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Some thoughts on conducting and implementing clinical practice guidelines in a pandemic

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A pandemic is a disease that spreads worldwide. When disease is new such as coronavirus disease 2019 (COVID-19), evidentiary basis, by definition, to prevent, diagnose, and treat the disease is limited. Nevertheless, clinical practice guidelines are urgently required to assist policy and healthcare workers to make informed decisions. But, acting in the high-quality evidentiary vacuum, that is, basing guidelines on poor-quality research can be counterproductive and potentially harmful.[1,2] Thus, guideline developers face a number of challenges during a pandemic like COVID-19 that we wish to address in this paper.

Should a standard guideline or a rapid advice guideline be conducted?

The World Health Organization (WHO) classifies the guidelines into four categories: standard guidelines, comprehensive guidelines (consolidated guidelines), interim guidelines, and emergency guidelines in response to an emergency or urgent need (rapid advice guidelines) (https://www.who.int/). In determining if a rapid advice guideline is appropriate, the key question is how quickly the uncertainty needs to be dealt with. The WHO recommends that rapid response guidelines can be developed within hours to 3 months based on evaluation of all the information from the public health emergency or pandemic.

Who develops a rapid advice guideline?

From national to state/province agencies, professional organizations, local hospitals etc., anyone can develop a rapid advice guideline as long as they have resource (such as sufficient human capital and adequate funding) and ability (such as guideline developers with relevantly clinical and methodological expertise).

Is it acceptable to develop non-evidence-based guidelines based on experts' opinion only?

Guidelines are classified into evidence-based guidelines and non-evidence-based guidelines.[3] Therefore, rapid advice guidelines may be evidence-based guidelines or non-evidence-based guidelines. One fundamental misconception about evidence-based guidelines is that they can be only developed if well-designed controlled trials exist. On the contrary, evidence-based medicine principles apply equally well to low or high quality evidence and the situations when only low quality evidence is available may be those in which clinicians most need guidance.[4] Non-evidence-based guidelines that neglect the underlying evidence may be bound to make different and potentially erroneous advices compared with evidence-based guidelines.[1]

We searched the ECRI Guideline Trust (https://guidelines.ecri.org/), the Center for Disease Control and Prevention library database, PubMed, Medline, Embase, WHO database (https://www.cdc.gov/library/researchguides/) for COVID-19 guidelines released up to May 19 2020. We found seven evidence-based guidelines that were based on a systematic review, and four non-evidence-based guidelines that were based on guideline developers' clinical experience rather than a systematic review, regarding antiviral treatment in adult patients with COVID-19 [Table 1]. This shows that different organizers can make different recommendations on the same topics and questions. There are many reasons why guidelines differ: some are warranted (*eg*, difference between settings,

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Table 1: Comparing recommendations for five antiviral drugs from different guidelines for treating adult patients with COVID-19.*

Country (first case confirmed time)	Guideline Organization	Published time	Literature search database	Lopinavir/ Ritonavir	Umofenovir	Chloroquine	HCQ	Remdesivir
Evidence-based guidelines								
China (A cluster of cases in Wuhan, was reported to WHO on December 31, 2019)	CETM in Wuhan University	Feb 6, 2020	PubMed, Embase, Cochrane library, CNKI, Wanfang, preprint platforms	No evidence from RCT to support specific antiviral drug treatment				
United States (Jan 20, 2020)	ACOEM	April 24, 2020	PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar	No recommendation	Not included	Recommended for selected patients	Recommended for supervised treatment of selected patients	Selectively recommended
	IDSA	April 27, 2020	Medline, Embase	Recommended the use in clinical trials	Not included	Recommended the use in clinical trials	Recommended the use in clinical trials	No recommendation
12 countries	ESICM and SCCM	March 27, 2020	Cochrane library, Medline	Recommended against the use	No recommendation	No recommendation	No recommendation	No recommendation
Six countries	NA	April 29, 2020	MEDLINE, Embase, PubMed, Cochrane, medRxiv	Suggested against the use	Suggested against the use	Suggested against the use	Suggested against the use	Not included
Korea (Jan 24, 2020)	KSID, KSAT, KSPID	May 19, 2020	PubMed	Could be used	Not included	Not included	Could be used	Could be used in clinical trials
Australia (Jan 25, 2020) and New Zealand (Feb 28, 2020)	CSANZ	April 9, 2020 (living)	Not specified	Not included	Not included	Recommended against the use	If prescription, consecutive ECG is mandatory	No recommendation
Non-evidence-based guidelines								
Italy (Jan 30, 2020)	ISITD	March 13, 2020	NA	Recommended the use with chloroquine/ HCQ	Not included	Recommended the use with Lopinavir/ Ritonavir or darunavir/ritonavir	Recommended the use with Lopinavir/ Ritonavir or darunavir/ritonavir	Recommended the use in severe or critical patients
China (December 31, 2019)	NHC, SATCM	March 3, 2020	NA	Could be used	Could be used	Could be used	Could be used (Not included, but it is a less toxic derivative of chloroquine)	Not included
United State	ATS	April 3, 2020	NA	No recommendation	Not included	Recommended the use on a case-by-case basis	Recommended the use on a case-by-case basis	No recommendation
	ASAIO	May 1, 2020 (living)	NA	Not included	Not included	No recommendation	No recommendation	Could be the use in clinical trials

ACOEM: American College of Occupational and Environmental Medicine; ASAIO: American Society for Artificial Internal Organs; ATS: American Thoracic Society; CETM: Center for Evidence-based and Translational Medicine; COVID-19: Coronavirus disease 2019; CNKI: China National Knowledge Infrastructure; ESICM: European Society of Intensive Care Medicine; HCQ: Hydroxychloroquine; IDSA: Infectious Diseases Society; ISITD: Italian Society of Infectious and Tropical Diseases; NHC: National Health Commission; NIH: National Institute of Health; RCT:Rrandomized controlled trial. *Green color represents supporting the use of the antiviral drug; red color represents against the use of the antiviral drug.

accessibility, implement ability of interventions, etc.) but most are unwarranted (*eg*, conflict of interest, failure to perform high-quality systematic reviews, lack of familiarity with evidence-based guideline's development methods, etc.).[5] However, the most serious difference among guidelines in terms of their consequences on decision-making and patients' outcomes is between evidence-based and non-evidence-based guidelines. Table 1 shows a typical case: non-evidence-based guidelines rarely or ever make recommendations against use of a particular treatment. Because the development process for non-evidence-based guidelines is not transparent, the accuracy of its recommendations cannot be assessed, and, therefore, the end users should not feel confident to implement them. Hence, we recommend that rapid advice guidelines, like all other types of clinical guidelines, should always be evidence-based. It is noticed that some living evidence-based guidelines are neither registered at the ECRI Guideline Trust nor published in a medical literature databases, such as the NIH treatment guideline for COVID-19 (http://www.covid19treatmentguidelines.nih.gov/).

Should rapid advice guideline developers follow the regular guideline reporting standards?

The guideline reporting checklist, the tool that assists guideline developers on how to report the guideline, is a key mechanism for assuring transparency. Therefore, it should be mandatory. In addition, it does not take too much time to complete.[6] It also helps the end users to assess the quality of guidelines using the guidelines appraisal tools such as AGREE II and AGREE-REX (https://www.agreetrust.org/) to facilitate decisions on whether to implement guidelines in clinical practice or not.

When should a guideline be updated due to continuously emerging evidence?

For the conditions that represent a serious public threat with new evidence emerging at fast pace that may make previous recommendations obsolete. The guidelines updating should be continuous. The "living" evidence-based guidelines that employ a combination of continuous literature surveillance, rapid updating of systematic reviews and virtual panel meeting represent the best mechanism to provide trustworthy recommendations on evolving basis (see http://metaevidence.org/COVID19.aspx for an example). However, to succeed, living guidelines require commitment and resources.

How should a rapid advice guideline be implemented?

Implementation of a rapid advice guideline should be taken into account right from the beginning of guideline development. Guideline development should include a plan of the steps and options for dissemination and implementation. Implementation tools, like decision aids or evidence tables must be easy to follow by all clinicians. Translating guidelines into clinical algorithms/pathways and decision-tree is particularly promising strategy for their implementation at the point of care.[7] Guidelines deemed impractical for use in local settings due to resource demands may be the biggest barriers for guideline implementation in a public health emergency. For example, the RT-PCR test is regarded as the reference standard to diagnose COVID-19, but was not available at some hospitals in Wuhan or other cities in Hubei province in China in January and February of 2020, and is still not widely implemented in other countries that are affected by the coronavirus pandemic.

Conclusions

According to the Institute of Medicine, a trustworthy guideline is to be developed via a transparent process, supported by a systematic review of the evidence and updated continuously. In the time of pandemic, this can only be achieved by developing "living" evidence-based rapid services. Historically, development of guidelines has not been well coordinated or funded, often resulting in their inefficient and duplicated production. Given international scope of pandemics such as COVID-19, we call for establishing an international center of "living" evidence-based guidelines. The existence of such a center with its branches in all continents would help avoid duplication of the efforts and pool resources to efficiently develop high quality systematic reviews and guidelines, which, in turn, could quickly be disseminated for local implementation across the globe.

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Conflicts of interest

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