Enhancing Rotavirus Vaccination: a Microbial Fix?

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Summary

Oral rotavirus vaccines have consistently underperformed in low-income countries. In this issue of *Cell Host & Microbe,* Harris et al (2018) explore whether vaccine response can be enhanced via antibiotic-mediated modification of the bacterial microbiota.

Full text

Diarrheal disease currently claims the lives of approximately 500,000 children each year. Although a range of intestinal pathogens contribute to this, rotavirus accounts for more severe cases and hospitalizations than any other. Globally, the virus is responsible for more than a third of diarrhea-associated deaths in children under 5 years of age.

Over the past decade, the burden of rotavirus disease has been gradually eroded by the roll-out of oral rotavirus vaccines, which have now been introduced in more than 90 countries. Yet current rotavirus vaccines have a crucial weakness – they are less effective precisely where they are needed most. Whereas more than 95% of infants in high-income countries are protected from severe rotavirus disease in the year following vaccination, protection is diminished in low- and middle-income countries, falling shy of 50% in parts of sub-Saharan Africa (Madhi et al., 2010). Thus, despite vaccine coverage of over 80% in many countries, rotavirus may remain the leading cause of hospitalized gastroenteritis (Platts-Mills et al., 2017).

This phenomenon is unlikely to have a simple explanation or a simple solution. Maternal antibodies, viral co-infections, and histo-blood group antigen genotype may all contribute to the impaired efficacy of oral vaccines in low-income countries (Parker et al., 2018a). In addition, the bacterial microbiota has been singled out as a potentially significant contributor. Indeed, microbiota composition is known: (i) to vary by geographic setting from an early age; (ii) to be important for the development of the mucosal immune system (Ruiz et al., 2017); and (iii) to influence the replication and immunogenicity of intestinal viruses, including rotavirus, in mice (Uchiyama et al., 2014).

To date, three observational studies have attempted to characterize the association between bacterial microbiota composition and rotavirus vaccine response. Among infants in Ghana (n = 68), immune response following two doses of the monovalent vaccine Rotarix was reported to be negatively correlated with relative abundance of the bacterial phylum Bacteroidetes and positively correlated with abundance of the class Bacilli at the time of the first vaccine dose (Harris et al., 2016). However, these taxonomic associations were not evident during a smaller study in Pakistan (n = 20)

(Harris et al., 2017). Instead, several distinct associations were highlighted, including a higher abundance of the phylum Proteobacteria in Rotarix responders. Finally, among infants in India (n = 170), there were no significant differences in the composition of the bacterial microbiota between rotavirus vaccine responders and non-responders after statistical correction for multiple comparisons (Parker et al., 2018b).

What should we make of these findings? On the one hand, they hint at several intriguing associations between microbiota composition and rotavirus vaccine response. On the other hand, the picture varies from study to study, and reproducible predictors of vaccine response across different geographic settings remain elusive. Additional studies exploring the link between microbiome composition and rotavirus vaccine response are likely to accumulate in the coming years, and may shed further light on this relationship.

If robust associations between microbiota composition and rotavirus vaccine response can be found, a crucial question will remain: can the microbiota be modified to improve vaccine efficacy? In this issue of *Cell Host & Microbe*, Harris et al (2018) report on a proof-of-concept study exploring this question. Specifically, the authors set out to test whether recapitulating some of the microbiota phenotypes that correlated with vaccine response in previous observational studies might improve rotavirus vaccine performance. The study included three arms, each containing 21 Dutch adults. In one arm, individuals received a 7-day course of oral vancomycin, an antibiotic that has been shown to deplete the relative abundance of Bacteroidetes while increasing the abundance of Proteobacteria (Isaac et al., 2017). In the second arm, the adults received a 7-day course of broad-spectrum antibiotics (oral vancomycin, ciprofloxacin, and metronidazole), aiming to induce a more extensive and indiscriminate depletion of the bacterial microbiota. In the third arm, individuals received placebo. Three days after completing treatment, all adults received a single dose of Rotarix. Vaccine immunogenicity was determined by measuring the titer of rotavirus-specific antibodies before treatment and 7, 14, and 28 days after vaccination. The presence of rotavirus in stool was also measured in the week after vaccination to provide an indicator of vaccine virus replication (‘take’).

As expected, antibiotic treatment induced marked perturbations in microbiota composition (determined by sequencing the bacterial 16S rRNA gene in stool samples). In both treatment arms, a significant reduction in microbiota diversity was seen at the time of vaccination. At phylum level, vancomycin induced a depletion in the relative abundance of Bacteroidetes and Firmicutes alongside a pronounced increase in Proteobacteria. Broad-spectrum antibiotics induced similar changes, albeit without the bloom in Proteobacteria.

There was no strong impact of treatment on the immune response to vaccination. Rotavirus-specific IgA titers did not differ between study arms 28 days after vaccination (the primary outcome of the trial), nor at any other timepoint. Only 2/63 (3%) of individuals exhibited a 4-fold rise in IgA titer at 28 days (a common immunogenicity measure in rotavirus vaccine trials). The authors did observe the ‘boosting’ of rotavirus-specific antibodies (defined as a 2-fold increase in IgA titer) to be more frequent in vancomycin recipients at day 7 (8/21 vs 1/21 in the other arms); however, this effect was not apparent at days 14 or 28 and is of equivocal significance given the multiple endpoints

considered. The low immunogenicity of Rotarix in this adult population is not surprising given the high baseline immunity observed: all individuals had detectable rotavirus-specific IgA at enrollment, reflecting the multiple rotavirus exposures that occur throughout life.

The results were more intriguing when considering replication of the vaccine rotavirus. Shedding in the week after vaccination was more common in vancomycin and broad-spectrum antibody recipients (8/21 each vs 1/21 in the placebo arm), while the quantity of viral shedding was significantly higher in vancomycin than placebo recipients. These findings are contrary to previous findings in mice, where antibiotic treatment decreased shedding but increased antibody response following subsequent rotavirus exposure (Uchiyama et al., 2014). Nonetheless, if comparable increases in vaccine shedding were translated to a rotavirus-naive infant population, it is plausible that this might prompt a corresponding improvement in vaccine-induced immunity.

The study by Harris et al (2018) must be interpreted within the context of several important caveats. Its study population is far removed from the infant populations at risk of impaired oral vaccine response, both in terms of baseline microbiota composition and rotavirus exposure history. During a trial of children in India, a 3-day course of azithromycin induced marked changes in microbiota composition but did not significantly affect the immunogenicity or shedding of oral poliovirus vaccine (Grassly et al., 2016). In mice, antibiotic exposure has been shown to deplete total secretory IgA expression, potentially via its effects on the bacterial microbiota (Ruiz et al., 2017). This mechanism, as opposed to the observed perturbations in microbiota composition, could potentially account for the observed differences in rotavirus shedding, further undermining the relevance of these findings to rotavirus-naive infants. Finally, although the study sought to broadly recapitulate phenotypes linked with rotavirus response in observational studies, the extent to which this was achieved is questionable. For example, in Pakistan the mean relative abundance of Proteobacteria at the time of the first dose was 2.7% in Rotarix responders and 1.7% in non-responders (Harris et al., 2017). In the present study, Proteobacteria were scarce before treatment but often made up the majority of the bacterial microbiota (>95% in one individual) at the time of vaccination in vancomycin recipients. Antibiotics remain a blunt tool for reshaping the microbiota.

These caveats notwithstanding, Harris et al (2018) have laid a novel path for translating observational data into hypothesis-driven intervention. Non-therapeutic antibiotic administration was used in this study not for its potential real-world application, but as a means of testing whether targeted microbiota perturbations can elicit changes in vaccine outcome. In the coming years, it will be important to improve our understanding of the relationship between microbiota composition and rotavirus vaccine response. We must consider not only whether microbiota composition is associated with vaccine response, but the strength of this link and the mechanisms that underpin it. Given the complexity of the microbiota and its significant geographic variability, we should not expect the emerging narratives to be simple. Meanwhile, our potential to elicit more nuanced changes in microbiota via prebiotic or probiotic intervention is likely to improve. The extent to which these can be harnessed to improve rotavirus vaccine response and thereby lessen the global burden of diarrheal disease remains uncertain, but it is undoubtedly an avenue worthy of exploration.

Declaration of Interests

The authors declare no competing interests.

References

Grassly, N.C., Praharaj, I., Babji, S., Kaliappan, S.P., Giri, S., Venugopal, S., Parker, E.P., Abraham, A., Muliyil, J., Doss, S.*, et al.* (2016). The effect of azithromycin on the immunogenicity of oral poliovirus vaccine: a double-blind randomised placebo-controlled trial in seronegative Indian infants. Lancet Infect Dis *16*, 905-914.

Harris, V., Ali, A., Fuentes, S., Korpela, K., Kazi, M., Tate, J., Parashar, U., Wiersinga, W.J., Giaquinto, C., de Weerth, C.*, et al.* (2017). Rotavirus vaccine response correlates with the infant gut microbiota composition in Pakistan. Gut Microbes *9*, 93-101.

Harris, V.C., Armah, G., Fuentes, S., Korpela, K.E., Parashar, U., Victor, J.C., Tate, J., de Weerth, C., Giaquinto, C., Wiersinga, W.J.*, et al.* (2016). Significant correlation between the infant gut microbiome and rotavirus vaccine response in rural Ghana. J Infect Dis *215*, 34-34.

Harris, V. C., Haak, B. W., Handley, S. A., Jiang, B., Velasquez, D. E., Hykes Jr., B. L., Droit, L., Berbers, G. A. M., Kemper, E. M., van Leeuwen, E. M. M., *et al*. (2018), Effect of antibiotic-mediated microbiome modulation on rotavirus vaccine immunogenicity: a human, randomized-control proof-of-concept trial. Cell Host Microbe, this issue.

Isaac, S., Scher, J.U., Djukovic, A., Jimenez, N., Littman, D.R., Abramson, S.B., Pamer, E.G., and Ubeda, C. (2017). Short- and long-term effects of oral vancomycin on the human intestinal microbiota. J Antimicrob Chemother *72*, 128-136.

Madhi, S.A., Cunliffe, N.A., Steele, D., Witte, D., Kirsten, M., Louw, C., Ngwira, B., Victor, J.C., Gillard, P.H., Cheuvart, B.B.*, et al.* (2010). Effect of human rotavirus vaccine on severe diarrhea in African infants. N Engl J Med *362*, 289-298.

Parker, E.P., Ramani, S., Lopman, B.A., Church, J.A., Iturriza-Gomara, M., Prendergast, A.J., and Grassly, N.C. (2018a). Causes of impaired oral vaccine efficacy in developing countries. Future Microbiol *13*, 97-118.

Parker, E.P.K., Praharaj, I., Zekavati, A., Lazarus, R.P., Giri, S., Operario, D.J., Liu, J., Houpt, E., Iturriza-Gomara, M., Kampmann, B.*, et al.* (2018b). Influence of the intestinal microbiota on the immunogenicity of oral rotavirus vaccine given to infants in south India. Vaccine *36*, 264-272.

Platts-Mills, J.A., Amour, C., Gratz, J., Nshama, R., Walongo, T., Mujaga, B., Maro, A., McMurry, T.L., Liu, J., Mduma, E.*, et al.* (2017). Impact of rotavirus vaccine introduction and post-introduction etiology of diarrhea requiring hospital admission in Haydom, Tanzania, a rural African setting. Clin Infect Dis, epub ahead of print.

Ruiz, V.E., Battaglia, T., Kurtz, Z.D., Bijnens, L., Ou, A., Engstrand, I., Zheng, X., Iizumi, T., Mullins, B.J., Muller, C.L.*, et al.* (2017). A single early-in-life macrolide course has lasting effects on murine microbial network topology and immunity. Nat Commun *8*, 518.

Uchiyama, R., Chassaing, B., Zhang, B., and Gewirtz, A.T. (2014). Antibiotic treatment suppresses rotavirus infection and enhances specific humoral immunity. J Infect Dis *210*, 171-182.