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Perspective

The missing pieces in the jigsaw and need for cohesive research amidst coronavirus infectious disease 2019 global response

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ARTICLE INFO

Article history:

Received 31 March 2020

Accepted 5 April 2020

Available online 7 April 2020

Keywords:

Coronavirus infectious disease 2019

Pandemic

Research needs

Knowledge gaps

Outbreak management

ABSTRACT

Identifying the research needs and gaps amidst this COVID-19 travelling across the countries is absolutely important for finely improving on the way we think and act. The natural history of the disease as well as viral shedding in different stages of clinical illness needs to be known which helps in triaging the patients in hospital settings. Animal and environmental interface need to be studied for defining the high-risk situations. Transmission dynamics in community or hospital and defining the laboratory criteria for the case confirmation will be most crucial.

Gene sequencing and validation and, suitable use of molecular based tests such as real-time polymerase chain reaction (qRT-PCR) should be clearly evaluated for diagnosis and/ or surveillance. The movement control strategy must be defined to prevent secondary transmission in healthcare as well as in community settings.

Repurposing of drug molecules is an elegant strategy to develop therapeutics in the case of pandemics quickly. Unproven practices and treatment protocols should invite critical scrutiny on the basis of ethics. Socioeconomic status of the community is also an important determinant for the compliance and sustainable public health measures.

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<https://doi.org/10.1016/j.mjafi.2020.04.001>

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Introduction

Severe acute respiratory syndrome coronavirus (SARS CoV) and Middle East respiratory syndrome (MERS) are two strains of Coronavirus family which were first identified in China in 2002 and Saudi Arabia in 2012, respectively with the potential to cause outbreak prone diseases in the past. World Health Organization (WHO) notified on 11th February 2020, that a new emerging infection named coronavirus infectious disease –2019 (COVID-19) is caused by 2019-Novel coronavirus. This was officially named as SARS CoV2 by International Committee on Taxonomy of Viruses.¹ The disease manifested as an outbreak of pneumonia of unknown aetiology and was first identified in Wuhan city, Hubei, Province of the Republic of China on 31st December 2019.² Subsequently, within a short span of one month, the disease spread to other countries around the world. COVID-19 was declared as an outbreak prone disease and subsequently a Public Health Emergency of International Concern by WHO on 30th January 2020 as per the International Health Regulation (2005) Emergency Committee.³ WHO characterized COVID-19 as a pandemic on 11th March 2020.⁴ The pandemic has clearly entered a new stage with rapid spread in many countries outside China. Various containment and mitigation strategies focus at delaying major surges of patient-load and levelling the demand for hospital beds while also protecting the most vulnerable groups such as elderly people and those with comorbidities.

To make every strategy work, a clear understanding of what we know and what we do not know is critically important to frame genuine strategies by subject experts. Hence, identifying the research needs and gaps amidst this pandemic is absolutely important for improving the way we think and the way we act.

Knowledge Gaps and Research Priorities for COVID-19 Outbreak Management

Virus natural history and transmission

It is important to know the natural history of the disease, as well as viral shedding in different stages of clinical illness. Viral shedding can vary from acute to convalescent to post-recovery phase as well. Host factors such as young children and immunocompromised population may also matter. Host infection after transmission of the virus is dependent on local mucosal immunity to natural immunity or cross-protection or vaccine-induced immunity. Virus stability in community or hospital environment may vary and determines a high or low risk of transmission depending upon the significant exposure of the host. Animal models may also help in studying the pathogenesis of COVID-19.

Human – animal interface

With COVID-19, we need to identify all possible animal sources and routes of transmission as they determine the persistence in animals ranging from infection to disease to being a

reservoir. Accidental or continuous spill-over to human beings usually determines the length of exposure and consequent outbreaks.⁵ Socio-economic and behavioural risk factors in various societies and geographic regions also play a critical role. Various risk reduction strategies at human, animal and environmental interface need to be studied for defining the high-risk situations.

Epidemiological studies

We need to understand the spread of the disease nationally, regionally, and globally with clearly defined surveillance case definitions for cases and contacts of COVID-19. Defining the susceptible population at risk and high-risk groups will be extremely useful to develop the containment strategy. Hypotheses developed for transmission dynamics in community or hospital and defining the laboratory criteria for the case confirmation will be most crucial in terms of clear understanding and interventions needed for containment of an outbreak. Non-pharmaceutical interventions on transmissibility can reduce the number of total cases. Social distancing can be one of the most effective measures to reduce the peak burden on the healthcare system.⁶ Overall, the impact of the outbreak, as well as the interventions also needs timely and frequent assessment. Surveillance of influenza-like illness (ILI) and severe acute respiratory infections (SARI) can contribute to the detection of COVID-19 cases.⁷

Diagnostics

Always an attempt should be made to collect the direct evidence of the disease by isolation or detection of RNA by polymerase chain reaction (PCR). SARS CoV 2 isolation is not recommended for diagnostic laboratories; however, it is useful for developing the diagnostic kits and candidate vaccines. Various types of protocols targeting various genes may require comparison only from research point of view; however, screening and confirmatory targets defined by regional reference laboratories may be followed by most for the purpose of traceability and reproducibility. Mechanisms to check the indeterminate results must lie with national reference laboratory. Gene sequencing must be submitted by all molecular biologists to GenBank to study the strain variations or mutations and molecular evolution. Serological tests for COVID-19 need to be validated with the relevant standards and maybe used for surveillance only. Validation and suitable use of molecular-based test such as real-time polymerase chain reaction (qRT-PCR) should be clearly evaluated for diagnosis and/or surveillance.

Clinical Management

In context of an outbreak or pandemic, it is extremely important for the healthcare delivery system to be adequately prepared with appropriate personal protective equipment (PPE) and know the clinical course of the disease along with the common and uncommon presentations. The understanding of natural history/course of COVID-19 will help in triaging the patients in hospital settings. Defining the clinical

case definitions and sampling strategy will help in differentiating COVID-19 from other similar illnesses with or without pneumonia. Ignoring other differential diagnosis can invariably be counter-productive from diagnosis and management point of view. Studying prognosis factors in COVID-19 confirmed cases will help in developing comprehensive management plan/approach with combination of various drugs or instituting newer therapeutics of proven or experimental efficacy. Transmission of COVID-19 in healthcare workers (HCW) is a cause of deep concern, hence, all three precautions – droplet, contact and air-borne must be suitably practiced by every health care personnel. Keeping daily records of medical examination of HCW can help in early detection and further spread. Continuous training appropriate at each level must also be documented. Hospital admission and discharge policies need to be defined in consonance with national policy. Logistics for PPE and other consumables needs to be ensured. Only trained personnel in batches may be allowed to work. The expert advice must be readily available in case of breach of unprecedented practice. Optimization and reuse of certain consumables/supplies may be permitted as per safety norms. The scope of newer diagnostics and treatment approaches will pave the way for defining the future guidelines. Collaborations with other departments and institutes will produce results of higher notch.

Infection prevention and control

For COVID-19, Infection Control committee should supervise on daily basis and identify the gaps and provide necessary resources and directions to minimize the transmission. Starting from entry in hospital premises, the movement control strategy must be defined to prevent secondary transmission in healthcare, as well as in community settings. Optimum and effective use of PPE in designated areas will play a crucial role in reducing the risk of transmission in HCW.⁸ Behavioural and cultural factors must also be taken into an account as they influence the compliance. Quarantine facilities should be well-designed and away from habitation. Isolation facilities with separate rooms and negative air pressure in case of suspected and confirmed COVID-19 positive cases will substantially be useful for containment, as well as protection of health workers. Personnel may be trained for DOs and DON'Ts in quarantine facility.

Research and Development of novel therapeutics and vaccine

Identification of candidate therapeutics for SARS CoV2 needs an overall strategy encompassing research, development and regulatory compliance. Repurposing of drug molecules is an elegant strategy to develop therapeutics in the case of pandemics quickly. The general plan for repurposing can involve computational approaches to determine the likelihood of a drug molecule to affect SARS CoV2 based on its similarity to the known target of that molecule.⁹ Another method is to experimentally study the interaction between proteins of SARS CoV2 and humans and use it to develop a list of therapeutic candidates. Prophylaxis will play an essential role in the elimination of COVID-19 in the long run. However, a

successful vaccine will require the development and standardization of animal models to check for the efficacy of vaccine candidates using a challenge study. Only after successful animal studies, vaccine candidates can be taken to clinical trials. The clinical trial phase requires standardized assays to evaluate immune response in humans. The other aspect which needs a more concerted effort is to have regulatory compliance for developed targets for therapeutics and vaccine. In the case of a pandemic, the usual route of clinical trials is too cumbersome and may take years to develop a therapeutic intervention. The use of adaptive clinical trial designs will help in expediting regulatory approval.¹⁰ Adaptive clinical trials such as multiarm multistage (MAMS) trials aim at using the real-world clinical practice of learning and reacting as and when an event happens. The flexibility of MAMS allows changing the course of a clinical trial without compromising its integrity or validity, thereby ensuring that more patients receive better treatments. Regulatory authorities and research bodies may allow such school of thoughts to expedite the development of therapeutics and vaccines.

Ethical considerations for research

In view of lack of established protocols and critical knowledge gaps, basic ethical standards must address the management issues regarding COVID-19 and maybe formed at the level of organization or as national policy. The national needs in terms of geography, population, social and cultural practices are different and hence, ethical considerations may be based upon reality and practices. Unproven practices and treatment protocols should invite critical scrutiny on the basis of ethics.

Social sciences in the outbreak response

We need knowledge, attitude and practice studies in terms of acceptance and adherence to public health measures and other health initiatives for COVID-19. Accessing and addressing the physical health and psychosocial well-being of HCW involved in care giving for COVID-19 from time to time. Risk assessment and communication to address the public health needs and measures will help the general public to address their issues of anxiety, fear, and stigma associated with the COVID-19. There is also a need to understand the effect of restrictive public health measures used for management of COVID-19 (such as quarantine, isolation, lockdowns, etc.) on the psychosocial and physical well-being of individuals. Socio-economic status of the communities is also an important determinant for the compliance of sustainable public health measures. Public health information system must address pertinent issues based on dynamics of COVID-19 and effectiveness of the control measures.

Suggested action plan for immediate research on COVID-19

First and foremost, a political commitment and funding from topmost level is essential. It is also essential to optimise the standard of patient care at different stages of the disease and take advantages of all available technological innovations to

improve the prognosis. Early evaluation of the effect of adjunctive and supportive therapies will be substantially useful. There should be a rational use of PPE and other infection prevention and control measures in healthcare and community settings. We should review the available scientific information to identify animal host(s) for preventing continued spill-over and better understanding of various aspects related to SARS CoV2 transmission such as time duration, severity of disease and host susceptibility. The evaluation of investigational therapeutics and vaccines needs to be expedited. We need to mobilize research on rapid point of care diagnostics at community level. It is very important that there is efficient data sharing for immediate public health purposes and conducting research activities.

Comprehensive strategy with a holistic approach in preparedness may allow the rapid activation of research and development activities during pandemic. Its aim should be fast-tracking availability of effective diagnostics, vaccines and therapeutics that can avert the crisis and lead to effective management of COVID-19 pandemic. Scientists working on Research and Development at various regional/national levels may also be aligned to global efforts for containment/control of COVID-19.

Disclosure of competing interest

The authors have none to declare.

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