

Preventing deaths from diarrhoea:

New vaccine holds promise for children in sub-Saharan Africa



Executive summary

An innovative new vaccine which could prevent large numbers of children dying from diarrhoea in sub-Saharan Africa has been trialled in Niger by Médecins Sans Frontières/Doctors Without Borders (MSF), with very good results.

Every day, an estimated 1,300 children die from severe diarrhoea – most of them aged five or under and living in Africa or South Asia. In the first two years of age, more than one case of severe diarrhoea in two is due to rotavirus infection, which spreads easily from person to person.

Rotavirus infection cannot be prevented by improvements in water and sanitation alone, as shown by its prevalence in high-income countries. The most effective way to combat it is by immunising children against the most common rotavirus strains.

Two vaccines are available but a supply gap exists and their widespread use is limited due to logistical constraints, the volume of packaging and the price.

Low-income countries have access to the existing vaccines at subsidized prices, but there is no guarantee that this will continue.

A phase III randomised controlled clinical trial was conducted in Niger to assess the efficacy and safety of a new vaccine, the BVR-PR. The results of the trial show that there were no safety concerns and vaccine's efficacy of 73.2% (95% CI: 61.0 – 81.5%) is comparable to the existing vaccines. The vaccine efficacy increased with the severity of rotavirus gastroenteritis. Also the new pentavalent vaccines includes strains found in sub-Saharan Africa, it is heat-stable meaning that it does not need to always be kept in the cold chain and it is less expensive than the current vaccine even when sold at subsidized prices.

We believe that, if approved by the World Health Organization (WHO) and included in the Expanded Programme on Immunization (EPI), the vaccine could be a future game-changer for children.

Background

There are an estimated 2.5 billion episodes of childhood diarrhoea per year worldwide. Children under the age of two are the most vulnerable.

DIARRHOEA

is defined as having loose or watery stools at least three times a day, or more frequently than normal for an individual. Most episodes of diarrhoea are mild; however, acute cases can lead to significant fluid loss and dehydration which may have severe consequences – and even be fatal – if fluids are not replaced.

While diarrhoea-specific mortality has decreased in recent decades, it is still a leading cause of death in children under five, and the second highest if you exclude babies under one month old. More than 500,000 children under the age of five are estimated to have died of diarrhoeal diseases caused by rotavirus infection in 2015 – or 1,300 children every day – the majority of them in Africa and South Asia¹.

Rotaviruses: the main cause of severe diarrhoea in children

Almost every child by the age of five will be infected by rotavirus. In low income countries the vast majority of the infections occur among infants (less than one year old) and in the first two years of age, the incidence of moderate to severe diarrhoea caused by rotavirus is double that of any other pathogen. About 90% of all rotavirus-associated deaths happen in low income countries in Africa and Asia and are related to poor healthcare.

The clinical presentation of rotavirus is wide, ranging from brief episodes of loose stools to severe acute diarrhoea and vomiting causing dehydration, which may lead to shock and death mainly in children less than one year of age.

Transmission

During the first episode of rotavirus infection, viruses are shed for several days in very high concentrations in the stools and vomits. The disease is spread primarily by the faecal-oral route, either directly from person to person or indirectly via contaminated objects and surfaces. The virus can survive on hands for at least four hours and on hard surfaces for days.

The fact that rotavirus infections occur globally even in settings with high standards of hygiene, states to the high transmissibility of this virus and suggests that clean water and good hygiene measures are not enough to stop the virus from spreading.



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Treatment

There is no specific treatment for rotavirus infections. During an episode of diarrhoea, fluids must be replaced to prevent dehydration, while zinc supplements can decrease the episode's severity and duration.

Prevention

THE SEVEN-POINT PLAN OF UNICEF AND WHO (2009)

Prevention

- **Vaccinate against rotavirus and measles.**
- Promote early, exclusive breastfeeding and vitamin A supplements.
- Encourage handwashing with soap.
- Improve quantity and quality of water supply, including treatment and safe storage of household water.
- Promote community-wide sanitation.

Treatment

- Replace fluids to prevent dehydration.
- Treat with zinc supplements.

Role of rotavirus vaccine in prevention of moderate and severe diarrhoea

Countries that have introduced rotavirus vaccines in their immunization programs have seen an improvement in child health, reducing severe diarrhoeal episodes and related deaths. To maximize impact, the rotavirus vaccines must be given before infection with rotavirus occurs.

Two rotavirus vaccines are currently available and pre-qualified by WHO: Rotarix (manufactured by GlaxoSmith-Kline) and Rotateq (manufactured by Merck).

These vaccines have been shown to be safe and effective in high and middle-income countries. However, recent trials of these vaccines in Africa and Asia have shown substantially lower efficacy in low-income countries, with efficacy from 50-64%, as compared to 80-90% in rich countries. However, the total num-

¹ <https://data.unicef.org/topic/child-health/diarrhoeal-disease/>

ber of cases and deaths that can be avoided through vaccination in countries with high disease burden counterbalances the lower efficacy and WHO recommends that rotavirus vaccines should be included in all national immunization programs and to be considered a priority particularly in countries with high rotavirus disease-associated fatality rates.

Introduction of rotavirus vaccines must go hand in hand with measures to ensure high vaccination coverage and timely administration of each dose. However this is difficult in the areas where the impact would be greatest. Children in the poorest, typically rural households with limited access to healthcare are at highest risk of mortality and seem to have the earliest exposure to the virus with the lowest level of vaccine protection.

Rotavirus vaccines can be administered simultaneously with other vaccines in the infant immunization program. To facilitate uptake, WHO recommends to be administered orally at the time of DPT1 and DPT2 with an interval of at least 4 weeks between doses.

Since 2011 with support from Gavi, the Vaccine Alliance, eligible countries are able to purchase these vaccines at a subsidised price (US\$2.50 per dose for Rotarix and US\$3.50 per dose for RotaTeq), but there is no guarantee that these subsidies will continue, which could lead to the vaccines becoming unaffordable for countries that need them.

New Alternative

BRV-PV (Pentavalent rotavirus vaccine)

The development of this vaccine, manufactured by Serum Institute of India Pvt. Ltd., was supported by a large-scale surveillance study, conducted by MSF which gathered data on the epidemiology of rotavirus in urban and rural Niger. This surveillance identified 30.4% (95% CI: 29.6-31.3) of episodes of diarrhoea to be rotavirus-positive, with 80% of all rotavirus cases found among children under one year of age.



ADVANTAGES OF THE NEW VACCINE

Adapted to Sub-Saharan Africa: The new pentavalent rotavirus vaccine (BRV-PV) contains five rotavirus serotypes, all of them relevant to sub-Saharan Africa, where the main disease burden is.

Thermostability: BRV-PV vaccine does not need to be kept in the cold chain. This is a significant advantage in much of Africa and South Asia, where cold chain capacity is limited.

Affordable price: The BRV-PV vaccine will be less expensive than the current vaccines, even at the subsidised price available through GAVI therefore making it affordable for countries that need it the most.

Small packaging: Its presentation, formulation and packaging are very convenient for storage and transportation.

Closing the supply gap: Increasing the number of doses of rotavirus vaccine available for countries, therefore contributing to improving vaccination coverage, especially in rural and remote areas.

The Ministry of Health of Niger, MSF and MSF's epidemiological wing, Epicentre, along with other partners, formed a research consortium to bring additional evidence on the potential value of the BRV-PV vaccine in an African setting, to help inform public health decision making.

A phase III randomised controlled clinical trial was conducted in Niger to assess the efficacy and safety of the BRV-PV vaccine. The results of the trial show that there were no safety concerns and a vaccine's efficacy of 73.2% (95% CI: 61.0 – 81.5%) comparable to the existing vaccines. The vaccine efficacy increased with the severity of rotavirus gastroenteritis.

Results of BRV-PV vaccine

RVGE ¹	BRV-PV (n=1780)		Placebo (n=1728)		Vaccine efficacy
	Cases (n)	IR ² (per 100 child-years)	Cases (n)	IR ² (per 100 child-years)	VE (%) (95% CI)
All	91	6.51	88	6.52	0.3 (-33.7 - 25.6)
Severe (≥11)	31	2.14	87	6.46	66.8 (50.0 - 78.0)
Very severe (≥15)	4	0.27	6	0.43	35.7 (-127.8 - 81.9)

¹ Rotavirus Gastroenteritis

² Incidence Rate

Conclusion

Rotavirus infection is the main cause of childhood deaths from diarrhoea. These deaths are directly linked to poor access to healthcare, particularly early access to rehydration. Taking into account the high burden of disease, and people's limited access to health facilities in rural areas of Africa, the widespread introduction of preventative measures is likely to have a huge impact.

Today, we have vaccines available against rotavirus infection, yet their widespread use is limited due to the huge logistical resources they require. In addition, these vaccines are not well adapted for use in Africa or South Asia, in terms of the serotypes included, the volume of packaging and the price. MSF supported the clinical trial to provide a viable alternative and to show the importance of strong and consistent support in advancing R&D processes so that needs are met where they are most required and thus increasing access to important vaccines.

The addition of the adapted, innovative, affordable and easy-to-use BRV-PV vaccine to the currently prequalified vaccines will increase the availability and effectiveness of rotavirus vaccines worldwide and boost vaccination coverage, especially amongst children most at risk of dying from severe diarrhoea. The new vaccine can complement other vaccines currently available to countries through internationally supported mechanisms, not only for routine activities but also to prevent loss of lives in humanitarian crisis.

Recommendations

- Serum Institute of India Pvt. Ltd should provide completed documentation for pre-qualification.
- Serum Institute of India Pvt. Ltd should provide assurances on price and production capacity.
- We encourage WHO to prequalify the new vaccine as soon as possible and to provide guidance to countries to include it in their immunization programs.
- The vaccine should be fully integrated in the offer of vaccines supported by Gavi that are available in routine immunization programs.
- Use of the vaccine in acute humanitarian emergencies for preventive and reactive mass vaccination campaigns needs to be encouraged.
- Research and development needs to continue to ensure that easy to use and affordable vaccines are available in developing countries.

