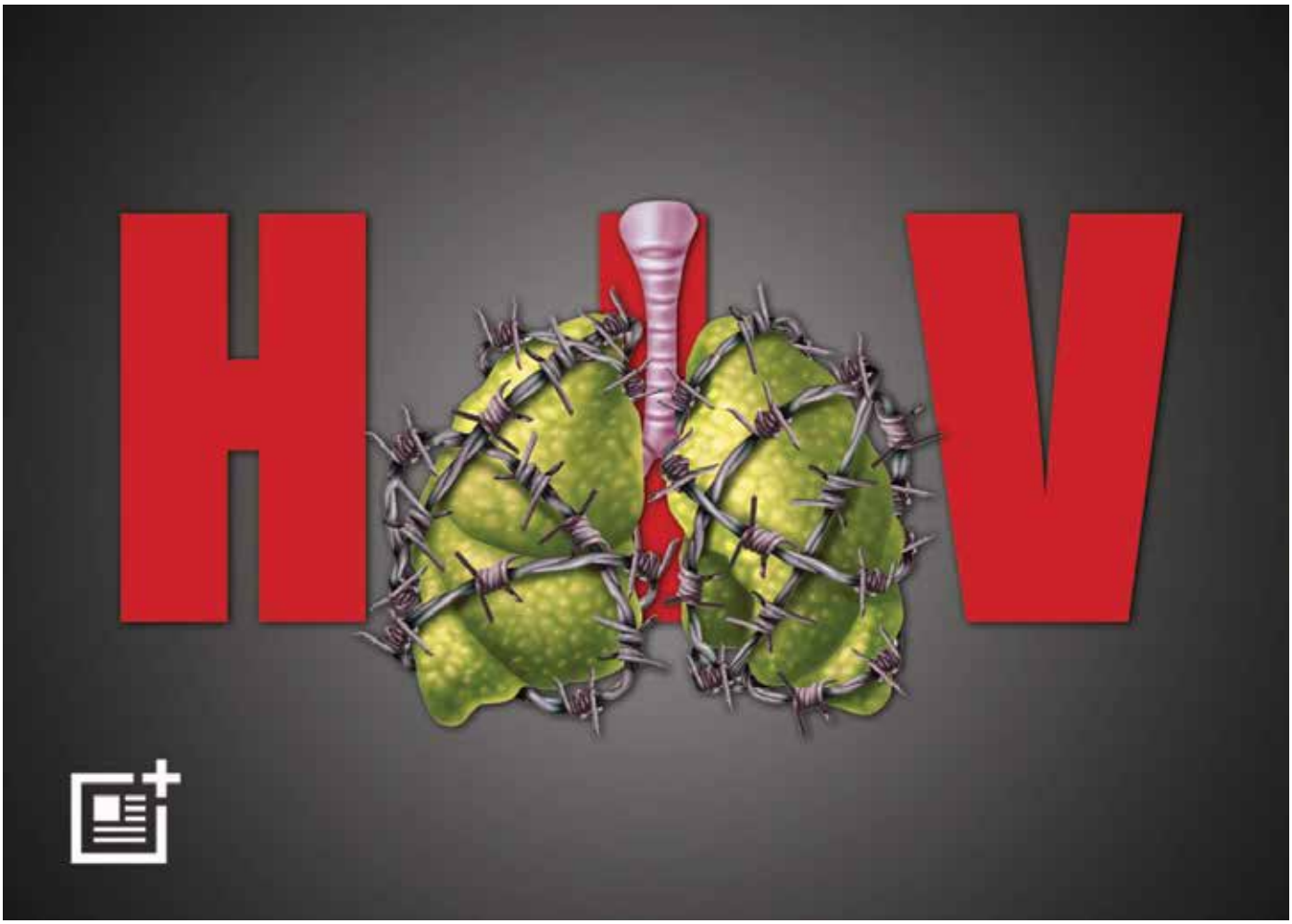


Abstract|

Tuberculosis (TB) and HIV co-infections pose a huge burden on health care systems. These two diseases cause diagnostic and therapeutic decision complexities coupled with challenges such as increased mortality and morbidity rates. Concurrent occurrence of these two diseases causes treatment challenges such as increased drug toxicities and adverse drug reactions. HIV infection is the most dominant known risk factor predisposing for Mycobacterium tuberculosis infection and progression to active disease, which increases the risk of latent TB reactivation 20-fold.

Tuberculosis is also the most common cause of AIDS related deaths. Thus, M. tuberculosis and HIV are collaborative diseases, accelerating the decline of immunological functions and leading to subsequent death if untreated. According to literature the mechanisms behind the breakdown of the immune defense of the co-infected individual are not well understood. The aim of the present systematic review was to identify factors reported in literature that influence HIV/TB co-treatment and evaluate clinical implications and to review key challenges that arise in decision due to HIV/TB co treatment.

Key words; Tuberculosis, Human Immune Deficiency Virus, TB/HIV confections

Impact of Personalised Medicine on Health Care Cost

The emergence of personalized medicine, exponential technologies, disruptive competitors, expanded delivery sites, and revamped payment models is injecting uncertainty into the global health economy and increasing the urgency for organizations to plan when and how to make future moves as a market leader, fast follower, or niche player to remain relevant and financially viable(-Bonter, K.,et al 2011) Battling health system cost pressures Global health care expenditures continue to escalate, shining a light on health systems' need to reduce costs and increase efficiency(Poisal, J.A.,et al 2016). Spending is projected to increase at an annual rate of 5.4 percent in 2017–2022, from USD $7.724 trillion to USD $10.059 trillion (figure 3), although cost-containment efforts combined with faster economic growth should maintain the share of GDP devoted to health care at around 10.4 percent over the fiveyear period to 2022(Truffer, C.J.,et al 2019

Background

Scientists believe that HIV originally came from chimpanzees in West Africa during the 1930s, and originally transmitted to humans through the transfer of blood through hunting. It is believed that over the decades, the virus spread through Africa, and to other parts of the world (Merson, 2008). It wasn't until the early 1980s, when rare types of pneumonia, cancer, and other illnesses were being reported to doctors that the world became aware of HIV and AIDS. In 1986 it was revealed that HIV can be passed from mother to child through breast-feeding. The first Canadian AIDS Research Conference was then held in Toronto (Smith, 2010).

In 1987 the first antiretroviral drug AZT was approved to be used HIV management. In 1988 CANFAR-funded researcher Dr. Mark Weinberg subsidized to the development of 3TC, a drug being used to treat HIV(Gilbert, et al, 2007).This drug therapy, brought about an immediate decline of between 60% - 80% in rates of AIDS-related deaths and hospitalization for patients who could afford it (Sharp,et al,2011).Till date a lot of research are put up in place to try and find out the cure of this disease. Many drugs have been developed to try and slow down the replication process of this virus (Prejean,et al, 2011).

On the other hand.In 1720, for the first time, the infectious origin of TB was conjectured by the English physician Benjamin Marten, while the first successful remedy against TB was the introduction of the sanatorium cure(Martini,et al,2018).The exact pathological and anatomical description of the disease was illustrated in 1679 by Francis Sylvius, in his work Opera Medica, in which he describes tubercles, their progression to abscesses, cavities and empyema in the lungs and in other sites of consumptive patients(O'Connor,2005).

RESEARCH AIM

To review literature on the factors that influence treatment decision in HIV/TB co infections and their outcomes.

OBJECTIVE

1. To identify factors reported in literature that influence HIV/TB co-treatment and evaluate clinical implications.
2. To determine key challenges associated with the identified factors that arise in decision due to HIV/TB co treatment

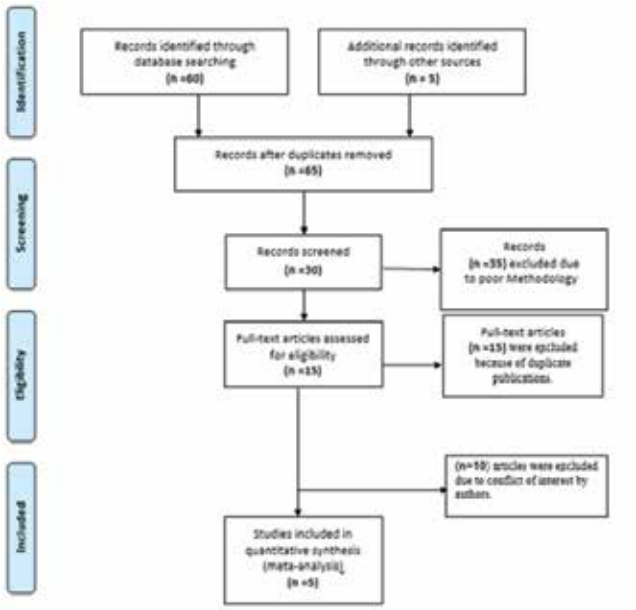
METHODOLOGY

In order to answer the aims and objectives of the research topic, secondary data was systematically reviewed. The databases used for attaining the information included PubMed, Google scholar. The utilization of the multiple databases presented the opportunity to gain accurate and reliable information that signified the primary aspects of the study. Also, the research study used the PRISMA tool for screening the research resources.

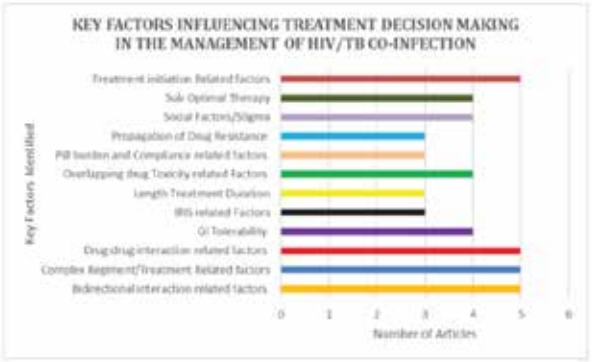
RESULTS

Recognized studies were uploaded into endnote (Thomas Reuters) and duplicates were removed. Studies selected after the first screening were further screened through a comprehensive full text browsing, to further eliminate studies meeting on the side of exclusion criteria. Out of 65 studies identified, 35 were excluded because poor methodology. Out of the 30 selected, 15 were further excluded due to duplicate publications then the other 5 also taken out due to conflict of interest by the authors. Only 5 were finally used for results synthesis.

Fig 1.0 | Prisma Flow Chart



Adapted from; Check,J and Schutt,R.K.,2011.
Fig 1.2| KEY RESULTS AND DISCUSSION



DATA ANALYSIS AND INTERPRETATION

Bidirectional interactions

The interaction between HIV and TB in persons co-infected with them is bidirectional and synergistic. A study by Korenromp, et al, (2016) found out that the course of HIV infection is accelerated subsequent to the development of TB and the inverse relationship between HIV viraemia and CD4+ count gets shifted to the right. Compared with CD4+ count-matched HIV-infected controls without TB, the relative risk of death and development of other OIs is higher in HIV-TB co-infected patients. Accelerated HIV progression is partly attributable to the increased systemic immune activation in patients with HIV-TB. The above study supports the data found from the articles. Before the prescriber can even treat HIV/TB he or she first has to understand the dynamics of these conditions and how the two conditions fuel one another. Increased HIV replication has been demonstrated locally, at sites of disease affected by TB such as affected lung and pleural fluid, in patients with HIV-TB (Toossiet al, 2019).

Moreover, the genetic diversity of thelocallyreplicating HIV viral population is higher than the circulating population and the local immune activation also favours the development of latent HIV infection of macrophages and dendritic cells, thereby potentially enhancing dissemination of HIV (Toossi, et al, 2003).

Treatment initiation factors

All the reviewed articles indicate that, physicians/doctors have to balance the risk of HIV progression if antiretroviral therapy is delayed, against the risk of paradoxical reactions. This information is supported by a study done by (Nikcolas,et al,2011) which indicated that, death in the first month of TB treatment was attributed to the TB progression, while late deaths in co-infection are due to HIV diseases progression.

Starting HAART early in HIV positive patient who present with TB lowers the progression of the disease and also decreases mortality. The articles suggest that, the best decision a physician/doctor can take is to initiate the treatment on a patient with a low CD4.ThE ARVs should be initiated within 8 weeks of TB treatment.

This information is also supported by the WHO guidelines which state that the perfect time to initiate ART in HIV/TB patient is between weeks 2 to week 8.

One factor that is crucial during HIV/TB treatment decision making is that of the period of duration. The chosen period should be such that the M.tuberculosis is completely cleared from the body. The standard duration of drug-susceptible TB in HIV infected patients is 6 months. This includes an intensive phase of four drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol) administered in two months, followed by a continuation of two drugs (isoniazid and rifampicin).The Botswana 2016 HIV/TB treatment guideline also supports the findings from the reviewed journals that ART should be initiated as soon as possible but no later than 8 weeks.

Complex drug regimen

Complex medication regimens are troublesome to patients and physicians due to the resulting problems of non-adherence, therapeutic failure, and adverse drug reactions. Majority of HIV positive patients diagnosed with TB arealready on other medication from other opportunistic infections or from chronic conditions like diabetes and hypertension.

Multiple medical problems are increasing. These trends, combined with recommendations from clinical practice guidelines and consumer demand for drugs, often result in complex medication regimens for many patients. The complexity of a medication regimen can be defined by the number of medications (polypharmacy) and the number of times per day or “doses” that the patient takes a medication (multiple dosing schedules).A drug drug interaction is a change in a drug’s effect on the body when the drug is taken together with a second drug.

Drug-drug interactions

A drug-drug interaction can delay, decrease, or enhance absorption of either drug. This can decrease or increase the action of either or both drugs or cause adverse effects. Drug interaction is the major factors that influence the decision making procedure in HIV/TB treatment. The interactions can either increase toxicities or lower drug concentration such that the desirable effect of the drug does not take place.

Drug used in the two conditions can interact leading to relapses, and treatment failure. For instance Rifampicin induces cyp450 3A4. This means that drugs such as Niverapine which are metabolized by this enzyme areaffected. In thiscase rifabutin can be used as an alternative. When giving Rifabutin with Kaletra, the prescriber should consider reducing the dose of Rifabutin to 150mg three times a week. Drug interactions are the major cause of drug toxicities in patient.

Stigma

Stigma indirectly influences treatment decision in HIV/TB co-infection, as stated by 80% of the reviewed journals. Stigma affects patience's adherence to medication. Adherence to medications determines treatment outcomes. Failure to adhere to medication can lead to treatment relapses and can warrant drug resistance. Increasing and continuous community awareness about this treatable disease is needed, using different channels to reach all levels of the population, such as working with the large numbers of traditional healers to also recognize the symptoms of HIV/TB and to refer patients for biomedical evaluation and treatment. Non-adherence due to stigma may also compel the prescriber to closely monitor the patient. The finding from the reviewed journals is similar to those of a study by Mario et al (2017) who found out that out of 156 patients, 114 stopped treatment due to stigmatization.

6. Immune Reconstitution Inflammation Syndrome

The paradoxical form of IRIS in patients with TB may have protean manifestations, most commonly fever, nodal enlargement, and worsening pulmonary infiltrates observed on a chest radiograph with or without recurrent respiratory symptoms. IRIS is one important factor that influences treatment decision in HIV/TB co-infection, even though only 60% of the studies reviewed seconded that. Therefore it is significant to consider the risk of IRIS when initiating treatment of the two diseases more especially that IRIS warrants the prescriber to add a corticosteroid Prednisolone.

These steroid even though they correct IRIS, they also suppress the already suppressed immune system. Mclleron and colleagues (2007) indicate that risk factors to the development of IRIS include; a shorter delay between commencing TB treatment and HAART, a low baseline CD4 cell count , a higher baseline viral load , a greater reduction in viral load while receiving HAART, and a greater increase in CD4 cell count or in CD4 : CD8 cell ratio. This information is also supported by a study reviewed in literature which found out that, 13 in 19 patients who were initiated on HAART after 41 days developed IRIS as compare as compared to 2 out of 19 when HAART was initiated after 8 weeks. Although just 12% of TB patients developed IRIS in a study from South Africa, the proportion was much higher (32%) among the sub-set who initiated ART in the first 2 months of TB treatment. In adjusted analyses, those initiating ART in the first month of TB treatment had a 70-fold higher risk of TB IRIS compared to those initiating ART after at least 3 months of TB treatment (Lawn, et al, 2007).

Overlapping drug toxicities

Over lapping toxicity of ARV and anti-tuberculosis is a major concern in HIV/TB co treatment. Four out of the five reviewed studies pointed out those adverse reactions to drugs are highly common among HIV/TB co infected patients, especially those on HAART. Rifampicin, isoniazid and pyrazinamide may cause rash, fever and hepatitis. Administration of the HIV/TB medication poses a difficult clinical management decision. The findings from the systematic review are supported by (Dean, et al, 2002) who conducted a study on adverse effects in HIV positive patients who were also on anti-tuberculosis therapy.

Gastrointestinal Tolerability

The reviewed studies highlighted that GI tolerability affects the treatment decision in HIV/TB co infection.GI side effects are common with antiretroviral drugs. Isoniazid, Rifampicin, and Pyrazinamide are well known for inducing hepatic failure. Pyrazinamide is the most hepatotoxic drug. Rifampicin is also associated with abdominal pain. The predisposing factors for hepatotoxicity are; excess doses of the drugs, alcoholism and HIV. The pyrazinamide hepatotoxicity is dose dependent.

The prescriber might consider its doses in patients with hepatic impairment).Patients taking rifampicin often complain of gastric pain, nausea and vomiting. In this case the doctor might either give the drug with meals or change the dosing time or giving 600mg of rifampicin daily. Malabsorption of the antibiotics has been reported especially with the first line therapy. The prescriber should consider these key points when deciding on the drug regiment for a patient.

Pill burden

Four articles emphasised that pill burden was an important factor to consider when deciding on the HIV/TB treatment. Patients mentioned pill burden as one of the major challenge of concomitant treatment with HIV/TB treatment. Some pill sizes are huge making it difficult for some patients to swallow. It is therefore important for the prescriber to offer a drug that a patient will be able to take. Failure to consider this during this can lead to medication noncompliance as most patients would not take the medication. Non-compliance eventually causes drug resistance to antibiotics as in the case of antibiotics.

Length of duration

The standard duration of therapy for treatment of drug-susceptible pulmonary TB in HIV-infected patients on antiretroviral therapy (ART) is six months. This includes an intensive phase of four drugs (isoniazid, a rifamycin (eg, rifampin or rifabutin), pyrazinamide, and ethambutol) administered for two months, followed by a continuation phase of two drugs (isoniazid and a rifamycin) administered for four months. According to Faiz et al (2010) there are serious concerns regarding current recommendations for treatment of HIV-tuberculosis co-infection. In a systematic review study including 21 cohort studies relapse was more common with regimens using 2 months rifamycin than with regimens using rifamycin

Sub optimal treatment

Treatment interruptions are a major challenge in HIV/TB treatment. Determination of whether or not treatment has been completed should be based on the total number of doses taken. 80% of the reviewed studies indicate that sub-optimal therapies influence the decision making in HIV/TB treatment. The prescriber should consider initiating; a six month daily regimen (given 7 days/week); the minimum number of doses of rifampicin and pyrazinamide are 130 and 40 doses. Treatment interruption occur during the initial phase of treatment and the interruption is 14 days or more in duration, the prescriber should be compelled to restart the treatment from the beginning. If the interruption is less than 14 days, the prescriber might continue the course. The most common reason for interrupting anti-TB treatment was hepatitis. This occurred mainly within the first 2 months of treatment, with a median time off antiTB treatment of 4 weeks. Thus, most interruptions necessitated full re-treatment. In contrast with other reports, we found this to occur at a similarfrequency in both HIV infectedand uninfected patients.

Drug resistance

The key challenge that arises due to improper decision making is multi drug resistance. Drug resistance also influences treatment decision in HIV/TB coinfection. The TB causing bacteria end up unsusceptible to a vast of antibiotics leading to frequent relapses, treatment failure with eventually leads to death. In retrospective studies, non-adherence with TB therapy has been linked with acquired rifampin mono-resistance; and among a small number of patients, the use of rifabutin as prophylaxis for Mycobacterium avium complex was connected with the development of rifamycin resistance. However, the manifestation of TB relapse with acquired rifampin mono-resistance also has been recognized among patients with TB who initially had rifampin-susceptible isolates and who was treated with a rifampin-containing TB regimen by directly observed therapy (DOT). The mechanisms involved in the expansion of acquired rifampinmonoresistance are notclearly understood but could involve the persistence of actively multiplying mycobacteria in patients with severe cellular immunodeficiency, selective anti-tuberculosis drug mal-absorption, and inadequate tissue penetration of drugs

CONCLUSION

From the reviewed studies, it can be concluded that treatment initiation related factors, drug-drug interaction, complex treatment regimen, bidirectional interaction related factors were the major key factors influencing HIV/TB treatment decision making, followed by sub optimal therapy, stigma, overlapping drug toxicity related factors and GI tolerability, while the least causal factors are propagation of drug resistance, pill burden, length of treatment duration and IRIS related factors as summarized in the result graph. These factors assist in deciding on a smooth and effective treatment that will eventually yield positive outcomes that is; complete eradication of the M.tuberculosis and elevation of CD4 cells. Limited knowledge, as well as rigid application of guidelines without the ability to adapt to patient challenges, contributes to program failure. In summary, the association between HIV co-infection and Mtb drug resistance remains unclear, with a number of studies yielding conflicting results

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Operating At The Speed Of Light

A Systematic Review of the Role of Physiotherapy Interventions in Palliative Care

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Abstract

The aim of this research is to conduct a systematic review analysing the role of the physiotherapy interventions in palliative care. PRISMA as a critical appraisal tool was utilised for the selection of the research articles. The inclusion criteria were based on the year of publication, ease of availability, language, geographical location, and study type. To ensure the credibility, databases such as Elsevier, Proquest, and EBSCO Host were used to filter the grey content. Data published in the past ten years (2009-onwards) was only included to ensure the selection of the most recent interventions used by the physiotherapists. A total of 11 articles were selected which determined that physiotherapy interventions involving breathing exercises, aerobic exercises, manual therapies, and educational awareness were critical to promoting the functional capability and empower the patients.

Keywords: Physiotherapist, Palliative Care, Physical Therapy, End-of-Life Care, Non-pharmacological Intervention

Background

World Health Organisation (WHO) defined palliative care as the approach which enhances the quality of life of the patients who are encountered with life-threatening diseases through the management and relief from the suffering through early intervention, impeccable evaluation, and treatment of pain and other associated issues [1]. Patients in palliative care experience a greater level of functional incapability and disability as a result of disease progression, direct local and systematic impacts, and deconditioning pain. Impairment in physical functioning is a predominant contributor to a significant decline in the quality of life of such patients. Palliative care patients expressed a high desire to stay physically active during the course of the disease while sustaining and retaining physical independence [2]. Thus, the notion of rehabilitation in palliative care Spatients is to promote adequate treatment provided with the objective to eradicate disability through optimising the functional status, independence, autonomy, and standard of living.

The World Confederation for the Physical Therapy has defined physical therapy or physiotherapy as the provision of services to the people for the development, maintaining, and restoring the maximum mobility as well as functional capability throughout the entire life-span [3]. Physiotherapy, in particular, encompasses the services in situations where the function and the movement are threatened by the ageing process or due to any injury/disease [4]. Physiotherapists form an integral component of the multidisciplinary team (MDT) in the palliative care by focusing on the processes and procedures for enhancing the function and quality of life through multivariate care dimensions [5]. Of these care dimensions, the physical dimension in the palliative care treatment and management is linked to symptom control, improving the flexibility, mobility, endurance, deformity, gait, balance, co-ordination, deformity, energy expenditure, and exercise tolerance along with maintaining adequate breathing. The functional dimensions, on the other hand, are related to improving the daily activities and functions that include the sensorimotor performance [6]. Physiotherapists aim to improve the successful performance of the complicated physical functional activities such as housekeeping and maintaining personal hygiene which requires the involvement of the affective and cognitive abilities.

The integration of physiotherapists into the palliative care plan is a relatively new concept despite the fact that the physiotherapy interventions in palliative management were identified during the early 1960s [1]. The primary objective of including a rehabilitation approach while treating the palliative care patients is through goal setting to enhance the functional ability while subsequently reducing the disease consequences as long as possible [7]. The ultimate goal of the physiotherapist is to promote independence as much as possible to ensure the accomplishment of important activities to ease the end-stage life of the people. However, in cases where improving the functional ability is not possible, physiotherapy intervention is to promote the patient as well as the ability of the carer to cope with the deteriorating condition of the patient through awareness and education to improve the quality of life [8]. Therefore, the overall aim of the physiotherapist is to facilitate the patient to reach the best possible quality of living for the remaining patient's life.

Methodology

Research Design

The research design for this study has been based on the systematic review of the literature to determine the interventions of physiotherapists in palliative care. Through a systematic review, the selection of the appropriate data sources enabled the researcher in collecting pertinent, credible, and reliable information through the use of databases for the selection of peer-reviewed journal articles [9]. Provided the nature and phenomenon of the research topic, systematic qualitative review of literature is optimal as it enables in determining the interventions of physiotherapists from previous authenticated researches without the involvement of any statistical testing as no variables are involved in this research.

Search Strategy

The search strategy for the attainment of the most desirable information comprised on the use of the keywords "Physiotherapy", "Physiotherapist" "Physiotherapy interventions", and "Palliative care" alone as well as in combination with the utilisation of the Boolean Operators "AND" and "OR". The Boolean Operators were incorporated into the search strategy of the most reliable, authenticated, and prominent databases in the field of health sciences which included Elsevier, ProQuest and EBSCO Host. Here, it is important to signify that the entire research was constituted using the widely used and openly accessed databases to ensure the reproducibility and credibility of the literature.

Data Extraction

The criterion for the extraction of data was based on the inclusion versus the exclusion criteria. The inclusion criteria facilitate in setting the boundaries and restrictions for collecting the most viable, authenticated, and reliable information [10]. Different approaches for the inclusion criteria which had been specified for this research included the language, publication year, study type, geographical aspects, design of the research, and the interest exposure. In the regard, through the use of the inclusion criteria, the researches which had been published in the English language only were opted while literature in a language other than English was excluded. In a similar manner, the research studies which had been published in the last ten years were selected for this study to ensure the inclusion of the most updated and relevant context. Thus, literature published before 2009 was excluded from the selection.

Selection of the Study

The selection of the study in the systematic approach is regarded as the critical appraisal which ensures the value and trustworthiness of the study. Critical appraisal is commonly regarded as the implications of the values and rules that predominantly assist in the evaluation of the resulting viability, method, and procedures while adhering to the ethics. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) are used for the assessment of the critical appraisal tool for determining the validity and reliability of the data collection [11]. PRISMA promotes in easy filtration of the research articles to comply with the standards of the quality. Thestep-by-step assessment of the PRISMA to determine the physiotherapy intervention in palliative care is illustrated in the following figure below [5]

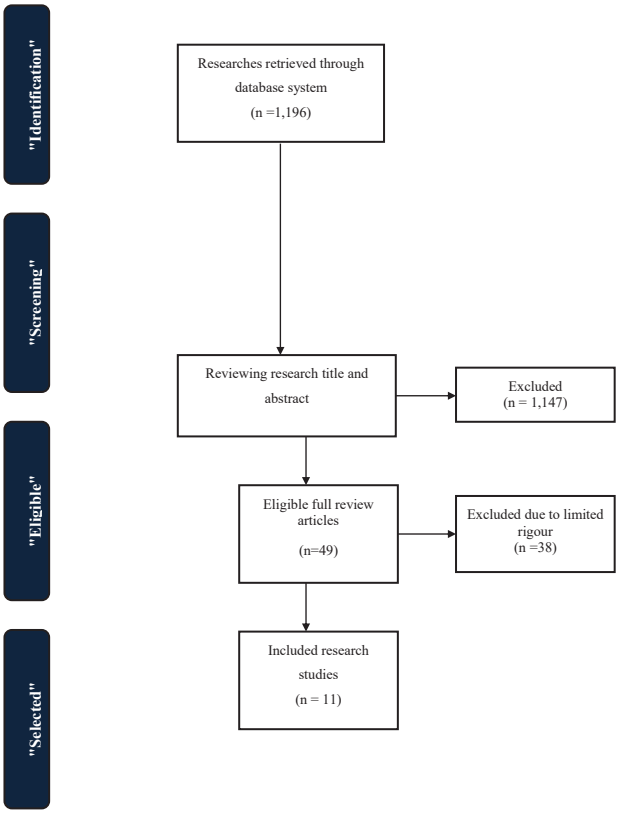
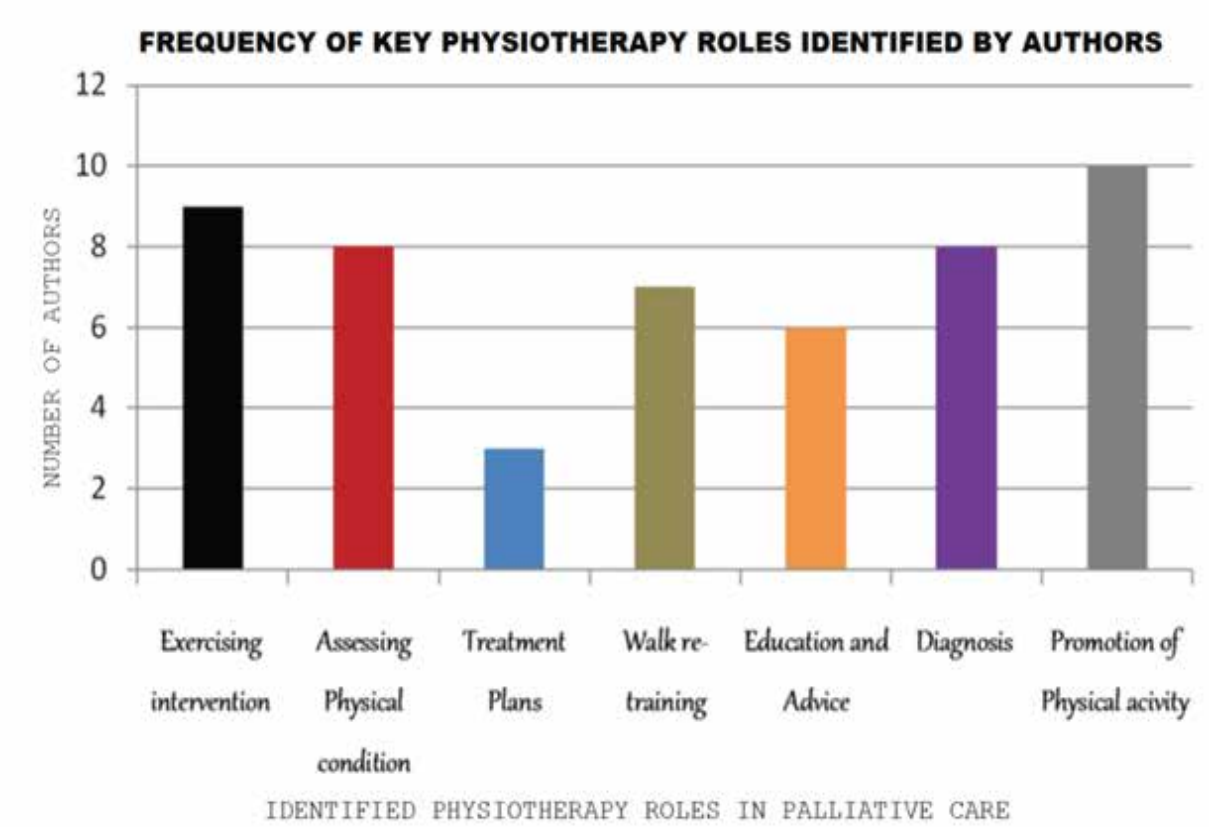


Fig 1| PRISMA Flow Diagram

Author	Year	Country	Methodology	Key Findings
Hegarty et al.	2016	Ireland	Cross-sectional Study	The key findings indicated that physiotherapy induced palliative exercising interventions in patients suffering from Parkinson's disease improved the strength of the lower limbs. The physiotherapist intervention specifically deduced that palliative exercising could serve as a potential modification for the accomplishment of clinically relevant results in the walking ability of the patients.
Lim and Ng	2015	Singapore	Mixed methodology	It was determined that improving the knowledge and skills of the physiotherapists through perception and knowledge in the palliative care domain could predominantly assist in analysing the challenges in acute hospital settings. Good palliative care is dependent on effective communication, education and advice, so physiotherapist intervention is based on developing communication skills to improve technical competencies.
Möller et al.	2016	Sweden	Pilot Study	Physiotherapist interventions in palliative care settings were determined through multiple therapeutic mechanisms focused on patient-centric needs, good diagnosis, promotion of physical activity, treatment plans. The pilot study determined that a better-nuanced investigation of the clinical complications could facilitate in the optimisation, clarification, and development of physiotherapy interventions.
Jensen et al.	2014	Germany	Retrospective, Descriptive Study	The key analysis indicated that physical exercise in advanced cancer patients had a beneficial impact on the mobility and functional ability with respect to the disease-related and socio-demographic aspects. Physiotherapeutic intervention including the relaxation and the breathing therapies improved the quality of living of terminally ill patients.
Przedborska et al.	2015	Poland	Quantitative Method	The findings indicated that though physiotherapy interventions did not exhibit a statistically significant relationship in enhancing the self-care and mobility of the

				patients in palliative care, however, prominent results were recorded in the management of the depression, anxiety, and intensity of dyspnea after the physiotherapy program. Walk retraining, education and advice on health as well promotion of physical activity.
Morrow et al.	2017	South Africa	Cross-sectional Descriptive Survey	Despite inadequate training, knowledge, and required skillsets, a large number of physiotherapists were able to manage the critical requirements of the patients during palliative care and thus proper inclusion of the palliative care knowledge in the graduate program could yield better and positive outcomes for optimising the individual functional capability.
Saher et al.	2018	India	Randomised Clinical Trial Retrospective Study	The final outcomes indicated that physiotherapists led interventions improved the functional capability while offering relief from the symptoms to the patients in palliative care. This signified the notion that physiotherapists in caring of patients could enhance the independence and quality of living during end-stage of life.
Cullum	2019	United Kingdom	Qualitative Semi-structured Interviews	Within the inpatient settings, rehabilitative palliative care has become a challenge for the inpatient hospice unit and physiotherapist could play an integral role in eradicating the barriers through effective communication and rehabilitative palliative care practices while improving the confidence and autonomy of the patients.
Wilson and Briggs	2017	United States of America	Review Article	Lack of the consistent integration of the physiotherapist within the hospital settings is constituted as a barrier in the provision of non-opioid alternatives for the management during the palliative care. Physical therapy supports pain management by improving the quality of life and reducing the dependency on opioid medication.
Pullen et al.	2014	Nigeria	Case Study Analysis	The key analysis interpreted a complete eradication of the shortness of breath (SOB) upon exertion and relief from pain due to the physiotherapy sessions. In addition, a prominent reduction was also observed in muscle endurance, strength, and resting heart rate. Hence, the physiotherapy interventions comprising of

				manual therapy and exercise were beneficial as an adjunct therapy.
Pyszora et al.	2017	Poland	Randomised Clinical Trial	Exercising program design led to a prominent decrease in the fatigue scores within the palliative care which positively influenced the day-to-day functioning. These findings led to the belief that physiotherapy is regarded as an effective and safe method in cancer-related fatigue to improve the quality of living.



Discussion

The data analysis has offered a comprehensive evaluation highlighting the contemporary role of the physiotherapist interventions in the treatment and management of palliative care, among key roles frequently identified was promotion of physical activity, exercise intervention, diagnosis and assessing physical condition, walk-retraining, education and advice and developing treatment plans in line with client need as well as involvement. Palliative care is regarded as a holistic practice which involves caring of the people living with life-threatening illnesses or individuals during the end stage of the lives. Though pharmacological interventions are the primary source to manage and treat the palliative care measures, exercise and the physical activity acts as a secondary mechanism to improve the quality of living thereby acting as a cornerstone to the non-pharmacological management [12]. In this context, a physiotherapist led palliative exercise programme (PEP-PD) was designed which was executed for a total of six weeks duration constituting of portable ankle weights. The outcomes of the study clearly signified that a progressive six-week physical therapy improved the muscle strength and intensity of the lower limbs in patients living with Parkinson's disease (PD).

Nonetheless, the improvement in the flexibility and strength did not incur any difference in the severity of the patient condition. Similarly, physiotherapy leads to the maximisation of mobility, independence, and mobility provided adequate treatment and monitoring [13]. In this regard, improving the attitude, knowledge, experience, and beliefs of the physiotherapists to improve the standard and quality of life for the patients in palliative care is important [14]. Hence, physiotherapy-led interventions are integral in promoting individual autonomy, independence, mobility, and body functioning during the end of life care.

Other physiotherapy interventions included the strengthening exercises offered to patients determined that physiotherapy has a positive and direct relationship in improving the patient outcomes and perceived well-being in populations demanding palliative care [15, 21].

Despite the fact that the profession has been under-valued and underestimated across the globe, there is a growing impetus for the improved physiotherapist's interventions and involvements in the in-patient as well as outpatient settings to offer relief from symptom and pain through non-pharmacological interventions. Specific physiotherapy interventions included breathing/aerobic exercises which are beneficial and recommended during the advanced disease progression to offer timely relief to the patients. Physiotherapy leads to a significant reduction in the rate of fatigue in patients receiving palliative care [16, 24].

Physiotherapy interventions are beneficial in the symptom management and alleviation of troublesome pain and discomfort through increased mobility and focusing on physical activity. Additionally, physiotherapy interventions in advanced diseases play a crucial role in improving the overall state of well-being of the patient while subsequently limiting the severity of the comorbid symptoms [17]. Hence, aerobic exercising, awareness, education, and alteration in the breathing mechanisms through physiotherapy interventions could play a positive role in improving the general state of the patients receiving palliative care.

Another physiotherapy intervention is based on generating awareness and improving the educational needs of the patients and the carers. Lim and Ng focused on the effectiveness and importance of the educational needs of the physiotherapists in the domain of palliative care [18, 23]. A lack of confidence and knowledge could lead to a negative influence on the quality of care services thereby affecting the patient well-being receiving palliative care. As opposed, good palliative care is highly dependent on effective communication skills as well as the technical competencies of the physiotherapists. In addition, multivariate role of the physiotherapists is involved in the specialised palliative care through prioritising the patient needs and addressing the emergent issues which directly hamper in the sudden alterations in the health status of the patients [19]. Therefore, educating the patient and creating awareness among the caregivers is also identified as a critical intervention through which the quality of life and well-being of the patients receiving palliative care could be addressed.

Along with educating the patients, education and development of the skillset of the physiotherapists are equally important in developing effective communication and interpersonal therapeutic relationships to provide ease and independence during the last stages of life.

Kumar and Jim (2010) discussed different physical therapy techniques and interventions comprising of therapeutic exercise, electrical modalities, thermal modalities, additional physical agents, and miscellaneous modalities (manual therapies) which offer an inherent role in improving the functional ability and care dimensions during the palliative care. The therapeutic exercises constituted of assisted active movement for offering relaxation, stabilisation, and mobilisation.

Electrical modalities, on the other hand, included the neuromuscular electrical stimulation which has been regarded as useful specifically in pain relief and management. Thermal modalities included the utilisation of heating and cold packs to promote flexibility. Physiotherapists play integral part in the multidisciplinary team involved with patients receiving palliative care [20]. This is done through physical therapy interventions which improve flexibility, muscle strength, durability, and functional mobility, as well as through optimising the respiratory, circulatory, cardiac, and muscular functioning to control pain and improve the functional independence [22]. Thus, physical therapy in palliative care patients is significant in promoting physical strength and independence.

Conclusion

The aim of this research study was to evaluate the role of the physiotherapist intervention in palliative care through critical analysis of the past literature. This systematic review of literature facilitated in analysing different intervention techniques which are globally utilised by physiotherapists for improving the quality of life during the end-stage of the patients. The analysis of the 11 research articles published in a period of ten years (2009 onwards) has identified multivariate intervention techniques which are adopted by the physiotherapists to enhance the general well-being through functional mobility, independence, and educational awareness. The findings also emphasised on the active role of the physiotherapists in pain relief and improvement in the symptoms through non-pharmacological techniques which lead to better outcomes for the patients. Hence, it is subjugated that involvement of the physiotherapists in the multidisciplinary team designed for patients receiving palliative care is essential in improving the physical strength, independence, and autonomy of the patients through optimised control mechanisms.

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DDT COM ACADEMIC DATES

12th-13th	January	Supplementary Exams
13th-14th	May	Registration
26th-27th	August	Registration
14th-15th	January	Registration
17th	May	Classes begin
30th	August	Classes begin
18th	January	Classes Begin
31st	May-3rd June	QUIZ 1
13th-17th	September	QUIZ 1
1st-4th	february	QUIZ 1
21st-25th	June	Midterm Exam
11th-15th	November	Midterm Exam
1st-4th	March	Mid term Exam
12th-16th	July	QUIZ 2
18th	November	Graduation
22nd -26th	March	Quiz 2
09th-13th	August	Final Exam
1st-5th	November	QUIZ 2
26th-30th	April	Final Exam
16th-20th	August	Orientation
29th	Nov-3rd Dec	Final Exam
20th	Decembe	College closes

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Jan 01st	New Year's Day
Jan 2nd	New year Holiday Day
Feb 14th	Valentine's Day
Apr 10th	Good Friday
Apr 13nd	Easter Monday
May 1st	Labor Day
May 21st	Ascension Day
Jul 1	Sir Seretse Khama Day Holiday
Jul 20th	President Day
Jul 21st	President Day
Sep 30th	Independence Day
Oct 1st	Holiday
Dec 25th	Christmas
Dec 26th	Boxing day

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