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Interrupted BCG vaccination is a major threat to global child health

At a meeting of the WHO Child TB Subgroup in Cape Town, South Africa, in December, 2015, critical BCG vaccine shortages were reported in many countries. These shortages started in 2013 and continued into 2015. The United Nations Children's Fund (UNICEF) is the main supplier of BCG vaccine to tuberculosis-endemic countries. During this period, two of its four suppliers, the Statens Serum Institute (SSI) in Denmark and the Serum Institute of India experienced technical difficulties that resulted in reduced production capacity. UNICEF reported shortages of 8 million doses in 2013, 23 million doses in 2014, and 17 million doses in 2015.¹ Delegates from many countries reported interruption of BCG vaccination programmes due to local stock-outs resulting from unreliable supply.

Bacillus Calmette-Guérin (BCG) is an attenuated strain of *Mycobacterium bovis* that is used as a live vaccine against human and bovine tuberculosis. BCG vaccination has several beneficial effects. First, BCG vaccination reduces rates of *Mycobacterium tuberculosis* infection, helping to shrink the pool of latent infection from which future cases of active disease may arise.² Second, BCG provides strong protection against disseminated forms of the disease in infants and young children;³ tuberculosis is a major contributor to under-5

mortality in tuberculosis-endemic settings.⁴ Third, BCG vaccination reduces all-cause mortality through beneficial non-specific (heterologous) effects on the immune system;⁵ the importance of these effects has been formally recognised by WHO.⁶

During 2015, BCG production was stepped up in all facilities delivering BCG to UNICEF, except for SSI.¹ SSI has a long history of BCG production and was the first UNICEF supplier.⁷ According to SSI, recent production problems stem from a breakdown and renewal of production equipment together with the loss of employees in the wake of a parliamentary decision in 2014 to privatise parts of SSI.⁸ SSI is also a major global supplier of *M tuberculosis* purified protein derivative (PPD), which is used for tuberculin skin testing in children with tuberculosis exposure or symptoms suggestive of disease. An SSI spokesperson said that they expect to be able to deliver BCG vaccine again in 2017. Fortunately UNICEF has been able to secure increased commitments from other suppliers at the competitive price of US\$ 0.08 per dose.¹ However, BCG vaccine prices are anticipated to increase by roughly 30% in coming years because of increases in overhead costs and essential refurbishment.¹

Global demand for BCG is estimated at 260 million doses per year.¹ Procurement by UNICEF increased

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from 123 million to 152 million doses in 2015 as a result of buffer stock replenishment and new requests from countries that usually self-procure.¹ To meet growing demand, UNICEF has awarded long-term contracts to supply 400 million BCG doses from 2016–18, including a new WHO prequalified BCG producer, Green Signal Bio Pharma (India), to boost supply.¹ Programmes in the UK that vaccinate badgers against *M bovis* placed an additional demand on BCG producers.⁹ In view of the supply shortages, SSI suspended production of BadgerBCG;⁹ one dose of this vaccine equates to 20 human infant doses. At present, human BCG is only provided in multi-dose vials and estimates suggest that up to 50% of BCG doses are wasted.¹ It is therefore important that all countries optimise BCG usage and delivery methods, and manufacturers should give consideration to single-dose packaging.

Vaccines for tuberculosis can be given as pre-exposure, post-exposure, or therapeutic vaccines.¹⁰ Pre-exposure vaccines are targeted at infants and children younger than 5 years. Options include recombinant (r) live mycobacteria and subunit vaccines designed to boost responses to BCG or its potential replacement. Postexposure vaccines target adolescents and adults with latent *M tuberculosis* infection; latency antigen subunit vaccines have been tailored for this application.¹⁰ Therapeutic vaccines aim to shorten

treatment or supplement the treatment of drug-resistant tuberculosis. Although various preparations of *Mycobacterium vaccae* showed no therapeutic benefit, killed *Mycobacterium indicus pranii* has been licensed for restricted use in tuberculosis therapy in India.¹⁰

Two BCG replacement vaccines are in advanced stages of development: rBCG VPM1002 and MTBVAC.¹⁰ In experimental mouse models, rBCG VPM1002 (rBCGΔUreC::hly), which expresses listeriolysin (hly) from *Listeria monocytogenes* with deletion of the urease C (ureC) gene, induced superior protection against *M tuberculosis* compared with BCG.¹⁰ This superior protection has been attributed to the translocation of vaccine antigens to the cytosol and increased apoptosis of infected macrophages, resulting in enhanced T-cell stimulation. Results from an unpublished phase 2a trial suggests that VPM1002 is safe and well tolerated in infancy.¹¹ MTBVAC is a double-deletion mutant of *M tuberculosis* from which a broad range of virulence genes and critical enzymes have been deleted. MTBVAC has shown similar safety and immunogenicity to BCG in a provisional phase 1 study.¹² Despite these exciting advances, field trials to assess potential BCG replacements are complicated by the excellent protection provided by BCG, the absence of reliable immune correlates of protection, and the lack of robust clinical endpoints in highly regulated vaccine trial sites. Widespread availability of a live attenuated vaccine that could replace BCG is likely to be many years away, but an unintended consequence of the expectation that new vaccines will soon replace BCG is a reluctance to invest in continued BCG production.

Given the important role of newborn BCG vaccination in reducing infant mortality, every effort should be made to ensure uninterrupted BCG coverage in all tuberculosis-endemic settings. UNICEF should be applauded for leading efforts to coordinate and bolster the BCG supply, but the interruptions experienced during 2013, 2014, and 2015 are unacceptable. It is essential that the global child health community speaks out and demands universal BCG coverage of the most vulnerable children, at a price that can be afforded by even the poorest countries.

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We declare no competing interests.

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