Surgery for Buruli ulcer in the antibiotic era

In the early 1970s, the Medical Research Council ran a research project on Buruli ulcer in Uganda, with the epidemiologist Dr David Barker on the team.

Among Barker's studies was one involving 170 individuals, including tsetse control officers and their families.[1] They lived in modest huts, clustered in small camps, which had no electricity or running water, usually close to the Nile river. Many of the inhabitants walked from their huts to the river, which was used both as a source of domestic water and for other purposes, and frequently passed through stands of a grass, *Echinochloa pyramidalis*.

In his research, Barker targeted the pre-ulcerative stage of *Mycobacterium ulcerans* infection, which is characterised by a small painless skin lump or nodule that becomes bigger over several weeks before ulcerating. He recruited a medical assistant, who informed, through meetings and by word of mouth, the tsetse control workers and their families about this early pre-ulcerative stage. Altogether, 45 cases of *Mycobacterium ulcerans* were identified in the 170 tsetse control workers and their families.[1]

Participants with possible early and pre-ulcerative Buruli lesions were encouraged to have them excised by a surgeon who regularly visited the area every few weeks. After excluding other possible causes of skin nodules (ganglions, insect bites), the suspect lesion was completely excised under local anaesthesia near the patient's residence and the resulting defect sutured. The excised specimen was sent for histological analysis and specialised mycobacterial culture. These examinations invariably confirmed the diagnosis. Healing took place by primary intention, and no ulceration occurred. Antibiotics were not used. Barker's study was a small non-randomised study and there was no longer-term follow-up.

This project showed that well resourced community awareness of the early pre-ulcerative stages of *M ulcerans*, combined with timely surgical interventions, can prevent ulceration and all its subsequent costs. Similar intense interventions, involving heightened community awareness of the early disease stages and early preventive surgery, might be of some benefit in parts of Australia currently affected by the recent outbreak of *M ulcerans* infection.[2]

I declare no competing interests.

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Protection of young children with cholera vaccine

In August, 2017, WHO released new recommendations for the use of oral cholera vaccine (OCV).[1] As part of the evidence review to support these new recommendations, we did a meta-analysis on OCV protection, using data from experimental and observational studies published up to July, 2016.[2] These analyses showed that two doses of OCV given 2 weeks apart are protective for at least 3 years. They also revealed two key features of OCV that are relevant to public health: first, children younger than 5 years are significantly less protected with the recommended two-dose schedule than are those aged 5 years or older and, second, a single OCV dose provides similar short-term protection (up to 6 months) as does two doses, which has been corroborated in a 2018 report from Zambia.[3]

In *The Lancet Infectious Diseases*, Firdausi Qadri and colleagues[4] showed that protection from a single dose in children aged 5 years and older in the first 2 years after vaccination was similar to corresponding protection estimates from two-dose trials. The study also found that children younger than 5 years had no significant protection over the 2-year period from the single-dose regimen, although the study was underpowered to find significant protection in this subgroup analysis (appendix). These results clearly indicate the need for alternative dosing schedules, new vaccine adjuvants, or new vaccines capable of inducing long-lasting protection in young children, given that both one-dose and two-dose regimens provide them with inadequate protection.

See Online for appendix

While we wait for the development of new solutions for inducing vaccine-derived immunity in young children, health officials and policy makers must use the best available evidence to design vaccination strategies, including the use of single-dose regimens, especially in response to outbreaks. During outbreaks, when short-term protection is most critical, most of the public health benefit of reactive vaccination campaigns likely comes from the first dose, regardless of whether or not the second dose is administered. It is in these situations that an appropriate balance between individual and herd protection is crucial to achieve the greatest impact,[5] especially if the vaccine supply is smaller than the size of the at-risk population.

Current global supplies of OCV are increasing and will one day reduce the need for public health officials to decide between covering more people with a single dose versus covering fewer people with two doses. In the meantime, the important results from Qadri and colleagues' study should reassure the public health community when single-dose regimens are used.

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Single-dose rotavirus vaccine at birth: is it effective or safe?

Graeme L Barnes[1] suggested that immunisation with one dose of rotavirus vaccine at birth might be enough to protect against subsequent infection and diarrhoea, and looked forward to assessing its feasibility in future clinical trials. However, the results of previous clinical trials do not support this view. Armah and colleagues[2] reported that high serum concentrations of neutralising antibody derived from maternal circulation could be detected in infants who have never been vaccinated with rotavirus. In a study by Moon and colleagues,[3] titres of rotavirus neutralising antibody after vaccination were higher in the antibody-negative group than in the antibody-positive group, indicating that the immune response of neonates to rotavirus vaccines is inhibited by rotavirus neutralising antibodies derived from maternal circulation. In their randomised controlled trial, Bines and colleagues[4] found that when the first dose was given in the first 5 days of life, 23% of infants in the vaccine group and 19% in the placebo group had an immune response to human neonatal rotavirus vaccine (p>0·01), whereas 42% of infants in the vaccine group and 1% in the placebo group had an immune response when the vaccine was given at age 8–10 weeks (p<0·001). The immune response remained stable after the full three doses, but was significantly less immunoreactive after the single-dose vaccine. Additionally, Bines and colleagues[4] found that the incidence of severe adverse reactions in the neonatal group was higher than in the infant group (2·0% *vs* 1·5%) after rotavirus vaccination. Therefore, we believe that a single birth dose of rotavirus vaccine in the neonatal period is not feasible at this time, especially because of its low efficacy and poor safety.

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Authors' reply

We thank Hai-Ling Lu and colleagues for their Correspondence, which questions whether a single birth dose of the oral human neonatal rotavirus vaccine (RV3.BB) is likely to be effective and safe.

Owing to the lack of a suitable serological correlate of protection, rotavirus vaccines have all required clinical assessment of efficacy. Differences in immune response definitions make comparing rotavirus vaccines difficult. As seen with other vaccines, developmental immaturity of the immune system and the presence of maternal antibodies make assessment of the immune response following a birth dose challenging. In a previous study,[1] infection of newborns with the wild-type, asymptomatic, neonatal rotavirus RV3 strain protected against severe rotavirus gastroenteritis in the first 3 years of life. Those infants experienced only neonatal dosing. Prime boosting is a well established concept in vaccinology, and it is biologically plausible that neonatal infection with RV3 primes the immune system, which is later boosted by exposure to a vaccine or a community disease strain.[2] Furthermore, three doses of RV3.BB in Indonesian infants resulted in 75% efficacy against severe rotavirus gastroenteritis when administered in a neonatal schedule (at ages 0–5 days, 8 weeks, and 14 weeks) compared with 51% when administered in an infant schedule (ages 8, 14, and 18 weeks), suggesting that the birth dose might enhance protection.[3]

Lu and colleagues are incorrect in their interpretation of the adverse events in the RV3.BB study in Indonesia.[3] Adverse events were compared between vaccine schedule (neonatal or infant) and age-matched placebo recipients. This method takes into account differences in the background rates of adverse events between newborns and infants aged 8 weeks or older. In fact, in the infant-schedule group, there were more adverse events after placebo than after vaccination.[3] During the years that the RV3 strain was known to be endemic in nurseries in Melbourne, VIC, Australia, no sibling of an RV3-excreting neonate contracted gastroenteritis associated with the RV3 strain, and no child