

# Rotavirus (RV3-BB) Vaccine

- A human, neonatal rotavirus vaccine to protect against rotavirus disease from birth

## The opportunity

Rotavirus infection is the leading cause of severe dehydrating gastroenteritis in infants and young children worldwide. In 1973, a team at MCRI led by Professor Ruth Bishop discovered rotavirus as a causative agent of severe dehydrating gastroenteritis.

By 2009, two commercial vaccines had entered the market and the World Health Organisation recommended that a rotavirus vaccine should be included in the childhood vaccination schedule.

Despite these vaccines, there have been ongoing challenges with the success of rotavirus vaccines, namely: lower efficacy in developing countries; cost and affordability; implementation into national immunization programs; and continued safety concerns.

These challenges have resulted in an inability to provide a low-cost rotavirus vaccine to meet global demand. Consequently, the burden of rotavirus disease is most pronounced in countries with developing economies, where the combination of rotavirus infection and malnutrition causes millions of children to suffer serious illness, and is responsible for more than 215,000 deaths per year.

The Rotavirus group at MCRI, led by Professor Julie Bines, is developing a low-cost, human, neonatal rotavirus vaccine, based on the strain originally identified by Professor Bishop, called "RV3-BB".

## The technology

The RV3-BB rotavirus vaccine is a liquid, presentation of three oral doses, which has been developed from a naturally occurring human (G3 P6) strain of rotavirus that was found in healthy babies in obstetric hospital nurseries in Melbourne in 1988.

**The advantages of the RV3-BB rotavirus vaccine** is that it:

1. **Is a novel, single human strain that is naturally attenuated and unlikely to pose risk for a newborn.**

RV3-BB is based on the wildtype RV3 strain that was found to be associated with asymptomatic infection

and showed to offer protection from subsequent severe and moderate rotavirus disease.

2. **Provides a birth dose strategy which is an ideal opportunity to safely administer a rotavirus vaccine**

Birth is an established EPI time-point in many countries and is seen as the "best" immunization opportunity in developing countries as contact with health care workers in these settings are limited.

The first rotavirus infection produces the most severe gastroenteritis with subsequent infections limited by a strong immune response. Currently, the first dose of marketed rotavirus vaccines occurs at 6-8 weeks with completion of course (max protection) at 5-6 months of age. In the developing world, the first rotavirus infection occurs much earlier than in the developed world, thus the current vaccine schedule may deliver vaccine too late to protect some infants.

Further, administration of rotavirus vaccines has shown to increase the risk of intussusception (the inversion of one part of the intestine within another). However, intussusception is very rare in the neonatal period providing further support that a birth dose rotavirus vaccine may be safer.

3. **Evidence of a robust immune response in  $\geq 90\%$  of infants receiving the RV3-BB vaccine.**

Phase I and IIa clinical trials have demonstrated proof of principle that the vaccine is immunogenic and well tolerated in neonates and infants.

### **Phase I trial (Completed in 2013; Melbourne, Australia)**

Assessed safety and tolerability of a single dose of vaccine in 60 participants: initially 20 adult males (Cohort 1, aged 18-50 years), progressing to 20 children (Cohort 2, aged 3-8 years), then to 20 infants (Cohort 3, aged 6-8 weeks).

**Method:** In each cohort, 10 participants received active vaccine and 10 received placebo and were followed up to 28 days post-dose for solicited and unsolicited adverse events

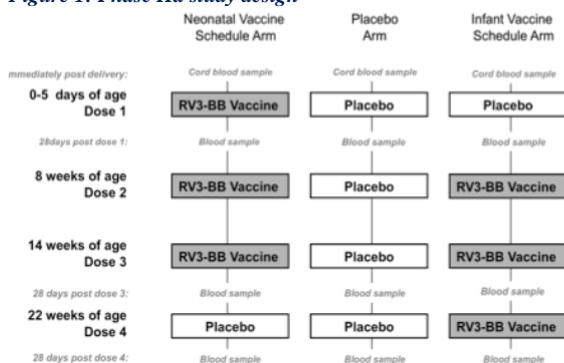
**Outcome:** The vaccine was well tolerated. No adverse events were considered to have definite or probable relationship to the vaccine.

### Phase IIa trial (Completed in 2014; Dunedin, New Zealand)

In collaboration with the University of Otago in New Zealand evaluated the safety and immunogenicity of three doses of oral RV3-BB rotavirus vaccine, with the first dose administered either at birth (0-5 days, neonatal schedule) or at 8 weeks (infant schedule), compared with placebo

**Method:** Randomized, double-blind, three-arm, placebo-controlled safety and immunogenicity trial, see Figure 1. The primary endpoint was cumulative vaccine take after three doses of RV3-BB. Vaccine take was defined as serum immune response and/or stool shedding of vaccine virus after any dose.

Figure 1: Phase IIa study design



**Outcome:** Proof of concept for the birth dose.

#### Neonatal schedule:

A cumulative vaccine take was detected in 27 (90%) of 30 participants in the neonatal schedule group after three doses of RV3-BB vaccine compared with four (13%) of 32 participants in the placebo group (difference in proportions 0.78, 95% CI 0.55 - 0.88;  $p < 0.0001$ ).

#### Infant Schedule:

25 (93%) of 27 participants in the infant schedule group had a cumulative vaccine take after three doses compared with eight (25%) of 32 participants in the placebo group (difference in proportions 0.68, 0.44 - 0.81;  $p < 0.0001$ ).

### Phase IIb trial (Completed 2016; Yogyakarta, Indonesia)

In collaboration with Gadjah Mada University (UGM) and Bio Farma, the trial in Indonesia (25 sites in Yogyakarta and central Java) enrolled 1649 babies. The primary objective of this study is to assess the efficacy of 3 doses of RV3-BB vaccine against severe rotavirus gastroenteritis up to 18 months of age administered using a neonatal or infant vaccine schedule compared to placebo and results are expected in Q4 of 2016.

### Applications

The RV-3BB rotavirus vaccine is a prophylactic vaccine intended for neonatal or infant dosing schedule as part of routine EPI vaccinations.

### Opportunity for partnership

MCRI are interested in partnering with a manufacturer who is able to manufacture the RV3-BB vaccine at large scale to meet global demand.

### Intellectual Property

This technology is the subject of an International (PCT) application (PCT/AU2013/000945) in the name of the Murdoch Childrens Research Institute. Further, there are national phase filings in New Zealand; Australia; Brazil; China; Cuba; Europe; India; Indonesia; Korea; Mexico; and the United States:

The applications relates to methods of culturing the RV3-BB strain in vero cells.

### Key publications

Bines JE, Danchin M, Jackson P, Handley A, Watts E, Lee KJ, West A, Cowley D, Chen MY, Barnes GL, Justice F, BATTERY JP, Carlin JB, Bishop RF, Taylor B, Kirkwood CD. Safety and immunogenicity of RV3-BB human neonatal rotavirus vaccine administered at birth or in infancy: a randomised, double-blind, placebo-controlled trial. *The Lancet. Infectious diseases* 15 (12) : 1389 - 97(2015)

Danchin M, Kirkwood CD, Lee KJ, Bishop RF, Watts E, Justice FA, Clifford V, Cowley D, BATTERY JP, Bines JE. Phase I trial of RV3-BB rotavirus vaccine: a human neonatal rotavirus vaccine. *VACCINE* 31 (23) : 2610 - 6(2013)

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