Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

AVA vaccine, as measured by anti-protective antigen antibody titres. This effect would diminish the AVA vaccine response when co-administered with raxibacumab. However, in *The Lancet Infectious Diseases*, Nancy Souka and colleagues[4] show in a phase 4 clinical trial that neither anti-protective antigen antibody titres nor toxin-neutralising antibody titres differ between AVA vaccination alone or when raxibacumab is given immediately before AVA vaccination. The findings of this phase 4 study further show that co-administration of AVA with raxibacumab is safe,[4] validating an effective means of defense against acute anthrax.

Whether co-administration of raxibacumab and AVA would prevent anthrax caused by vaccine-resistant isolates is unclear.[5] Raxibacumab treatment of anthrax in animal models has focused on using the *B anthracis* type strain Ames. However, diversity of the *B anthracis* pathogen does exist,[6] and new anthrax-like diseases are evolving in nature.[7,8] Future work investigating the ability of AVA and raxibacumab to prevent anthrax from a *B anthracis* diversity panel consisting of wildlife-outbreak isolates and genetically unique vaccine-resistant strains using an animal model would be of considerable value. Demonstration of anti-toxin efficacy against the *Bacillus cereus* biovar *anthracis,* an anthrax-causing *B cereus* variant, would also be an important milestone for raxibacumab. Although currently isolated to areas in west and central Africa, *B cereus* biovar *anthracis* infects many forest-dwelling primates and farm animals, including goats, cattle, and sheep, in the region;[9,10] while not yet confirmed in humans, new screening could reveal *B cereus* biovar *anthracis* as a source of human anthrax.[11] When *B cereus* biovar *anthracis* is grown in CO_2 or bicarbonate buffering systems, analogous to growth in the host, it expresses genes on the toxin expression pXO1 plasmid to a higher level than does *B anthracis*, indicating a potential for higher toxin production in anthrax caused by this pathogen.[12]

Anti-toxin treatment with raxibacumab is an effective, safe, and valuable addition to the current AVA vaccination regimen for anthrax post-exposure prophylaxis, with the capacity to substantially reduce morbidity and mortality of human infection. However, the broad effectivity of raxibacumab against anthrax caused by new and diverse forms of anthrax pathogens remains to be shown.

We declare no competing interests.

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When does a major outbreak become a Public Health Emergency of International Concern?

Could the pandemic of the century have been averted? The process by which WHO decides whether to declare a Public Health Emergency of International Concern (PHEIC) under the International Health Regulations has drawn criticism. Reports have condemned the 4-month delay by WHO after the international spread of Ebola in west Africa before

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declaring a PHEIC.[1] The Democratic Republic of the Congo, now experiencing the second largest Ebola outbreak in recorded history, notified WHO of the outbreak on Aug 1, 2018, but WHO required four Emergency Committee meetings, including on Oct 17, 2018 (216 confirmed cases, 139 deaths, and 64% case fatality ratio), and April 12 and June 14, 2019 (four confirmed cases in Uganda). Justifying their response, the Emergency Committee said that "the cluster of cases in Uganda is not unexpected".[2] A PHEIC was finally declared at the fourth Emergency Committee meeting on July 17, 2019 (2501 cases and 1668 deaths), almost a year after initial notification. The International Health Regulations[3] do not require actual international spread, only a high potential for that spread, and thus the criteria for a PHEIC had already been met by the second Emergency Committee meeting.[4] Notably, the PHEIC declaration coincided with increased resourcing and international focus, leading to a major reduction in Ebola cases.

For the **situation reports on Ebola in the Democratic Republic of the Congo** see https://www.who.int/emergencies/diseases/ebola/drc-2019/situation-reports

Global health scholars have criticised the Emergency Committee process as lacking transparency, using "irrelevant considerations, undue influence and political interference",[5] and delaying declaration when International Health Regulations criteria have been met.

The coronavirus disease 2019 (COVID-19) outbreak originating in China and reported to WHO on Dec 31, 2019, suggests that little has changed. The PHEIC declaration for COVID-19 occurred well after most public health experts had concluded that this outbreak posed a major international threat. At the first Emergency Committee meeting on Jan 22, 2020 (309 cases and six deaths reported in mainland China; five confirmed cases in four countries or territories), the Emergency Committee said it did not have key facts from China. It extended the meeting to the next day, when cases had risen to 571, with 17 deaths and ten cases in seven other countries or territories. Yet, the Emergency Committee could not achieve consensus, and the Director-General concluded that the outbreak was "an emergency in China, but it had not yet become a global health emergency".[6]

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Again, the process appeared "more political than technical", as a *Lancet* Editorial described Ebola in the Democratic Republic of Congo, adding that "the committee seems to have favoured local protectiveness over global galvanising".[7] By the time the Emergency Committee declared a PHEIC for COVID-19 on Jan 30, 2020, 7736 cases and 179 deaths had been confirmed in mainland China, with 107 cases confirmed in 21 other countries.

For the **London School of Hygiene & Tropical Medicine's COVID-19 tracker** see https://vac-lshtm.shinyapps.io/ncov_tracker/

Delays in declaring a PHEIC could have serious detrimental consequences, lulling governments and donors into a false sense of security, because they could reason that if WHO does not consider the situation an international emergency, then it does not require a surge response.

The legal definition of a PHEIC is clear, as "an extraordinary event that may constitute a public health risk to other countries through international spread of disease and may require an international coordinated response."[3] The purpose of the declaration is to focus international attention on acute public health risks that "require coordinated mobilisation of extraordinary resources by the international community" for prevention and response.[3]

The PHEIC process requires urgent reform. First, the all-or-nothing nature of the assessment generates confusion. We therefore propose a multilevel PHEIC process with each level defined by objective epidemiological criteria and paired with specific readiness actions. Level 1 PHEIC alert should indicate a high risk outbreak in a single country, with the potential for international spread requiring concerted public health efforts to contain and manage it locally. Level 2 PHEIC should imply that multiple countries have had importations and that limited spread has occurred in those countries. Level 3 PHEIC would indicate large clusters in multiple countries, with evidence of ongoing local transmission. This tiering would provide less ambiguous risk signalling, while also encouraging earlier, proportionate public health measures when they are most effective.

Second, WHO should convene an expert consensus meeting to establish objective, evidence-based epidemiological and containment criteria to transparently guide its decision making processes. The draft algorithm under Annex 2 of the International Health Regulations[8] (appendix) already includes critical elements, but there are also subjective considerations, such as restraints on international travel and trade. The algorithm contains perverse relative weightings, treating the five categories as equivalent.

The clear purpose of a PHEIC declaration is to catalyse timely evidence-based action, to spur increased international funding and support, and to limit the public health and societal impacts of emerging and re-emerging

disease risks. In the aftermath of the COVID-19 pandemic, International Health Regulation reform must be an ethical imperative for more rapid and effective responses to novel infectious diseases.

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Dengue virus on the rise in Nepal

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Accounting for nearly 100 million symptomatic cases worldwide annually, dengue virus continues to expand to new territories.[1,2] Nepal, a Himalayan country which lies between the world's two most populous nations—India and China—had the largest dengue outbreak in 2019 with more than 14 600 cases and six deaths.[3] With altitudes from 70 m to the highest point in the world and climate types ranging from dry to polar, Nepal is a unique environment to study the changing distribution of infectious diseases.

Although circulation of all four dengue virus serotypes was shown as early as 2006,[4] dengue remained only a minor public health issue causing less than 100 cases annually before 2010.[3,5,6] In 2010, more than 1000 cases were reported mainly in the southern lowlands (altitude <800 m).[3,5-7] Since 2010, major dengue outbreaks have occurred in Nepal every 2–3 years, causing up to 2100 cases (appendix p 1). A time-series analysis over the past 15 years[3,5,6] shows an exponentially increasing and significant trend (p=<0·0001) in the number dengue cases. The 2019 outbreak; however, was truly unprecedented and catastrophic, causing nearly double the number of dengue virus cases (14 662) compared with all cases combined (7792) between 2005 and 2018 (appendix p 1).

Dengue cases began to appear in Nepal in May 2019, following early arrival of the rainy season, and eventually spread to 67 of 77 districts covering all seven provinces, with 16 districts reporting more than 100 cases (appendix p 1). Nepal's capital Kathmandu (altitude 1400 m) reported more than 2500 cases, whereas the district Kaski (mean altitude 2600 m), a popular tourist destination, had its first major dengue outbreak with more than 2800 reported cases.[3] Plotting cases and districts from the highest to lowest mean elevation (appendix p 1) clearly shows recent spread to higher elevations and the unprecedented rise in infections in 2019. Although dengue-transmitting mosquitoes have been found at elevations up to 2100 m in Nepal,[8] patient travel histories are not always collected making the exact altitude reached by dengue difficult to estimate. Although detailed information on the cause of the 2019 outbreak, including the responsible serotypes, is still unavailable, serotype 2 and 3 were confirmed in travellers visiting Nepal during the 2019 outbreak.[7,9] This outbreak also coincided with larger dengue outbreaks in Pakistan and Bangladesh, and other parts of Asia, and South America. Once official statistics become available, 2019 will most likely be the year with the highest number of global dengue cases ever recorded.

See **Online** for appendix

Since a devastating earthquake hit Nepal in 2015, dengue control has become one of the country's fastest growing public health challenges. The Epidemiology and Disease Control Division (EDCD) is the national