Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Covid-19 pandemic research opportunity: Is the Middle East & North Africa (MENA) missing out?

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ABSTRACT

Background: The Covid-19 pandemic has caused fear and panic worldwide, forcing healthcare systems to disregard conventional practices and adopt innovation to contain the infection and death. Globally, there has been a rapid proliferation of research studies and clinical trials assessing risks, infectivity and treatment.
Methods: This review assesses the opportunities and challenges in the Middle East North Africa (MENA) region to engage in the conduct of high quality clinical trials during the Covid-19 pandemic.
Results: Opportunities are abundant for conducting clinical trials in MENA countries, including substantial cost savings, academic health centers, integrated health information systems, international accreditation, and international collaborations. Yet, the MENA region has missed out on opportunities to advance patient research during prior infectious disease outbreaks caused by the Severe Acute Respiratory Syndrome, Ebola, and the Middle East Respiratory Syndrome, as evidenced by the lack of concerted research and clinical trials from the region. A large vulnerable population, especially the poor expatriate work force, the current isolation of the health centers, and the lack of an expert network or field trained task force, all contribute to challenges preventing the formation of a pan Arab research enterprise for epidemics.
Conclusion: Quality clinical research is critical during public health emergencies to identify treatments and solutions. The efficient conduct of clinical trials requires innovative strategies in research design, approval, and dissemination. Many countries in the MENA region have an opportunity to quickly ramp up research capacity and contribute significantly to the fight against the Covid-19 global threat.

1. Background

SARS-coV-2, a novel and highly communicable pathogen, emerged from Wuhan, China in December 2019, and soon spread to the Middle East and North Africa (MENA), an area that is geographically close to China and home to several business and tourist travel hubs. The MENA region occupies a strategically important geographic location between Europe, Africa and Asia. The population currently exceeds 450 million, or 6% of the world's inhabitants. Supported by its control over a large petroleum supply, the region has become a major global force. In particular, the Gulf Cooperation Council (GCC), a political and economic union of six Arab states, including Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and the United Arab Emirates (UAE), have witnessed substantial growth in the business, tourism, and healthcare sectors in recent decades. To diversify financial reliance on oil, the GCC countries have made efforts to build ecosystems to bolster more knowledge-based economies. Yet, these advancements have not translated into a significant increase in research participation, and the region sponsors less than 1% of global clinical trials [1].

Conducting patient-centered clinical research is critical during an outbreak of a new or re-emerging infectious disease in order to identify effective therapies, guide clinical patient care, and inform the public health response. However, like many of its international counterparts, the MENA has missed several past opportunities to build its research capability in preparation for the current threat. The 2009 H1N1 influenza pandemic affected hundreds of millions of people worldwide, and yet, there are no published placebo-controlled randomized clinical trials (RCTs) conducted in hospitalized patients [2,3]. In the 2014 Ebola

Abbreviations: GCC, Gulf Cooperation Council; GCP, Good Clinical Practice; IRB, Institutional Review Board; MENA, Middle East and North Africa; UAE, United Arab Emirates; RCT, Randomized Controlled Trials

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outbreak, which had it not been contained, would have likely spread to the MENA region, experimental medications were used given the lack of alternative treatments and the high mortality rates. However, significant delays in setting up proper research protocols resulted in inadequate trial recruitment [4]. As a result of this lack of RCTs, it is still unknown if any of the experimental Ebola treatments were efficacious [4]. Further, during prior coronavirus epidemics in the MENA, including the Severe Acute Respiratory Syndrome (SARS) outbreak in 2002 and the spread of Middle East Respiratory Syndrome (MERS) in 2012, inability to rapidly implement clinical research protocols and generate evidence during the outbreak itself resulted in gaps in pandemic research preparedness [5]. Experience from past epidemics highlights significant delays in the research response, resulting in missed opportunities for research conduct. Due to the lack of RCTs studying antiviral efficacy during these prior outbreaks, current treatment decisions for COVID-19 infected patients are made based on previous observational data, which is often retrospective, lacks methodological rigor and does not control for confounding factors or biases [5,6]. Even promising treatments may ultimately prove to be ineffective, or even harmful, further necessitating the need for RCTs to determine whether experimental treatments work [7]. This review identifies current challenges and potential solutions for the expansion of clinical research in the MENA region, and describes the opportunities to conduct meaningful and relevant clinical trials during the COVID-19 pandemic.

2. Challenges

2.1. Academic isolation

The MENA countries vary considerably in regards to population density, gross domestic product and healthcare access and infrastructure. Deep-rooted historical and political tensions have also hindered regional cooperation, including international academic collaboration, which is further complicated by differences in healthcare infrastructure, resources and cultural variations in approaches to research. For individual investigators, large multinational collaborations can threaten personal autonomy and ownership of intellectual property. Differences in research ethics boards, frequent regulatory restructure, and disparities in research capacity and funding can also cause extended delays, or even insurmountable barriers, to cross-border collaborations [8].

Establishing a MENA-wide surveillance system for rapidly identifying new pathogens and disease outbreaks would be instrumental to avoid delays in outbreak identification and control, and can help foster cross-country academic collaborations. During pandemics, communicating epidemiological and effectiveness data between countries is essential. Yet, formal dissemination of confidential or country-specific data is fraught with challenges. Even within countries, sharing local data or clinical samples is often difficult and ad-hoc. During pandemics or other public health emergencies, the routine collection of de-identified clinical data and samples for research purposes would bypass the need for additional studies to collect these. Coordination by an independent research foundation, could help facilitate timely cross-national information sharing.

2.2. Vulnerable populations

Infectious disease outbreaks can disproportionately affect vulnerable populations. The MENA, in particular the GCC, experience unique challenges during an epidemic because of their large expatriate population, comprising up to 80% of the total population of some countries, where a majority are unskilled laborers [9,10]. Given their low wages and often crowded housing conditions, expatriate laborers are at higher risk of contracting communicable diseases, and the task of identifying, isolating and treating them can overwhelm healthcare systems. Providing clinical care to the elderly, children and pregnant women, as well as to the burgeoning refugee populations, offer additional challenges to potentially already over-burdened healthcare systems. There are no concerted studies from the region to understand the hardships encountered by these patient populations during a public health crisis. Their poor economic status also makes the expatriate laborers and refugees a vulnerable population, and great care must be taken to avoid exploitation of their financial status during clinical trial recruitment.

Further, informed consent challenges for clinical trials in the MENA include language, cultural, social and health literacy concerns, and are similar to other emerging regions [11]. Alternative strategies that can be implemented during pandemics can include deferred (consent is provided at a later date) or opt out consent (where study information is publicized on hospital wards or in waiting rooms and patients can choose to opt out), especially when collection of clinical research samples occurs as a part of routine testing [12,13]. Prepared patient information form templates that include deferred and opt out informed consent options can be readily deployed in pandemic situations. In a recent multinational study of over 6000 patients, respondents overall supported clinical research during pandemics [14]. Survey participants also proposed consent waivers for low risk studies and expressed support for the use of routinely collected, de-identified biologic samples for clinical research, even without formal consent [14]. Therefore, simplified consent processes could be pre-identified and implemented during infectious disease outbreaks to overcome barriers while safeguarding research subjects.

2.3. Research infrastructure

The conduct of RCTs involves considerable structure and organization. For example, the regulation of investigational new drugs occurs through a lengthy series of three phases of clinical research, during which access to the treatment is tightly restricted until it can be determined that the therapy is safe and efficacious. Regulatory and oversight capacity, including importation procedures for new investigational drugs, can vary substantially across the MENA. Drug importers must adhere to national requirements, but in several countries, including Egypt and Jordan, the process can average 60–90 days for overall approval time for investigational new drug importation [10]. During a pandemic, regulators must find a balance between pursuing scientific evidence of safety and efficacy while allowing timely access to potentially life-saving treatments to very ill patients. During the AIDS epidemic of the 1980s, for instance, the US Food and Drug Administration relaxed its policies on therapeutic access to investigational medications, allowing many patients early access to the antiviral, zidovudine [15]. In the MENA region, however, other than local ministries of health, there are currently no regional expert regulatory bodies, such as equivalents to the US-based Food and Drug Administration or National Institutes of Health.

To avoid bureaucratic and logistical barriers, clear frameworks could be developed for protocols ready to deploy during the next crisis. For example, regulatory restrictions on access to investigational medications might be eased, as they often are to allow compassionate use in an emergency situation. In countries where appropriate research infrastructure and safeguards are still emerging, Data Monitoring Committees (DMCs) can be used to oversee clinical trials [16]. DMCs are independent committees who have access to unblinded interim data to monitor real-time safety and efficacy results of ongoing trials and can, thereby, safeguard trial participants [16]. This is especially important during infectious disease outbreaks, particularly those with new pathogens, such as COVID-19, where no known treatment exists and investigational drugs are used based on observational data. Formal interim monitoring by DMCs allows for early stopping of studies when a treatment proves to either be clearly superior or ineffective [16].

2.4. Industry interests

Pharmaceutical involvement in research has long been a controversial issue. While industry can provide necessary funding and expertise, conflicts of interest can erode public trust, which is critical during a pandemic. A review of the United Kingdom's response to the 2009 swine flu pandemic revealed that a substantial majority of expenses went towards pharmaceuticals, including the antiviral oseltamivir, concluding that industry focus on financial interests persists even during a public health crisis [17]. Rising concerns relating to pharmaceutical sponsor bias in the conduct of clinical trials has compelled Tawam Hospital, an academic medical center in the UAE, to develop a clinical trial governance framework, in accordance with the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines, which include a conflict of interest resolution algorithm that provides surveillance to detect and resolve conflicts at all stages of the clinical trial life-cycle [18]. Further, comparison between industry-sponsored and investigator-initiated clinical trials in the UAE revealed increased GCP compliance adherence for industry-sponsored studies [11]. As such, there are emerging regulatory mechanisms in the region that can be improved to facilitate and organize a clinical trial during an epidemic.

3. Opportunities

3.1. Cost savings

High trial costs in the United States have encouraged outsourcing of clinical research internationally, resulting in approximately one-third of phase 3 trials for the 20 largest US pharmaceutical companies being conducted outside of the United States [19]. Using gas/price index as a marker for cost of living [20], the MENA region may prove to be a promising site for trial cost savings. Conducting clinical trials in MENA countries can result in substantial cost savings (59% of the cost), as compared to the average cost of 300 million US dollars to complete a clinical trial in the US [10], making the region a financially lucrative site for large scale clinical trials.

3.2. Healthcare oversight

When faced with a public health crisis and a highly communicable and deadly disease, front-line clinicians and physician-researchers may experiment with different cocktails of existing and experimental drugs. This approach has indeed occurred with the current COVID-19 pandemic in China and several European countries, with inconclusive and conflicting results [21]. Clearly, this approach does not serve the public interest. Anticipating this reaction, many MENA countries provided comprehensive treatment pathways and detailed therapeutic protocols for COVID-19 patients. This standardization allows for the analysis of the effectiveness of treatment modalities on large populations of patients. The existence of expansive public healthcare systems with unified electronic medical records also facilitates real-time accurate analysis of management protocols, allowing for treatment modifications on a large-scale basis as needed. In several countries, flexible funding models allowed for the shifting of grant money to support COVID-19 related research initiatives. This strong regulatory clinical oversight by ministries of health in many MENA countries can facilitate rapid epidemiologic data collection and analysis, which is critical during a pandemic.

3.3. International partnerships

The MENA has a long history of international collaboration. In recent decades, academic partnerships have developed in the education and healthcare sectors, including Weill Cornell Qatar, Royal College of Surgeons in Ireland-Bahrain, and New York University and Cleveland Clinic in Abu Dhabi. These relationships can serve as strong foundations for the interdisciplinary and multinational research collaborations that are pivotal during infectious disease outbreaks. Efficient knowledge transfer and sharing of data and expertise can lead to a strong global pandemic response. Further, conducting multinational studies can enhance recruitment, expedite the completion of trials, and increase the generalizability of results [22].

3.4. Media and messaging

Infectious disease outbreaks will invariably incite public confusion and fear. However, studies have shown that, even in stressful situations, patients are willing to be approached about research [13,23]. In one multinational survey, 82% of respondents believed that it was important to conduct medical research during infectious disease outbreaks [14]. Factors contributing to increased willingness to participate in clinical trials included greater knowledge about the disease and increased trust in healthcare workers and in the government [14]. Therefore, active efforts are required to engage and educate the public about pandemics and the value of research. Good media communication can influence public opinion of research and potentially affect recruitment decisions. Key messages include highlighting the distinction between routine clinical care and research participation, as well as proper framing the purpose of research studies to produce generalizable, population-wide results [24]. Many MENA countries already have the existing infrastructure to deploy mass marketing campaigns through television, print, and social media. Targeted community initiatives should be employed early to open dialogue, dispel misinformation and help build research literacy.

3.5. Academic health centers

Perhaps the greatest opportunity to conducting high quality clinical research in the MENA derives from the presence of many large academic medical centers in the region. Several of these institutions have been internationally recognized and are accredited by the Joint Commission International and Accreditation Council for Graduate Medical Education-International, indicating a strong foundation in evidence based medicine and scholarly activity [25]. As such, the MENA is already home to scores of clinician-educators and physician-scientists [26]. The development and support of research departments in each of these academic centers can greatly increase research productivity. These investigators have research expertise and can be trained to quickly ramp up research capacity in emergent situations. Education can take place during non-emergent research projects to develop and refine lean processes, including efficient recruitment strategies [27]. Pre-approved research agendas can include clear details about the types of studies that will be conducted during a pandemic and timely approval of research projects can be facilitated by the development of pre-formulated templates, or “sleeping,” study applications that can be either fully or partially pre-approved by institutional review boards (IRBs) [27]. Further, regulatory mechanisms should be developed to expedite IRB review, while ensuring that ethical standards are upheld, even during the challenging circumstances of a pandemic.

4. Conclusion

Since the COVID-19 outbreak was first identified in December 2019, there has been a strong response from the research community and a proliferation of studies and publications. However, a review of approximately 90 studies conducted by researchers in China, including 10 hydroxychloroquine/ chloroquine trials, has revealed inconclusive and conflicting results [21]. High quality clinical research can and should be done during public health emergencies to identify effective treatments and ensure the health and safety of the population. The efficient conduct of clinical trials requires innovative strategies for research

design, approval, and dissemination. The MENA is home to many large academic medical centers with strong healthcare oversight, local expertise in research and education, and pre-existing international collaborations. As such, many countries in the MENA region have an opportunity to quickly ramp up research capacity and contribute significantly to the fight against this global threat.

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Author contribution

Conceptualization: HI, AK, TH, SCN, Data Acquisition: HI, AK, TH, WHG, SCN, Writing Original Draft: HI, SCN, and Writing Review/Edits: AK, TH, WHG.

Declaration of Competing Interest

The authors report no conflicts of interest.

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