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Seeking the Solution to COVID-19 in Border Areas of Thailand: Experts' Perspectives

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ABSTRACT

This summarized article is taken from information provided during a panel seminar focused on seeking the solution to coronavirus disease-19 (COVID-19) in the border areas of northern Thailand, on 29 March 2021. World-class health professionals and academics who are working in the field were invited to deliver both information and their perspectives on different aspects of the pandemic. The information is divided into three levels, namely, the global situation and challenges, including further recommendations; the local lessons learned in Thailand and further action and collaborations required of society; and the cutting age research developing COVID-19 vaccines and their implementation and practical recommendations. In conclusion, vaccines are just one of the tools that can be used against the disease, and these vaccines need to be considered as a whole picture, including the prioritization of the administration of vaccines under limited supply, the equity of availability to all people in the world, and the negotiation of affordable prices. Moreover, our traditional prevention and control measures, such as social distancing, face-mask use, and maintenance of personal hygiene, are still strictly recommended.

Keywords: *COVID-19; Solution; Vaccine; Prevention and control measures; Lessons learned; Thailand*

Background

The information in this article is presented by three international experts (a WHO representative in Thailand; a member of the advisory board of the Department of Disease Control, Ministry of Thailand; and an international expert in medical virology and vaccinology from Chulalongkorn University, Thailand) who give their perspectives on COVID-19 by using the current scenario in Thailand; the information is summarized from a seminar panel that occurred on 29 March 2021 at Mae Fah Luang University, Thailand. All information presented herein is based on the knowledge and personal experts' ideas as of the date of the seminar. Three topics are critically presented in the article: COVID-19: global challenges and a sustainable future; lessons learned and how to better prevent and control future serious epidemics in Thailand; and pathogenesis, clinical management, and the COVID-19 vaccine. The article is summarized by the team from the Center of Excellence for Hill Tribe Health Research, Mae Fah Luang University, Thailand.

A. COVID-19: Global challenges and a sustainable future

Global situation

More than 126 million cases and 2.8 million deaths attributable to COVID-19 have been reported globally. A million new infected cases were reported every 2-3 weeks with an 8.0% increase over the previous weeks (up to March 14, 2021), while deaths plateaued, slowing to 100,000 new deaths every 11-13 days. According to regional epidemic curves, there were increases in the epidemic severity, which could be due to new severe variants of the virus, while the effectiveness of global vaccines is not yet known.

Thailand has demonstrated effectiveness in the prevention and control of the disease in recent months, as evidenced by fewer reported cases. Almost the entire Thai population has complied with prevention and control measures, including case tracing and case isolation, which has resulted in a low number of new cases (29,127 cumulative confirmed cases) and a low number of cumulative deaths (below 100 deaths). However, several clustered outbreaks in Thailand have

been reported in Samut Prakan Province (the index case was a migrant construction worker that was symptomatic, and 15 out of 17 cases were identified as symptomatic), the Suan Plu and Bang Khen immigration detention centers (98 out of 1,888 detainees (5.2%) were positive for COVID-19), the Rama II cluster (the index cases were 2 migrant workers that were symptomatic, and 30 out of 71 screened individuals were positive for COVID-19), and the Bang Khae market, where a market vendor was the index case (the vendor experienced the onset of symptoms on 1 March 2021 and tested positive on 5 March 2021).

Thailand's achievements

Several effective approaches have been used in Thailand to minimize the risk of COVID-19 in the past months: a) a timely effective response to minimize the risk of widespread transmission; b) excellent laboratory capabilities to confidentially confirm a timely diagnosis; c) a highly visible risk communication platform to encourage broad public awareness and engagement; and d) a sound vaccination plan to deliver safe and effective vaccines to Thai citizens. However, vaccination is just one of the several tools used to address the problem.

Globally, more than 459 million doses of vaccine have been administered in 178 countries, but 42 countries have not yet commenced vaccination (30 countries of which are low-income countries (LICs) or low-middle-income countries (LMICs)). Currently, the efficacy and resulting immunity of all vaccines are well documented; however, some points are not clearly answered, such as the efficacy in some age categories (children and other special groups of populations), duration, required booster, and impact on transmissibility.

On 5 March 2021, seventy-nine COVID-19 candidate vaccines were in the stage of clinical development, of which 12 vaccines were in phase III trials and 4 vaccines were in phase IV trails. There are another 182 candidate vaccines in preclinical development. More than 90.0% of all the top candidate vaccines will be delivered through intramuscular injection. A study of the Pfizer vaccine effectiveness in Israel found that that the vaccine could prevent infection by 94.0% (87.0-98.0%), could reduce hospitalization by 87.0% (55.0-100.0%), and could reduce progression to the severe stage of disease by 92.0% (75.0-100.0%) [1]. A retrospective cohort study on the effectiveness of the Pfizer and Moderna vaccines in the United States reported their effectiveness to be 89.0% (68.0-97.0%) and documented a 3.7% hospitalization rate in individuals vaccinated with two doses [2]. According to data from a prospective cohort study in Scotland on the effectiveness of the Pfizer and AstraZeneca vaccines, the effectiveness rates on days 28-34 after vaccination were reported to be 85.0% (76.0-91.0%) and 94.0% (73.0-99.0%), respectively [3].

Since the vaccine demand outweighs the supply, the World Health Organization (WHO) recommends first providing the vaccine to prioritized groups, such as older adults, persons with underlying conditions, and health care workers. This method aims to reduce the severe cases among those populations, to relieve congestion in health care settings, to provide easy access for the entire population in need of health care that is not related to COVID-19, and to reduce mortality. Moreover, the WHO suggests that vaccines are just one of the tools for use against COVID-19; maintaining social distance, using face masks and regularly washing hands are still required.

Thailand started administering vaccines on 28 February 2021 using the SINOVAC vaccine (CoronaVac) in 13 priority (high-risk) provinces. This plan is aligned with the WHO COVID-19 vaccine road map. Three objectives have been preliminarily considered from the implementation: a) to reduce the severity and fatality rate, especially in those aged over 60 years; b) to protect the public health system from being overwhelmed; and c) to ensure that the economy and society can move forward.

Under the Thailand national vaccine plan, two vaccines have been used: SINOVAC and AstraZeneca. SINOVAC recommends two doses with an interval of 2-3 weeks between doses, and this vaccine is mainly used to prevent progression to the severe stage of disease after infection. AstraZeneca recommends two doses with an 8-12 week time interval between doses. This vaccine has been demonstrated to have no severe side effects and to produce a strong immune system response. The WHO is concerned about the side effects of the various vaccines and the acute effects following immunization (AEFI). Today, the WHO is working closely with all national authorities to monitor the quality, safety, and efficacy of vaccines to ensure they meet the global standard. Several concerns arising from the WHO on vaccine monitoring are as follows: a) a billion people will be vaccinated, which means that some side effects are possible; b) are there any side effects other than those that are expected?; c) is there a plausible biological mechanism for these side effects? and d) how can authorities understand the difference between association and causation with regard to vaccines and side effects? Regarding thromboembolic problems and AstraZeneca, the WHO reported that there was no strong evidence to make a conclusion because the proportion of vaccinated persons and general persons with thromboembolisms was not significantly different. Thus, the WHO recommends continuing to implement this vaccine.

Challenges

a) Mutations of the virus increase its transmission ability, increase the severity of the infection, and reduce the efficacy of vaccines.

b) There is currently unequal to access vaccines, especially by those who truly need to receive them. This is one of the greatest challenges of the limited supply of the vaccine and a large subgroup of the population who are in need of the vaccine. Having a hundred percent vaccination in a certain country, while other countries are not able to access the vaccine might not be a good strategy as a whole. Rather, providing access to the vaccine without economic barriers to those who truly need it, i.e., both those who need it due to underlying conditions and those who are working in high-risk circumstances, would be economically beneficial for the global population.

c) Proof of vaccination or immunity for international travel is not recommended by the International Health Regulation (IHR) Emergency Committee due to critical knowledge regarding the efficacy of vaccination in reducing transmission and the limited availability of vaccines.

What next?

Given the current information about COVID-19, the pandemic will not end soon, and an infection risk in one place is equivalent to an infection risk everywhere. It is clearly known that the vaccine is not the only sufficient tool used to combat the virus. For Thailand, many things need to be considered, such as a) the introduction of new variants with increased severity in a community, including B-1.1.7, b) cross-border introductions from national political conflicts in neighboring countries, and c) the challenges of vaccine supply to first-priority populations. Two major patterns of transmission are closely monitored: a) high-density population areas, particularly in migrant worker residences, and b) community markets, which are common places for people to gather in a community.

B. Lessons learned and how to better prevent and control future serious epidemics in Thailand

Introduction

This section aims to review the lessons learned from previous public health emergencies of regional and global concern that Thailand has experienced during the past years. The presentation is focused on the current good COVID-19 pandemic responses and the remaining challenges.

Key lessons learned

1) Since 1980, Thailand has experienced HIV/AIDS, SARS, avian influenza both in animals and humans, imported cases of MERS, the 2009 H1N1 pandemic, and the current COVID-19 pandemic. The crucial lessons learned include the need for transparent alerts and unified emergency responses.
2) Thailand has made major improvements by implementing the 1st-4th National Strategic Plans for Emerging Infectious Diseases, especially in the areas of establishing surveillance and rapid response teams (SRRTs) in every district, increasing laboratory capacity in every regional center, collaborating closely between human and animal health worker sectors and passing a new infectious disease control act that delegates the control of decisions to the provincial level.
3) Thailand was the first country outside of mainland China to report a case of COVID-19. There were two major waves of COVID-19 in March and December 2020 (lasting until 29 March 2021). Except at the beginning of the first wave, thus far, the country has contained its COVID-19 outbreaks.
4) Good practices in regard to COVID-19 responses are as follows: a) appropriate reporting for surveillance; b) laboratory surge capacity to test RT-PCR in every province; c) investigations with extensive contact tracing and the containment of many important clusters of COVID-19 outbreaks; d) systematic and reliable quarantine at state and local levels; e) field hospitals for mild cases; f) social distancing, hand washing, universal face-mask wearing in public areas; g) rapid and transparent risk communication; h) vaccine procurement and research; i) existence of a Provincial Infectious Control Committee; and j) whole government responses coordinated by National COVID-19 Administrative Centers.
5) The vaccine is a new important tool used to control COVID-19 and will be made available widely. This strategy is focused on the transition from strict containment to long-term stability with the hope of resuming domestic and international travel and trading in the last quarter of 2021.

Suggestions for future actions

Thailand will become increasingly stronger by addressing both the public health system and social determinants of health. We should maintain and increase public health capabilities by investing in an epidemiological workforce and robust surveillance tools, laboratory networking and vaccine research. We should also do our best to reduce at least the following three vulnerable conditions. The first condition is reducing noncommunicable diseases by controlling risk factors, which will help reduce mortality and intensive care needs in the next pandemic. Second, vulnerable settings should be reduced, especially migrant working and living conditions, inmate and prisoner conditions, and crowded slums in large cities. This area needs strong policies to be effective. Third, risk behaviors should be reduced by promoting safe social behaviors, for instance, by encouraging people to have small and meaningful events instead of large events, which will save the environment and responsibly promote social justice.

Conclusion

Each of us can make a difference in preparing our country for future serious epidemics or pandemics by practicing, advocating and enabling our own community.

C. COVID-19 Impact, Management, and Vaccine

Presently, one major problem posed by the going COVID-19 globally is the emergence of virus variants of concern (VOC). A large number of new confirmed cases were reported a week ago (between 20 March 2021 and 27 March 2021) in Europe despite ongoing vaccination [4]. For Thailand, the national health system records showed several positive impacts of COVID-19. Increased awareness of better personal hygiene has reduced the incidence of the flu and other infectious respiratory infection [5]. Limitation in movements resulted in a marked decrease in traffic accidents [6]. However, COVID-19 seems to have little impact on mosquito-borne diseases such as dengue fever, which are more influenced by environmental management than personal hygiene [4].

Today, the development of COVID-19 vaccines offer new hope for the global population. Thailand had three options for vaccination: developing its vaccine, cooperating with other international companies in vaccine development, or buying the vaccines. To be widely accepted by the general population, an ideal vaccine (preferably offered as a single dose) should have minimal side effects, be relatively effective and affordable, and be easily shipped and stored at room temperature. Since coronavirus can mutate and re-infect humans, it makes vaccine development challenging.

There are currently ten platforms or types of COVID-19 vaccine. 1) inactivated SARS-CoV-2 grown in cell culture and then chemically inactivated, 2) live attenuated but genetically weakened SARS-CoV-2 grown in cell culture, 3) recombinant whole spike protein, 4) recombinant receptor-binding domain of spike protein, 5) genome-devoid virus-like particles displaying surface spike protein, 6) replication-incompetent vector capable of expressing the spike protein, 7) replication-competent vector capable of expressing the spike protein, 8) chemically inactivated virus vector with spike protein on the surface, 9) plasmid DNA encoding the spike gene under a mammalian promoter, and 10) messenger RNA encoding the spike protein packaged in lipid nanoparticles [7].

There are more than 300 research institutes involved in vaccine development. Thirteen vaccines in four platforms have been approved under emergency use [8]. They are inactivated virus (SINOVAC and Bharat Biotech), virus vector (AstraZeneca, Sputnik V, Johnson&Johnson, CanSino Biologics), RNA-based (Pfizer and Moderna), and recombinant protein (Novavax). More vaccines are expected to be approved in the future.

Messenger RNA vaccine

Naked RNA is intrinsically unstable. It is typically present with 5' and 3' non-coding region with 5' cap and 3' poly-A tail and is often associated with membrane proteins. RNA encoding the spike protein is made stable by combining with lipid nanoparticles in glycerol to make a vaccine. When injected into the muscle, the spike-encoding RNA molecules which made it to the cellular ribosomes are translated. The presence of the spike protein eventually stimulates an antibody response. This mechanism is the basis of the Pfizer and Moderna vaccines, which have never been used in a human vaccine. A study reports a very high efficacy (95.0%) after two doses of such vaccine [9]. This technology has the potential for other vaccine development in the future.

Virus vector vaccine

The Ebola vaccine is an example of a virus vector vaccine. Virus vectors often utilize adenovirus (36,000 base-pairs) to induce foreign protein expression in host cells. Wild-type adenovirus typically causes acute respiratory tract infection and diarrhea in humans. Coronavirus spike gene is large (approximately 4 kilobases or more than 1,000 amino acids), which in comparison is larger than the hepatitis B virus spike glycoprotein (226 amino acids). In order to include the spike gene into the adenovirus vector, the adenovirus E1 gene, which has a viral replication function, is deleted. As such, the adenovirus vector can express the spike protein but cannot replicate itself. Expression of the coronavirus spike from the adenovirus-encoded DNA in the cellular cytoplasm eventually stimulates antibody production. This platform is the basis for COVID-19 vaccines by Astra Zeneca, Sputnik, Johnson & Johnson, and CanSino. In particular, the Sputnik vaccine developed by Russia uses two different adenoviruses, Ad26 for the first dose and Ad5 for the second dose. The purpose is to avoid the host antibody to Ad26 from the first dose and improves the booster effect to the spike proteins (92.0% efficacy). For the Johnson &Johnson vaccine, only Ad26 is used in a single dose, while CanSino Biologics of China uses Ad5.

Inactivated vaccine

For over 50 years, this traditional method has been used to produce vaccines for polio, hepatitis A, and rabies. Cultured virus stock is inactivated with beta-propiolactone, which is easily disintegrated. After purification by centrifugation, the inactivated virus is absorbed with aluminum salt as the adjuvant.

SARS-CoV-2 Recombinant Protein

This process is used for the hepatitis B vaccine, in which virus-like particles are produced from yeast

cells. Novavax uses a baculoviral vector encoding the spike genes and a novel "Matrix-M adjuvant" extracted from the Quillaja sapoaria from Molina tree to make its COVID-19 vaccine. This adjuvant can effectively stimulate the human antibody response.

In conclusion, almost all COVID-19 vaccines developed thus far have sufficient efficacy and meet the WHO criteria in preventing mortality from COVID-19. Most vaccines cannot prevent infection but can alleviate COVID-19 severity. Some vaccines have been shown to elicit cross-protection against the South Africa variant (B.1.351).

Final recommendations

There are several recommendations for vaccination and clinical practice: 1) Vaccination can prevent severe COVID-19 requiring hospitalization; 2) Vaccination should be done soon as possible on a voluntary basis. More than 530 million doses (as of 29 March 2021) have been administered worldwide, and 15 million doses are administered every day. High immunization coverage can reduce the number of new cases and deaths, which should help the economy recover; 3) Any vaccine is good to use under emergency use authorization at the moment, given the limited supply; 4) Price of vaccine is one of the considerations for real-world implementation; 5) Acceptance is important in vaccine implementation given the 10% vaccine hesitancy rate among Thais surveyed; 6) Risks and benefits of a COVID-19 vaccine have to be compared. Vaccination is a much more positive impact on social and economic dimensions. A small proportion of vaccination side effects will require medical attention; 7) Antibodies to the coronavirus nucleocapsid result from either natural infection or vaccination with an inactivated vaccine, while antibodies to the spike protein will result from vaccination. Nucleocapsid antibody is detectable earlier than spike antibody, and the IgM and IgG are detectable in the same period. In practice, IgG is detected in routine work. Detection of IgG for nucleocapsid will be more practical to identify natural infection since titers are higher than for the spike protein; 8) Rapid COVID-19 test could be used. The highest antibody is detected in the third week of the infection. The detection rate by using the rapid test in week-1 and 2 is around 50%. Patients who progressed to severe pneumonia are associated with higher antibody titer. Nevertheless, antibody detection depends on the method and the target antigen; 9) After vaccination, it is not necessary to detect the antibody. Antibody to spike from vaccination is generally higher than from natural infection. A very high title of antibody to spike and a very low antibody to nucleocapsid suggest an infected individual who was vaccinated; 10) AstraZeneca confirms that the wide gap between the first dose and the second dose would yield a better antibody response; 10-12 weeks is recommended; 11) If anyone has been infected and lives in an epidemic area, they should be vaccinated 6 months after recovery; 12) The significance of a booster vaccination after the second dose has not been reported, but it is a possibility if the antibody titer decreases to a level lower than the protective level; and 13) COVID-19 vaccination is not recommended for pregnant women, but there is no need to test women for pregnancy before vaccination. In most cases, the benefits outweigh the risk from the vaccination.

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