Letter to the Editor

The urgent need for multi-site controlled trials for CMV pneumonia in African children

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Dear Editor,

Jeena et al's paper on cytomegalovirus (CMV) in South African children with severe pneumonia, and the accompanying editorial by Gie & Goussard in the December 2017 issue rightly highlight a neglected but very important issue [1-3].

Bacterial pneumonia is considered the most important cause of death in children globally [4], [4] and vaccines for *Haemophilus influenzae* type B (Hib) and *Streptococcus pneumoniae* are widely available as are the appropriate broad spectrum antibiotics. Our autopsy studies (Ref) showed that the causes of pneumonia in children are diverse, involving bacterial (including mycobacterial), viral pathogens with co-morbdiities between multiple respiratory pathogens (and with non-communicable respiratory diseases) [5-8]. Revised WHO guidelines focused only on definitions and antibiotic regimens [9, 10] and failed to address several pertinent issues.

1) Drug resistant bacterial pneumonia non-responsive to first and second line therapy
2) Undiagnosed tuberculosis (TB), viral or fungal respiratory infection unresponsive to antibiotic therapy
3) A co-infection with multiple pathogens, or NCD co-morbidity.
4) Late referral so too ill to save

The first 3 are primarily addressable through improvements in diagnostic technology and services. Jeena et al rightly suggest that high fidelity diagnostics could be designed for CMV and other pathogens, exploiting existing PCR platforms, such as those rolled out for TB or HIV viral loads. There is also a need for RCTs to assess the impact of empirical treatment for some common pathogens in high risk HIV-infected or exposed infants, as has been proved extremely successful with respect to cotrimoxazole prophylaxis and *pneumocystis jirovecci pneumonia* [11] . Could empirical treatment of CMV and TB, both ubiquitous highly immunomodulatory and immunologically dominant pathogens, and proven causes of paediatric pneumonia deaths [12, 13], deliver broader benefits for African children?

The efficacy of GCV in treating CMV infections has not been evaluated in randomised clinical trials (RCT). GCV causes neutropenia and other side effects. Apart from South Africa, GCV is unavailable in SSA and is not standard of care due to the high cost and lack of clear guidelines. Jeena et al's study and our autopsy studies of African children, present a compelling case for conducting randomised clinical trials (RCTs) of GCV. South African researchers with experience of administering GCV to

young infants should look to partner with other researchers in the region to design and implement such trials.

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