Dexamethasone for COVID-19: data needed from randomised clinical trials in Africa

Over the past 6 months, potential COVID-19 treatments have come under intense scrutiny on social media, shifting the public discourse without a strong scientific rationale. There are now preliminary data showing that, in patients from Europe, low-dose dexamethasone reduces mortality by up to 33% in the most severely affected patients needing invasive ventilation (rate ratio 0·65, 95% CI [0·51–0·82]; p<0·001) and by 20% in those needing oxygen (rate ratio 0·80, 95% CI [0·70–0·92]; p=0·002).[1] We welcome the RECOVERY trial[1] results and support the implementation of dexamethasone as standard of care in settings similar to the trial sites. However, there is a need for caution regarding the results of a single, albeit well designed, trial done in a high-income country to change guidelines elsewhere in the world where the population and the context of care might be vastly different.

Despite a slow start in Africa, the incidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections is rapidly evolving, with more than 468 000 confirmed cases and 11 144 known deaths as of July 5, 2020.[2] As SARS-CoV-2 spreads through Africa, already weakened health systems and the few critical-care facilities will come under increasing strain, with potential for higher COVID-19-associated mortality and more collateral damage than observed in high-income countries. The African pandemic has not yet reached its peak in most countries, many of which are easing social restrictions to minimise the effect on livelihoods. Hence, COVID-19 prevalence and mortality are likely to accelerate further over the coming months. Dexamethasone has substantial potential to prevent death as this treatment could be easily deployed in an African setting. Nevertheless, the medical and scientific community should be wary of assuming that evidence for steroids generated in Europe also applies to African populations and robust African data are urgently needed.

In a search for COVID-19 treatments we should be guided by context-specific evidence, learning from previous controversies on the use of steroids in Africa. Antenatal corticosteroids, a cornerstone of modern obstetric care to reduce mortality in premature neonates, are an example.[3] Antenatal corticosteroids were recommended as standard of care for threatened preterm labour based on evidence mostly from high-income countries. Four decades after the first randomised controlled trial, a large cluster-randomised controlled multicentre trial in low-income and middle-income countries showed no benefit of antenatal corticosteroids for the smallest neonates, increased mortality for all neonates, and increased risk of maternal infection.[4] The increased mortality outcomes were mostly observed in African sites, with speculation that increased infections and undetected hypoglycaemia contributed to worse outcomes.[4] The results generated much controversy and resulted in more targeted promotion of antenatal corticosteroids by WHO. However, as the evidence emerged long after the acceptance of this treatment as standard of care, delineating and implementing appropriate use in low-income and middle-income countries has been challenging. Similarly, the use of steroids as adjuvant treatment for presumed bacterial meningitis is supported by evidence from high-income countries, and recommended by guidelines in these settings.[5] However, steroids have shown no benefit when studied in well designed trials in low-income and middle-income countries.[6] Corticosteroids might also precipitate sepsis in some parasitic infections prevalent in Africa (eg, strongyloides),[7] and are associated with progression of latent to active tuberculosis and development of opportunistic infections in immunosuppressed patients,[8] all of which might be undiagnosed in patients from Africa with COVID-19 and could result in unintended consequences.

There are still many unknowns about the epidemiology and severity of risk factors for COVID-19 in Africa. The effect of infectious disease comorbidities, such as malaria, parasitic infections, HIV, and tuberculosis, as well as genetic factors, nutritional status, and vaccination history on the inflammatory response to COVID-19 is not yet fully understood. Such effects might be important for the response to, and safety of, treatments, including steroids. The risk of secondary bacterial infection has not yet been quantified and cannot be assumed to be equivalent to high-income country settings, as prevalence of nosocomial bacterial infections is greater in low-income and middle-income countries.[9] Limitations within health systems in any setting might influence the effectiveness of the intervention and change the risk–benefit balance. For example, a reduced capacity to monitor blood sugar concentrations or detect comorbidities in which steroids are contraindicated might result in adverse outcomes. Conversely, steroids could have an even greater mortality effect in the absence of critical-care facilities and adequately trained staff than in high-income settings, which could transform COVID-19 management in Africa.

As much as we welcome dexamethasone as a treatment for severe COVID-19 pneumonia in high-income countries, the scientific and medical community must adhere to the principle of "first, do no harm". Therefore, we advocate for timely generation of region-specific data for and against steroid efficacy from well designed African randomised controlled trials before recommending the incorporation

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of dexamethasone into treatment guidelines for COVID-19-associated severe pneumonia in Africa.

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