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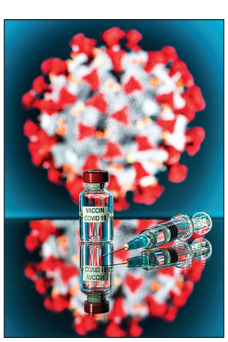
Emergency use authorisation for COVID-19 vaccines: lessons from Ebola

Russia and China have begun COVID-19 vaccinations outside of clinical trials. This move has been met with widespread criticism because the safety profiles of these candidate COVID-19 vaccines remain uncertain without data from phase 3 trials.[1,2] Emergency use authorisations—a regulatory mechanism that enables the public to gain access to promising investigational medical products when those products have not yet received regulatory approval and licensure[3]—have previously been used for unlicensed vaccines in public health emergencies and can be ethically justified provided that certain conditions are met. So why have the actions of Russia and China drawn such criticism? And how can other national regulatory authorities ensure future emergency use authorisations for COVID-19 vaccines are issued in a way that is scientifically and ethically sound? Experience of emergency use authorisations for investigational Ebola virus vaccines in Guinea and the Democratic Republic of the Congo (DRC) can elucidate key lessons that can guide ethical emergency use authorisations for COVID-19 vaccines.

In 2016, Guinean authorities made a request for expanded access to the then experimental recombinant vesicular stomatitis virus (rVSV) vaccine expressing the glycoprotein of Zaire Ebola virus (ZEBOV).[4] After the submission of a WHO-prepared protocol to the national regulator in Guinea, the Comité National d'Ethique pour la Recherche en Santé, and the WHO Research Ethics Review Committee, expanded access was granted to provide rVSV-ZEBOV to contacts of confirmed cases of Ebola virus disease as part of a ring vaccination strategy.[4] In addition to initially restricting emergency use to this target population, the ring vaccination strategy involved community engagement and was time-limited.[4] Subsequently, beginning in 2017, the DRC similarly authorised the emergency use of two Ebola virus



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vaccines (rVSV-ZEBOV and adenovirus type 26-vectored vaccine encoding Ebola virus glycoprotein boosted by a modified vaccinia virus Ankara–Bavarian Nordic Filo-vector [Ad26.ZEBOV/MVA-BN-Filo]), which were in phase 3 trials but had not yet been licensed.[5,6] rVSV-ZEBOV received conditional market authorisation by the European Commission in 2019 and was approved for medical use by the US Food and Drug Administration in late 2019, and is now licensed in the DRC, Burundi, Ghana, and Zambia.[7,8] In early 2020, the European Commission approved Ad26.ZEBOV/MVA-BN-Filo for medical use.[9,10]

Two key differences exist between the emergency use authorisations of Ebola virus vaccines and emergency use authorisations or conditional approvals of COVID-19 vaccines. Understanding these differences can help national regulatory authorities navigate scientific and ethical considerations if and when emergency use authorisations are considered for COVID-19 vaccines.

The first key difference concerns the coordinated and transparent way in which vaccines were authorised for use during the Ebola outbreaks in Guinea and the DRC. The 2013–16 outbreak of Ebola virus disease in west Africa prompted WHO to develop an Emergency Use Assessment and Listing (EUAL) procedure to expedite the availability of vaccines.[11] The EUAL was intended as guidance for national regulatory authorities in circumstances when the "community may be more willing to tolerate less certainty about the efficacy and safety of products, given the morbidity and/or mortality of the disease and the shortfall of treatment and/or prevention options".[11] The EUAL was used to help determine the acceptability of using investigational vaccines during that outbreak of Ebola virus disease on the basis of available quality, safety, and performance data.[12]

In January, 2020, WHO updated the EUAL with their Emergency Use Listing (EUL) procedure.[12] Central to the EUL is an assessment of whether submitted data demonstrate a reasonable likelihood that a vaccine's quality, safety, and performance data are acceptable, and that the benefits outweigh the foreseeable risks and uncertainties in the context of a Public Health Emergency of International Concern.[12] It is the sole prerogative of WHO member states to use the EUL procedure as the basis to authorise the use of unlicensed vaccines.[12] However, the COVID-19 vaccines that have thus far been approved for use in Russia and China have not followed the EUL procedure and have not been listed for emergency use.[13] Consequently, it is unclear whether these COVID-19 vaccines meet WHO manufacturing quality norms and standards, including whether the benefits outweigh the foreseeable risks. This situation and an absence of transparent ethical review or oversight stand in stark contrast to how the Ebola virus vaccines were approved for emergency use.

A second key difference concerns the perverse influence of geopolitics and vaccine nationalism that plagues the COVID-19 vaccine landscape unlike that of Ebola virus vaccines in 2016. Some countries, particularly those with clinical trial capacity, have put national interests first in securing access to a vaccine for their own citizens, which has created the potential to corrupt the rigour with which candidate COVID-19 vaccines are evaluated for emergency use authorisation.[14] The incentive to develop and license a COVID-19 vaccine first, or at least earlier than other countries, could compromise the integrity of an emergency use authorisation risk assessment. Privileging national interest in this way also risks the welfare of the public and could sow public distrust in COVID-19 vaccines. Appreciating that commercial or national interests are never absent, the process by which emergency use authorisations were pursued and granted for Ebola virus vaccines did not engender a similar battle of national interests.

These differences highlight four ethical conditions that, if satisfied, would improve the ethical quality of emergency use authorisations for COVID-19 vaccines. First, the evaluation criteria, process for evaluating emergency use authorisation vaccine candidates, and data submitted for evaluation should be made transparent to the public. Second, emergency use authorisation decisions for COVID-19 vaccines should require a favourable benefit–risk ratio based on available quality, safety, and performance data. Third, since emergency use authorisations are designed for circumstances when the public is probably willing to tolerate less certainty about the efficacy and safety of medical products,[11] exactly what constitutes a favourable benefit–risk ratio should be informed by engaging relevant communities. Finally, an accountable system of ethical and regulatory oversight and monitoring that aims to satisfy these conditions should guide emergency use authorisations for COVID-19 vaccines. These four conditions can be optimally met by following the WHO EUL procedure and its associated

governance and accountability structure, or by national regulatory authorities aiming to meet the WHO EUL assessment and listing standards for COVID-19 vaccines, which are under development.[13] Satisfying these conditions is likely to ensure the scientific and ethical integrity of, and public trust in, emergency use authorisations for COVID-19 vaccines, and mitigate the potentially pernicious influence of national politics on global vaccine efforts.

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Leveraging the COVID-19 response to end preventable child deaths from pneumonia

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Pneumonia kills people, young and old. The world has been reminded of the toll of pneumonia as countries struggle to control the COVID-19 pandemic. COVID-19 has claimed more than 1 million lives so far in 2020,[1] but other infectious diseases have caused pneumonia-related mortality for decades. Although there has been a commendable 54% decline in pneumonia-related deaths among children younger than 5 years since 2000, pneumonia is still the leading infectious cause of child deaths and claims more than 800 000 children's lives every year (WHO Maternal and Child Epidemiology Estimation, unpublished).[2,3]

Although most children have less illness related to COVID-19 than adults,[4,5] the potential secondary impacts of the pandemic could cause a reversal in progress in child survival. Roberton and colleagues used a model to estimate that, depending on the degree of severity, service disruptions, reductions in access to care because of lockdown measures, and increased rates of wasting due to food shortages over 12 months could cause between 506 900 and 2 313 900 additional deaths among children younger than 5 years.[6] The data suggest that about a third of these preventable deaths could be from pneumonia and newborn sepsis. Review of routine health information and programme data across several countries indicate that since the onset of the pandemic there have been reductions in the numbers of children who attend outpatient services and who receive correct diagnosis and treatment of illnesses and immunisation services (UNICEF and Save the Children, unpublished). Drops in coverage of the pertussis, *Haemophilus influenzae* type b, pneumococcal, and measles vaccines, which all offer protection against pneumonia, put millions of children at risk of severe and potentially fatal infections.[7]