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Clinical research networks are key to accurate and timely assessment of pandemic clinical severity

Influenza pandemics range in severity—from catastrophic (eg, 1918) to relatively mild (eg, 2009). For this reason, WHO is working to include clinical severity measures in its pandemic risk index, which is intended to help guide the public health response.[1] To be most useful, information about clinical severity should be available soon after a new pandemic threat emerges, whether the threat is from influenza or another emerging virus. One measure of severity is the risk of death among cases, variably defined as people presenting for care, people with symptoms, or people infected (with or without symptoms).[2] Another measure is the expected demand for health care—hospital space, and availability of respirators and adequate beds in intensive care units. Government officials need timely, accurate estimates of severity to allocate resources effectively and communicate the risk to the public appropriately.

As the 2009 experience revealed, rapid assessment of pandemic clinical severity presents a challenge. The first studies in Mexico predicted the H1N1p virus would kill as many as 2% of laboratory-confirmed cases, on par with the 1918 pandemic, whereas another early study suggested that 0·4% of people with influenza-like illness would die, similar to the moderately severe 1957 Asian H2N2 pandemic.[3] The estimated mortality burden fell more heavily on younger people, which was also reminiscent of the 1918 pandemic. Only several months later did studies from the USA and New Zealand establish that the pandemic was likely to be relatively mild, even though young people were still more affected.[4,5] The early overestimates were probably the result of selection bias that skewed study enrolment toward sicker patients, and without baseline data from normal influenza seasons the measurement of clinical severity of the novel pandemic virus compared with seasonal influenza was not possible. The result was that early warnings of a pandemic severity on par with that which occurred in 1918 frightened the world unnecessarily.

Global clinical research networks in operation before a pandemic virus emerges could be decisive in obtaining accurate early assessments of pandemic severity and clinical care needs. Ongoing multinational cohort studies, operating in both the northern and southern hemispheres, could provide a baseline clinical severity estimate against which to compare the novel emerging disease. Multinational networks with a wide global presence have a good chance of operating in an area affected by the outbreak. Such expert networks could also provide information on natural history, pathophysiology, biomarkers, pathogen tropism, host and viral genetics, optimal clinical care management, and forecasts of hospital and intensive care unit needs. Additionally, ongoing clinical research networks—with preapproved emergency protocols ready to go—could readily test the efficacy of available antivirals and other treatment options in randomised trials set in the areas of earliest outbreak.

During the 2009 pandemic, the US National Institutes of Health adapted the HIV clinical research network INSIGHT to study influenza.[6] After enrolling a patient with known or suspected influenza, network sites collected demographic, medical history, risk factor and other data, archived biological specimens, and followed up to establish case outcome (on day 14 for outpatients, and on days 28 and 60 for inpatients). Influenza testing was done locally and at a central laboratory. Inclusion of all subjects with acute respiratory illness allowed comparison of clinical severity between seasonal and pandemic influenza, as well as other respiratory illnesses. The combination of the conditional risks of disease progression in the inpatient and outpatient settings enabled estimates of case fatality, and hospital resource needs, with fewer patients, allowing an accurate assessment, even when the virus is not highly lethal.[7]

Pre-established global clinical research networks can not only provide faster, more accurate clinical severity assessment, but can also allow physicians to learn how to best treat infected patients, and can serve as platforms for clinical testing of new drugs and vaccines. To fulfil this role, they should first be fully integrated into global pandemic preparedness, with standardised First Few 100 protocols,[8,9] regular simulation exercises, and clear plans for how to accelerate crucial clinical research when an emergency arises; data from countries

with timely national electronic health data could also be folded into such a framework. In May, WHO and the World Bank jointly established the Global Preparedness Monitoring Board to track pandemic preparedness at the country level. The board will examine key indicators of preparedness, such as a country's capacity to conduct clinical research.[10] The goal is to get all hands on deck quickly—a task made easier if the ship has already launched when the crisis begins, and one that will improve the probability of providing an accurate and timely picture of the true clinical severity of an emerging pandemic, and the ability to respond effectively.

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