

## WHO International Health Regulations (IHR) vs COVID-19 Uncertainty

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**Summary.** One of WHO primary function is to control and monitor internationally the spread of infectious diseases of the common killers. After SARS-COV, the International Health Regulations (IHR) was adopted in 2005 by all 194 member states to set up national preparedness for an efficient “early alert and response system”. COVID-19 is a novel virus with an unpredictable course and many uncertainties about its biological, clinical and epidemiological characteristics. COVID-19 is a game changer and calls for a revision of IHR as well as a more biological, clinical and community-cantered preparedness strategy. ([www.actabiomedica.it](http://www.actabiomedica.it))

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### WHO and IHR: historically shaped by Coronaviruses

The World Health Organization (WHO), since its constitutional establishment in 1946, has a central and historic role in the coordination and management of global health and diseases, from communicable diseases like influenza and HIV or non communicable diseases like mental health or obesity. In order to be able to efficiently engage in this monitoring function at the global level, the WHO Constitution<sup>1</sup>, under Articles 21(a) and 2, gives authority upon the World Health Assembly, to adopt conventions or regulations « designed to prevent the international spread of disease » as to ensure international and national health security (1).

Transnational concern for controlling and regulating the transmission of deadly diseases beyond national borders with quarantine measures is not new. In 1838, the Superior Council of Health of Constantinople was established to supervise the Sanitary Regula-

tion of the Turkish port between Asia and Europe to prevent the contagion and spread of cholera. This was followed by fourteen “International Health Conferences” from 1851 to 1938, the first being organized by the French Government, with the objective to standardize international quarantine measures for all Mediterranean ports to combat the contagious spread of cholera, plague and yellow fever. According to historical analysis, these conferences and standards played an important reference role for World Health Organization international regulations (2). The late XIXth century framework was based on scientific knowledge and infectious diseases control structured with primary measures of medical inspection, quarantine and isolation of the ill (3, 4).

During last Century, the technological and post WWII industrial revolution substantially increased travel and trade between nations in the world, escalating the emergence (or re-emergence) of communicable infectious diseases threats. The growing concern of transborder contagion transmission led to the adoption in 1969 by WHO member states of the first legally-binding *International Health Regula-*

1 - The Constitution was adopted by the International Health Conference in New York (19 June - 22 July 1946), signed on 22 July 1946 by the representatives of 61 States, and entered into force on 7 April 1948.

tions (IHR) with six « *quarantinable diseases* »<sup>2</sup> which was reduced by an amendment in 1981 to three main global diseases to be closely monitored : *yellow fever, plague and cholera*. The earlier efforts of WHO were to merely “patrol borders” against the incursion of epidemic diseases which historically were major and common killers in the absence of antibiotics and preventive vaccines (2). One could add that medical and clinical expertise was at that time considered as the centre stage of disease control. At the turn of the XX-Ist Century, the 2002-03 global outbreak of SARS-COV (Severe Acute Respiratory Syndrome caused by SARS Coronavirus) became the first public health emergency of international concern (PHEIC) of our newly webwide globalized Century. The WHO Director-General then, Dr Gro Harlem Brundtland, took the lead in coordinating this global health emergency by immediately releasing transparent communication about the knowns and unknowns, claiming full disclosure of data after late notification from China, and firmly recommending travel restrictions and preventive actions from every country. This was accomplished through a huge information and data gathering/tracking/tracing operation of SARSCOV (or SARS-COV) with multiple parallel actions Such as isolating cases. Furthermore, WHO made an appeal to the international scientific community to further research on COV and animal-human transmission. In eight months, WHO was successful at eradicating the SARS-COV epidemic that affected 26 countries and caused 8096 cases and 774 deaths mainly owing to early isolation of the ill and quarantine measures (5).

The lessons learnt by SARS-COV, in particular by the transborder epidemic and epicurve surge due to information delays on reporting and lack of border containment, triggered the spread of SARS worldwide and led to the thorough revision of the “IHR 2005”, adopted during the 58<sup>th</sup> World Health Assembly in 2005 by 194 member states across 6 regions<sup>3</sup> (6).

IHR 2005 was designed to be practical and useful with detailed yet culturally adapted measures and rules: new criteria for early reporting, four typologies

included in PHEIC events and potential pandemic: (1) infectious (human + zoonoses), (ii) foodborne, (iii) chemical and (iv) radionuclear. A new methodology was put in place with more precise step-by-step risk assessment and a decision tree algorithm (Annex II). New tools and protocols/certifications are included for control and inspection at borders (entry points: land, ports, airports), quarantines and isolation measure and risk communication tools (7).

The identified weaknesses in epidemic/pandemic national management of SARS-COV triggered the need for training and preparing countries at the best to an “early warning alert and response system” with a 24h/7days surveillance and monitoring system. Strong “outbreak readiness” would prevent and mitigate the highly contagious infection transmission within and between borders and avoid outbreaks and subsequent risks of uncontrollable spread of disease. Those capacities were implemented by WHO with three universities through multiple training and i-course with WHO regional focal points (6, 8).

After recent other outbreaks such as MERS-COV in the Middle East or Ebola in West Africa (9), many experts raised concern about the need for updating and adapting IHR to reinforce early detection, thus early measures to contain the spread and criticized the lack of preparedness which, in the case of Ebola, led to a high toll for a very contagious but usually “easy to contain” infection (10).

### **Uncertainties of Coronaviruses: a challenge for IHR**

Human coronaviruses were first characterized in the 1960s and were found out to be responsible for high prevalence of upper respiratory tract infections in children; the SARS-COV epidemic highlighted the zoonosis and challenge of the animal-human transmission (11).

Since 2003, many new human coronaviruses have been identified with existing tests, including the severe acute respiratory syndrome coronavirus, which caused significant morbidity and mortality. Although much effort has been focused on developing a SARS vaccine, years after its outbreak was over, no viable vaccine emerged beyond the animal testing (12). To this

2 - Six “quarantinable diseases” : cholera, plague, yellow fever, small-pox, relapsing fever and typhus

3 - WHA88.3 : [https://www.who.int/ipcs/publications/wha/ihr\\_resolution.pdf](https://www.who.int/ipcs/publications/wha/ihr_resolution.pdf)

date, no vaccine has developed from animal testing, as the Coronaviruses have complex configurations, are host specific and can infect humans and a variety of animals, resulting in newly infected humans with different strains and development such as with MERS-COV (13).

IHR 2005 most important instrument for “detection and early notification to WHO and investigation” is the Annex II decision-making tool. Four epidemic diseases require immediate notification irrespective of context: smallpox, poliomyelitis, human Influenza new subtypes and SARS. However the fact that different Coronaviruses family are not explicitly mentioned although associated (i.e. MERS-COV) might be misleading into underestimating high risks of the Coronavirus family subtypes in light of numerous scientific articles describing not only the risks, but its clinical symptomatology, and clinical uncertainties (12, 13).

Despite the fact that the WHO IHR is an important instrument based precisely on the coronaviruses family, the COVID-19 shows it has reached its limit and a deeper reflexion is needed for the future. Furthermore, According to a recent WHO study reviewing IHR implementation in the world, 50% of the 182 countries analysed have “strong operational readiness capacities in place” (9). This result certainly reflects the readiness of past PHEIC and pandemics, but the reality shows that new unknown agents can remain unknown for an extended time and remain unpredictable with high contagious rates. Thus, “readiness” criteria at all levels need to be revisited and upscaled to effective response to toxic agents of health concern with obscure origins, unknown characteristics and unpredictability patterns with high risk for specific groups; for example, the elderly with or without comorbidities and/or specific biosystemic and biosecurity conditions. Many experts have expressed concern about it and asked for a revision of IHR to adapt it to experiences and lessons learnt (10, 14).

### **COVID-19: a moving and mutating target**

COVID-19 is unfolding in a timeline in the world with different patterns like a flock of multiplying and mutating invisible birds following airways. New initia-

tives are flourishing in different regions all facing the same contradictions and uncertainties.

As described in March 2020 by Cucinotta and Vanelli (15), COVID-19 is a novel disease with incompletely described clinical course and uncertain risk factors and risk transmission. During the course of the COVID-19 spread throughout the world, more testing, tracing and tracking has been put in place, however the data collected remains incomplete, marked by inconsistencies and contradictions between and within countries. Comparability of health systems response to the pandemic or between countries of regions will pose a central methodological problem: populations have not been all tested for COVID-19 epidemic characteristics: infected healed vs died, infected (a) symptomatic vs asymptomatic, (a)symptomatic infected contagious vs non contagious vs unknown infected immune but contagious.

A lack of global and local scientific consensus on COVID-19 outbreak remains to this date on a wide range of issues: origin of the virus (i.e. case 0), different mutations of the virus, dynamics and lifetime of the virus (i.e. mutation, elements of HIV), characteristics and determinants of transmission rate of contagion ( $R_0$  scale), multi-epidemiological approach, inconsistent clinical manifestations, standard treatment vs differential symptomatology, socio-environmental factors, post-exposure and reliability of immunity solutions with a mutating virus (i.e. antibody tests, vaccines for a given strain). The current uncertainty and unpredictability of COVID-19 calls for the emergence of a new scientific consortium of expertise in all those domains to proceed to a large data and case mapping, which will serve in the construct a new preparedness paradigm based on multilevel expertise. The “readiness” to future uncertain outbreaks will depend on our capacity to be best prepared to prevent and respond rapidly to scientific and clinical uncertainties locally, while collaborating internationally towards consensus building. For example, as presented on Michigan University School of Public Health by the chair of epidemiology, the contagious indicator  $R_0$  was found to be dependent on the setting and the population density (16) or to the blood type (protection of Type 0) (17).

## The Way Forward...

One of the key challenges in understanding when the pandemic will end is to recentralizing the core question onto the lifecycle of the virus, as well as to the transmission control defying and failure to detect asymptomatic infectious cases. A recent study might bring light to explain why regions such as the North of Italy with a high percentage of older persons, have been more affected by COVID-19. A recent study reports that half of residents of a skilled nursing facility (27 of 48) tested positive while asymptomatic at testing. Furthermore, live COVID-19 at high concentrations from the nasal cavity were found even before symptom development (18). Those results could indicate that asymptomatic persons, maybe older persons in particular given a life of anti-bodies, could be playing a major role in the transmission of COVID-19 outbreak in the areas with a high density of elderly persons live.

For now, the consequences of this uncertainty is creating panic and decisions based on a given hypothesis and course of action, which has led to a lockdown and global confinement measures creating social and economic disruption never seen before in history. The current uncertainties call for precautionary measures such as washing hands, using face masks and keeping social distancing, especially when in crowded outdoor or indoor spaces until we have more evidence.

The situation calls for re-thinking how we collectively handle emergency investigation and clinical case evidence, how we communicate and collaborate globally and how experts of different disciplines and communities can organise their preparedness and implementation plans.

The United Nations and WHO as well as the international community with no doubt recognize the importance to join expertise and further research and financial investment into high risk coronaviruses type in order to create adapted preparedness basic protocols that could serve as a basis for advancing with common knowledge for next "uncertain virus" outbreaks (19).

Globalisation, information and communication technologies and the COVID-19 threat to every citizen has brought the world and the people together in new ways like never before, allowing increased interaction, awareness and participation, as there is no driver

in this global uncertainty. People are left to their own judgement with contradictions, fake news and worse harmful news amidst a collective grief, confinement and self-management. With no doubt, the world will not be the same after COVID-19....

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