The enormous health benefits conferred by PCVs are without doubt, but we should recognise that their widespread use has induced a massive perturbation in the population-level immunity to pneumococcus over a very short period of time. The organism is certain to adapt in an effort to evade the consequences of that immunity and assure its survival. There is an essential need for ongoing multidimensional assessments of PCV impact in the community across diverse epidemiological settings, yet there is no consensus on what this portfolio of evidence should include to optimise the billions of dollars spent on PCV. Failure to adapt schedules could mean administration of unnecessary doses, dosing schedules that are not optimised for the age distribution of remaining cases, and the potential for unrecognised resurgence of some serotypes could mean we lose some value of these vaccines. Although studies of vaccine impact and effectiveness have not been afforded the same attention as more upstream links in the vaccine value chain, these post-licensure studies are absolutely necessary to assure us that the promise of vaccines, and of PCV in particular, is realised.

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Challenges in estimating RSV-associated mortality rates

Respiratory syncytial virus (RSV) is the leading viral cause of respiratory morbidity and mortality in infants and young children worldwide.[1,2] The burden of disease is particularly high in developing countries, where 97% of hospital admissions and 99% of deaths caused by RSV occur.[1] However, estimates of mortality rates due to RSV-related lower respiratory tract infection (LRTI) are based on scarce primary data.

Results from a systematic review[1] suggest that RSV LRTI fatalities in children younger than 5 years occur in 66 000–199 000 children per year worldwide. Findings from another study[2] examining causes of death in 187 countries over 30 years, estimated RSV-related mortality in children younger than 5 years at 239 000 children per year.

The Bill & Melinda Gates Foundation has launched the Child Health and Mortality Prevention Surveillance initiative, which aims to track the causes of childhood death globally, with a focus on prevention. A surge in RSV vaccine and monoclonal antibody research in the past 5 years, and the imminent availability of a vaccine against RSV, have helped to focus the conversation on burden and impact. In response to this evolving landscape, the Bill & Melinda Gates Foundation convened a panel of experts in RSV and childhood mortality to discuss available information, identify knowledge gaps, and explore available tools to monitor the impact of upcoming interventions on RSV-associated LRTI mortality rates.

Many structural and process-associated challenges contribute to the underestimate of facility-based and community-based RSV-associated mortality rates in the developing world. Facility-based mortality

For more on **RSV vaccine development** see http://sites.path.org/vaccinedevelopment/respiratory-syncytial-virus-rsv

***Panel*: RSV cause-of-death ascertainment**

Hospital-based mortality

Gold Standard

Autopsy or minimally invasive sampling of tissues for molecular and histopathological evaluation of lung tissue.

Recommended

rtPCR of respiratory secretions obtained using nasopharyngeal aspirates or nasal swabs.

If unable, consider:

Rapid test for RSV in secretions obtained using nasopharyngeal aspirates or nasal swabs.

Community-based mortality

Gold Standard

Autopsy or minimally invasive sampling of tissues for molecular and histopathological evaluation of lung tissue, and verbal autopsy.

Acceptable

rtPCR of respiratory secretions obtained using nasopharyngeal aspirates or nasal swabs, and verbal autopsy.

If unable, consider:

rtPCR in secretions of household contacts obtained using nasal swabs, and verbal autopsy.

An understanding of the RSV season in the region should guide exploration.
rtPCR=real-time PCR.

often takes place in areas with limited access to viral testing. Furthermore, collection of respiratory samples from critically ill patients for RSV testing is often challenging. Moreover, physicians might be reluctant or unable to approach families of deceased children to request consent for post-mortem cause-of-death investigation.[3] Therefore, focused studies are needed to estimate the burden of RSV-associated mortality.

A crucial challenge for cause-of-death ascertainment in children younger than 5 years is that, in vast areas of the developing world, deaths in the community outnumber those in health-care facilities, which hinders our understanding of the underlying causes of death, and precludes aetiological diagnoses. Indeed, only 4% of children who died in 2008 worldwide had a medically certified cause of death.[4] In view of this, verbal autopsies (standardised interviews based on symptoms present during illness leading to death) are important.[5] Verbal autopsy, done weeks to months after the fatal event through interviews with family members of the deceased, are often the only available way to investigate causes of death. This method has been extensively used in India, in a pioneering endeavour to track national causes of death on a scale not previously done.[6] However, while verbal autopsies might provide information about the disorder, and identify LRTIs, they cannot establish the identity of offending pathogens. The frequent overlap of clinical signs in paediatric diseases further hinders the precise recognition and differential diagnosis of fatalities with respiratory manifestations.[7]

Autopsies remain the gold standard for cause-of-death ascertainment (panel). However, because full diagnostic autopsies in developing countries are often challenging to do because of poor infrastructure; absence of expertise; poor acceptability; and ethical, social, and cultural implications, better practical tools need to be developed for cause-of-death ascertainment in childhood mortality. This gap has led to the development of a new approach to determine cause and aetiology of death—minimally invasive sampling of tissues.[8]

Minimally invasive sampling of tissues is a collection of post-mortem tissue sampling procedures that use fine needle biopsies,[8] and represents a promising way to address acceptability issues, because it is less invasive, and leaves virtually no visible marks, while simultaneously providing invaluable sample material (panel). Pathogens can then be detected in the tissues with targeted testing, including PCR and immunohistochemistry.[9] Furthermore, histopathology supports the interpretation of results, especially in circumstances in which molecular and other diagnostic tests identify multiple pathogens. When more than one pathogen is recovered, definitive cause-of-death determination often proves challenging; in the specific case of RSV LRTI, the virus might coexist in the lungs with other pathogens, potentially defying the traditional single pathogen casual paradigm.

In the absence of tissue diagnosis, confirmation of RSV infections as causes of death in the community can be achieved by testing nasal secretions. Given the difficulties in obtaining samples from a deceased child in the community, an alternative approach for ascertaining RSV as a cause of death in infants is to test household contacts for the virus (panel).

Interventions that have the potential to decrease the RSV-associated mortality rate could become

available in the near future. Carefully designed studies will be needed to understand their impact. Real-time PCR testing of respiratory secretions, examination of lung tissue using histopathology and molecular techniques, or both, will be necessary to assess hospital-based mortality due to RSV. Use of verbal autopsies and community RSV surveillance, together with examination of tissue or testing of respiratory secretions, should improve cause-of-death ascertainment in the community.

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See **Online** for appendix

Outbreak of multidrug-resistant tuberculosis on Daru Island

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The growing crisis of multidrug-resistant tuberculosis (MDR-TB) is so serious that tuberculosis specialists have called it a "time bomb",[1] and multiple deadly explosions have already been reported globally.[2] On Daru Island in Papua New Guinea, an unprecedented outbreak of MDR-TB is occurring.[3]

The 6 km² island has a population of about 15 000 individuals; in 2015, almost 200 people were being treated for MDR-TB. These numbers suggest that nearly 1% of the population is diagnosed with MDR-TB every year, and this is probably just the tip of the iceberg, because active case finding has yet to be implemented. Most patients with MDR-TB in Daru have never taken tuberculosis drugs, meaning primary transmission is occurring at an extraordinarily high level, which is especially concerning given that there are very few HIV cases in Papua New Guinea.[4] Whereas WHO estimates that roughly 1000 MDR-TB cases emerge across Papua New Guinea every year, isolated studies from different settings suggest a much higher burden.[5,6] Despite direct evidence of high rates of MDR-TB transmission from as early as 2008,[7] data remain scarce, mainly because Papua New Guinea has no facilities for tuberculosis culture or drug susceptibility testing. Access to MDR-TB treatment also remains poor, with the Australian government stepping in to procure emergency supplies of second-line medicines in 2013–14.[8]

The national and international response to the Daru outbreak has been inadequate. In January, 2015, the