# Recommendations for Increasing the Efficacy & Coverage of the Rotavirus Vaccination Program in Ghana

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## Abstract

Rotavirus is the most prevalent cause of severe diarrhea in children worldwide, accounting for up to 600,000 preventable deaths in young children each year. The burden of rotavirus is particularly high in sub-Saharan Africa, the site of 150,000 to 200,000 of these annual deaths. There are two live, oral rotavirus vaccines available globally: RotaTeq, administered in three doses and Rotarix, administered in two doses. In May 2012, Ghana became one of the first countries in the sub-Saharan region to administer a rotavirus vaccine, namely Rotarix. However, when comparing results of clinical trials conducted on children in developing nations to those conducted on children in higher-income nations, it is evident that there is a decreased level of success of rotavirus vaccines in Ghana and other developing nations. In Ghana, longer rotavirus infection seasons, younger ages of infection, poorer health and nutrition of children and decreased access to adequate healthcare are the most relevant obstacles to the success of the rotavirus vaccination program. Therefore, there is a need for a unique set of vaccine delivery strategies to maximize the success of the rotavirus vaccination program in Ghana. This paper explores the most relevant issues through literature reviews, in-person forums with mothers in Ghana and on-site interviews with the Head of Program Planning and Evaluation at Ghana's Ministry of Health and a rotavirus expert from the University of Ghana's Noguchi Memorial Institute for Medical Research. Recommendations for improving vaccine success in Ghana include administering a probiotic and micronutrient supplement with the vaccine and broadening age restrictions for the vaccine from eight months up to two years old. In addition, further studies should be conducted to evaluate the risks and benefits of a neonatal dose at two weeks of age, examine the potential impact of restricting breast-feeding 30 minutes before and after immunization and determine the safety and effectiveness of the vaccine in HIV-positive infants. Importantly, the investigation of new candidate vaccines may ultimately be necessary to provide protection against uncommon viral strains found at increasingly higher rates in children in developing nations. These recommendations aim to circumvent the challenges to vaccination to maximize performance of rotavirus vaccines in Ghana and in other developing nations worldwide.

## Introduction

### Global burden of rotavirus

Rotavirus-induced gastroenteritis is the single most prevalent cause of severe diarrhea worldwide, accounting for about 400,000 to 600,000 preventable deaths annually in children younger than five years old.1 According to the World Health Organization (WHO), the burden of rotavirus is particularly high in sub-Saharan Africa, which is the site of 150,000 to 200,000 of the aforementioned annual deaths (Figure 1). This increased disease burden is due to longer rotavirus infection seasons, younger ages of infection, poorer health and nutrition of children and decreased access to adequate healthcare.[1] There are currently two rotavirus vaccines available for use: RotaTeq and Rotarix, live, oral vaccines that have been licensed for use in over 100 nations around the world. However, clinical trials of these vaccines have demonstrated decreased efficacy in low-income nations in sub-Saharan Africa.[2] Moreover, of the over 100 nations in which these vaccines are licensed for use, only 27 nations, the vast majority of which are in Europe and the Americas, have incorporated them into their national infant immunization programs.[3]

### Rotavirus in Ghana

Ghana is a nation in sub-Saharan Africa that has a relatively well-developed healthcare system and infant immunization program compared to surrounding countries.[4,5] I chose Ghana as a case study because I believe that policy makers in this country are extremely dedicated to creating a rotavirus vaccine program that can effectively decrease the burden of this disease and can provide coverage to all children throughout the country. Throughout my work in Ghana, I interacted with community members, physicians and government workers who are passionate about improving the country's infant immunization program as well as the overall healthcare infrastructure.

Data from a recent multi-center study conducted by the Department of Child Heath at the University of Ghana Medical School from January 2008 to December 2009 showed that of the over 16,000 children hospitalized during the study time period, 13% were hospitalized due to acute gastroenteritis (infectious diarrhea causing abdominal pain, cramping, vomiting and dehydration). Of those hospitalized for acute gastroenteritis, 49% of them were confirmed as rotavirus-positive. The majority of children affected by rotavirus were between the ages of three and 14 months old, with peaks between six and 12 months old.[6] Due to the high morbidity and mortality rate of rotavirus in Ghanaian children, the incorporation of a rotavirus vaccine has been a top priority for Ghana's Ministry of Health in recent years. In May 2012, Ghana, along with Morocco, South Africa and Sudan, became one of the first African nations

to administer a rotavirus vaccine.[7,8] The Ministry of Health in these nations chose Rotarix because this vaccine is administered in two doses unlike RotaTeq, which must be administered in three doses. A two-dose vaccine is more likely to yield higher rates of compliance as opposed to a three-dose vaccine, which could ultimately lead to higher vaccination rates. [8,9]

**Decreased performance in developing nations**

It is important to note that trials conducted by the African Rotavirus Surveillance Network in Ghana and other developing countries in Africa and Asia have demonstrated decreased performance of RotaTeq and Rotarix compared to performance in higher-income nations. In a large-scale placebo-controlled study (during which half of participants received the vaccine and the other half received a "placebo" or inactive vaccine) conducted on infants in six nations in Europe, two doses of Rotarix demonstrated 90.4% protection against severe rotavirus disease.10 However, data from a separate study conducted by the African Rotavirus Surveillance Network showed that two doses of Rotarix induced only 58.7% protection against severe rotavirus disease in children in South Africa and 49.4% in children in Malawi. In that same study, two years post-vaccination, the RotaTeq vaccine protected against severe disease at rates of 55.5% in Ghana, 63.9% in Kenya and merely 17.6% in Mali.[11]

Though discouraging, these results are consistent with results from previous trials in the region with other live oral vaccines, namely poliovirus and cholera. These studies, published in highly-regarded journals including the Journal of Infectious Disease and the International Journal of Epidemiology, among others, demonstrated that these live oral vaccines showed decreased rates of protection against polio and cholera in children in developing nations.[12] Importantly, these studies show that the decreased success of the vaccine may be due to a higher severity of rotavirus infection in poorer nations, which is attributed to longer lengths of rotavirus infection seasons, younger ages of onset of rotavirus infections and higher instances of malnutrition and affliction with multiple other diseases.[13-16] These findings render even more crucial the urgency to modify policies regarding vaccine administration in order to optimize delivery and efficacy of these vaccines.[11]

> Of the over 100 nations in which these vaccines are licensed for use, only 27 nations have incorporated them into their national infant immunization program.

Though the Rotarix vaccine has been used in Ghana for more than a year, experts have begun to identify a number of outstanding issues that must be further investigated and policies that should undergo revision in order to maximize the success of the new vaccine program.[2] These recommendations include administering a probiotic and micronutrient supplement with the vaccine and broadening age restrictions for vaccine administration up to two years old. In addition, further studies should be conducted to evaluate the risks and benefits of a neonatal dose at two weeks old, examine the potential impact of restricting breast-feeding 30 minutes before and after immunization and determine the safety and efficacy of the vaccine in HIV-positive infants. Importantly, the investigation of new candidate vaccines may ultimately be necessary in order to provide protection against uncommon viral strains found at increasingly higher rates in children in developing nations. This paper presents in-depth rationales for each of these recommendations, with the intention of circumventing outstanding issues to ultimately maximize performance of rotavirus vaccines in Ghana and developing nations worldwide.

## Recommendations for vaccine administration

**Administer vaccines with a micronutrient and probiotic supplement**

The overall nutritional status of children in developing countries like Ghana is much poorer than children in more affluent nations. Young children in these areas often experience malnutrition and are frequently afflicted with bacterial, viral and parasitic infections.[2,17] Studies published in the Pediatric Infectious Disease and Pediatrics journals suggest that infants in developing nations are more likely to have diseases in their gut, including viruses that are not normally present in the guts of otherwise healthy infants.[2,18,19] Consequently, these studies demonstrate that infants who are experiencing upset stomachs or any diarrheal symptoms from infections other than rotavirus at the time of vaccination show a decreased absorption of the rotavirus vaccine.[18,19] One of these studies, which examined the oral cholera vaccine in children in Chile, showed that bacterial overgrowth from infections other than cholera in the small intestine impaired response to the vaccine.[18] Similarly, an additional study in Bangladesh with the live oral poliovirus vaccine indicated that rates of response to the vaccine were decreased in children who were experiencing diarrheal symptoms resulting from infections other than polio at the time of vaccination.19

Previous literature overwhelmingly suggests that a child's enteric balance can be properly maintained with probiotic and micronutrient supplements, especially in the context of childhood diarrhea.[2,19,20] Recently, a study published in Pediatrics demonstrated that continuous zinc supplementation significantly reduced the severity and frequency of diarrheal morbidity in infants, further suggesting that micronutrients may play a role in stabilizing the environment within an infant's gut.[19] In addition, probiotics have been shown to increase an infant's absorption of a live oral vaccine. For example, a successful intervention study in Finland of a previous rotavirus vaccine, RotaShield, showed that administering a probiotic Lactobacillus GG supplement at the time of vaccination improved infants' response to the vaccine.[20] These few studies provide evidence supporting a widely understood concept in pediatric medicine that micronutrient supplements and probiotics are beneficial for infant digestion and immune function.[19-21]

In order to maximize absorption and effectiveness of the rotavirus vaccine in Ghanaian children, policymakers should require administration of a micronutrient and probiotic in conjunction with rotavirus vaccination. Ideally, continuous probiotic and micronutrient administration would be the most successful way to ensure optimal health in children in developing nations. However, administering a supplement that contains a probiotic such as Lactobacillus, at least during the actual time of vaccination, would support a more optimal balance in gut flora by supplying beneficial bacteria that can combat any ongoing infections other than rotavirus that are occurring in the gut.[19,20] Moreover, since infants who are experiencing upset stomach or any diarrheal symptoms at the time of vaccination show a decreased absorption of the vaccine, a micronutrient supplement could help promote maximal absorption of the vaccine.[19] According to the World Health Organization (WHO), these types of campaigns are currently in operation in numerous developing nations worldwide, including the coupling of measles vaccines with Vitamin A supplements in order to combat Vitamin A deficiencies in young children.[21] Since this type of intervention is already widely used in developing regions for measles vaccines, it could also serve as a potentially feasible intervention for rotavirus vaccines in these regions.

**Broaden vaccine age restrictions for infants in Ghana**

In addition to optimizing an infant's absorption of the vaccine, the age range for vaccination should be broadened in order to maximize the number of infants who can be successfully vaccinated in Ghana. Currently, infants in Ghana receive the vaccine at six and ten weeks of age, with the final dose administered sometime prior to eight months of age. However, this age range should be broadened to extend the age limit of the final dose up to 24 months old.

### Rationale for current age restrictions

Currently, infants in the US receive doses of Rotarix at two and four months old. In Ghana, infants receive Rotarix at six and ten weeks old, per recommendations made by the Centers for Disease Control and Prevention (CDC).22 This recommendation is based on the fact that infants in Ghana are often susceptible to rotavirus infections at younger ages than children in the US and it is important to ensure that infants receive the vaccine before they contract natural rotavirus infection.23,24 The first dose given at six weeks old in Ghanaian children corresponds to the approximate age at which an infant's digestive tract is mature enough to be able to absorb the majority of the vaccine.3

The CDC recommends that the worldwide maximum age for the first dose of vaccine is 14 weeks and six days, while the maximum age for the second dose is eight months old.[22,25] This recommendation was created after the removal of the previously licensed RotaShield vaccine just a year after it was implemented in the United States because it increased the risk of intussusception.[25] Intussusception is the most common cause of intestinal obstruction in children under 5 years old and is characterized by the invagination of a proximal portion of the bowel within a more distal portion. This condition often requires emergency surgery.[26,27] Merck & GlaxoSmithKline, the manufacturers of RotaTeq and Rotarix, respectively, recommend a maximum vaccination age of eight months due to the fact that in normal infants, the risk of intussusception peaks just before eight months old.[27]

However, large-scale global trials of RotaTeq and Rotarix vaccines demonstrate that these currently licensed vaccines, unlike their predecessors, do not show any increase in rates of intussusception.[28-30] Therefore, the risk of intussusception may no longer be relevant for these newer vaccines. A top priority during post-licensure surveillance studies will be to confirm that RotaTeq and Rotarix indeed do not increase intussusception risk, in order to ensure the safety of extending the vaccination age limit beyond eight months.

### Extend age limit to eight months for first dose, 24 months for second dose

In order to prevent infants who are above the vaccination age limit from being denied the vaccine, the age maximum for vaccination should be increased to 24 months old. As a result of limited access to health clinics in more rural areas of Ghana, delays in vaccination and missed follow-up doses are not uncommon. These delays and missed follow-up doses can lead to infants becoming too old to receive the second dose of vaccine.[2,11] A recent study published in the Journal of Infectious Disease conducted in the rural Kassena-Nankana district projected that 70% of rotavirus-related deaths in Ghana could be prevented if there were no age restrictions on the vaccine, while only 53% of deaths would be prevented if children were required to receive all three doses between the age of 12 and 32 weeks.[31] Similarly, a study published in Vaccine estimated that extending the age of vaccination up to one year would save 28% more additional lives worldwide.[32]

A study published in the New England Journal of Medicine demonstrated that at 24 months old, nearly 100% of children have some degree of natural immunity against severe rotavirus infection due to previous naturally acquired rotavirus infections.[33] Namely, it is crucial to vaccinate infants all the way up to two years of age, because before this age, it is not certain that all children would have naturally-acquired protection against severe rotavirus disease. Therefore, many children will still be susceptible to severe infection before the age of two. After two years old it is almost 100% certain that infants would have gained some degree of protection against severe rotavirus disease, so an infant presenting after the age of two would no longer need to be vaccinated.[33]

Similarly, the age limit on the first dose should be extended to eight months old, at which time only about 40% of infants are likely to have contracted their first natural rotavirus infection.[56] In addition, there should be no restriction on the length of time between doses, provided that the first dose is given by eight months old, and the second dose is administered within this broadened 24-month time frame. Though patients should still be highly encouraged to receive the vaccine on the recommended dosing schedule of six and ten weeks, extending the age maximums will allow for much wider vaccine coverage and fewer infants who are turned down due to late arrival to scheduled immunizations.[31,32]

## Areas where further studies are needed

### Benefit of restricting breast-feeding 30 minutes before and after vaccination

In order to maximize Ghanaian infants' response to live oral vaccines, the effect of breast-feeding directly before and after administration of the vaccine must be considered. Experts have suggested that a correlation could potentially exist between breast-feeding and decreased effectiveness of live oral rotavirus and poliovirus vaccines. Although circulating antibodies (proteins of the immune system that fight off infection) acquired maternally are considered to be important in protecting a young infant against natural rotavirus infection, during vaccination with a live oral vaccine, the presence of these antibodies may actually decrease vaccine efficacy.[2]

### Studies needed to address the effect of breast-feeding during immunization period

A review conducted by the University of Maryland cited multiple studies that suggest that breast-feeding can interfere with immune reaction to rotavirus vaccines. However, the results of these studies were not always statistically significant.[34] On the other hand, more recent large-scale trials of both currently licensed vaccines have shown negligible differences in vaccine efficacy between mothers who self-reported breastfeeding and those who did not.[25,28,35] However, these studies showing no correlation between breast-feeding and decreased immune response to the vaccine only examined whether mothers self-reported breast-feeding their infant, but did not specifically examine the feeding practices directly surrounding administration of the vaccine.[25,28] Therefore, there is a need for further studies to investigate whether breast-feeding specifically during the time frame surrounding vaccination decreases effectiveness of the vaccine.

A study published in the Journal of Infectious Disease supports the notion that further investigation of this issue is warranted. This study showed that when breast milk and rotavirus were mixed outside of the body, 60% of the breast milk samples were able to neutralize (destroy) at least 90% of the virus and 30% of the breast milk samples were able to neutralize up to at least 99% of the virus.[2,34] These data suggest that if an infant has breast milk in the digestive tract from a recent feeding specifically during the time at which the vaccine is administered, maternal antibodies may be able to neutralize the relatively small amounts of live rotavirus contained in the vaccine. This initial neutralization could subsequently decrease the potential protective effect of that dose of vaccine compared to an infant who did not have breast milk present in the gut.[2,34,35]

A priority for clinical investigators should be to conduct trials that examine whether withholding breast-feeding 30 minutes before and 30 minutes after immunization has an effect on immune response to the vaccine. This time frame is based on the estimated 30 minutes to one-hour period that is required for infants of this age to digest breast-milk. Upon presenting to the clinic, health workers would require mothers to restrict feeding 30 minutes before giving their infants the vaccine. Health workers would then observe mothers for an additional 30 minute period after immunization during which breast-feeding would be prohibited. This approach is not completely novel, given that during recent trials of novel candidate rotavirus vaccines (namely, I321 and 116E), investigators required that mothers withhold breast-feeding 30 minutes before their infants were given the vaccine so that the presence of breast-milk would not interfere with vaccine absorption.[36]

### Evaluating cultural feasibility of breast-feeding regulations

Before trials of this potential breast-feeding regulation can be performed in lower-income nations like Ghana, the feasibility of this type of feeding restriction must be examined. In Ghana, nearly all infants are breastfed at least up to six months of age, as the Ministry of Health encourages breast-feeding to protect in-

fants from a host of diseases that can result in premature death.[37] My hypothesis is that confusion stemming from this contradiction may cause obstacles such as non-compliance with the feeding restriction and could possibly cause a decreased willingness of mothers to bring their infants to vaccination appointments.

In an effort to provide a preliminary exploration of the feasibility of regulating breast-feeding for the one-hour immunization period, I travelled to Ghana to conduct forums with mothers. Participants were recruited during their infant's six-week-old immunization visit as a part of an ongoing randomized controlled trial of Rotarix conducted by the Noguchi Memorial Institute for Medical Research. Mothers were recruited at two sites: the Navrongo Health Research Center in the rural Kassena-Nankana district in Northern Ghana and the Agogo Presbyterian Hospital in the urban city of Agogo in the Ashanti Region of Southern Ghana. A total of 11 mothers were surveyed from the Navrongo Health Research Center (divided into two separate forums of four and seven participants each) and a single forum of eight mothers was held at the Agogo Presbyterian Hospital. Translators from the Navrongo Health Research Center and the Agogo Presbyterian Hospital aided with the questionnaires.

During the forums, I asked the mothers about their current breast-feeding practices and their willingness to adhere to a potential 30-minute feeding restriction directly prior to and following immunization of their infant with the rotavirus vaccine. Health status and HIV status of mothers was not recorded during these forums. Results demonstrated that all of the mothers self-reported exclusive or partial breast-feeding of their infants. However, the forum discussions revealed an overall enthusiasm of these few mothers to comply with a proposed breast-feeding restriction surrounding vaccination.

In all three forums, 100% of the women reported that they would be willing to comply with this feeding regulation. Due to the very real threat of rotavirus diarrhea in young children in these communities, the participants agreed that they would be willing to restrain the child from feeding for one or two hours in order to protect the child from this potentially deadly disease. Overall the participants were very willing to comply with these regulations in hopes of improving the success of the vaccine and ultimately benefitting their infants. One woman remarked that the women in the community do their best to adhere to the current vaccine schedules in order to protect their children, and that she would be enthusiastic and willing to adhere to any further rules for a future vaccine. Similarly, another participant cited the success of the measles vaccine in eliminating that disease from their communities and expressed her enthusiasm that these new rotavirus vaccines could help to do the same for rotavirus in their communities. A few women did express concern that breast-feeding is one of the only ways that they can console their infant when he or she is crying. However, since the restriction is only one hour, they were hopeful that they would be able to withhold feeding their infant during this short period of time.

Though these forums represented a very limited sample of mothers from two health centers in Ghana, these preliminary discussions are certainly encouraging. Much larger and more comprehensive studies should ultimately be performed in order to determine whether this breast-feeding restriction would indeed be feasible and well received in Ghana and other developing nations worldwide.

**Studies examining safety & effectiveness of a neonatal dose**

During the period between two weeks old and the first Rotarix dose at six weeks old, infants in Ghana remain susceptible to rotavirus infection. Though maternal antibodies protect infants from rotavirus during the first two weeks of life, after two weeks the protective effect of maternal antibodies largely declines.[17] A recent study published in Vaccine suggested that a neonatal dose of the rotavirus vaccine could further decrease rotavirus hospitalizations and deaths in extremely young infants in developing nations.[38] In terms of safety, a study published in the Pediatric Infectious Disease Journal demonstrated that infants given the first dose of the previous rotavirus vaccine, RotaShield, during the neonatal period did not develop any adverse reactions.[39] However, since the digestive tract of neonates is not yet fully mature, a neonate's absorption of this live oral vaccine may not be significant enough to induce protection against rotavirus this early on in life.[3] Therefore, further clinical trials of a neonatal dose at two weeks old should be conducted in order to discern whether this early dose would be effective and beneficial for children in developing nations. If trials are successful, the suggested age range of immunization should be broadened to include a neonatal dose.

**Studies examining the vaccine in HIV-positive infants**

In addition to children who are afflicted with bacterial, parasitic and other viral infections, children in Ghana who are infected with HIV are at equal risk of acquiring rotavirus infections during early infancy and childhood. To date, both Merck and GlaxoSmithKline, the producers of RotaTeq and Rotarix respectively, affirm that their vaccines have not yet been evaluated in HIV-positive populations.[40,41] Therefore, vaccination is not recommended for HIV-positive infants until further trials have confirmed its safety. However, this recommendation effectively excludes an equally susceptible cohort of infants from receiving this important immunization. In Ghana, there are over 21,000 children under the age of 15 who are HIV-positive, many of whom acquired the virus at birth as a result of limited access to anti-retroviral therapy to prevent transmission of HIV from the mother to the child.[42] Preliminary data from a moderate-sized study in the African nation of Malawi conducted by the University of Malawi showed that severity of rotavirus disease and response to treatment with oral rehydration therapy did not vary significantly between HIV-positive and HIV-negative infants. However this study did not examine whether HIV-positive infants respond in a similar manner to rotavirus vaccines as HIV-negative infants.[43] It should therefore be a priority to conduct studies to determine whether rotavirus vaccines are safe and effective in HIV-positive infants in order to potentially extend the use of these vaccines to thousands more infants in Ghana and millions more worldwide.

> It is crucial to vaccinate infants all the way up to two years of age, because before this age, it is not certain that all children would have naturally-acquired protection against severe rotavirus disease.

## Develop new vaccines that can fully protect Ghanian children

Studies have shown that there are significant differences in rotavirus strain types between children in developing nations and children in higher income nations.[2] Rotavirus strains are classified using both a G and a P type, which corresponds to the two proteins on the outer surface of the virus particle. Globally, the most common strains are G1P[8], G3P[8], G4P[8], G9P[8], G9P[6] and G2P[4].[44] Though the G1P[8] strain contained in Rotarix has been shown to be one of the most prevalent strains in both Ghanaian children and children worldwide, the incidence of rare viral strains is higher in Ghanaian children than in children of higher income nations. Therefore, it may ultimately be necessary to design novel vaccine candidates that are able to target the variety of

strains found in Ghanaian children and other children living in poorer regions around the world.[2,45]

### Higher Incidence of Uncommon Viral Strains in Ghanaian Children

In the multi-center study conducted with 16,000 infants in Ghana, the most common G strains were G1 and G2, which are also reported as two of the most common strains in infants worldwide.[6,44] In addition, the P[6] strain was the most common P strain, which is known to be the second most prevalent P strain worldwide (second to the P[8] strain).[46,47] However, a study on global rotavirus strain distribution published in the Review of Medical Virology showed a 27% prevalence of strains in African children that were not among the top six most globally prevalent strains. Children in Europe and North America demonstrated significantly lower rates of these uncommon strains, ranging from rates of 1.4% to 5%.[45]

Specifically in Ghana, recent national surveillance studies have identified emerging strains that are becoming more prevalent, including the G8, G9, G10 and G12 strains. These strains are thought to have come about from transmission of the virus from animals to humans due to people living in close contact with livestock and other animals.[13,48] A few regional surveillance studies in Ghana have identified the G9 strain as the most predominant G strain in these regions, at rates ranging from 26% to 29%.[49,50] Similarly, the G8 strain was first isolated in Ghanaian children in 1999 and subsequent studies to date have shown the persistence of this strain in children in this nation.[6,48-50] The very rare G10 and G12 strains are detected at rates of up to 5% and 3.5% respectively in Ghanaian children as compared to approximately 0% in children elsewhere.[6,51,52]

In nearly all of the rotavirus surveillance studies conducted on Ghanaian children, there is also a prevalence of "mixed" G-type and "mixed" P-type infections. This means that instead of having an infection with a virus that has only a single G and a single P type, these viruses contain hybrid or mixed G or P strains. A host of mixed G genotype infections have been detected in Ghanaian children, including G1G2, G2G8, G3G8, G3G12 and G10G12. In the large multi-center study, these mixed G strains accounted for 7.6% of all rotavirus cases, while mixed P strains accounted for 26.5% of the P strains.[6,53] By comparison, these mixed strains are detected at much lower rates, if at all, in children in higher-income nations. One such study published in the European Journal of Epidemiology detected a mixed G strain prevalence of merely 2.0% in children in Spain.[36] This emergence of uncommon strains in Ghanaian children is a result of the tendency of these infants to be infected with multiple different rotavirus strain types at the same time, allowing for mixing of multiple strains to create new, hybrid strains.[13,48]

### Development of New Vaccines to Target Uncommon Strains

Due to the increased incidence of rare strains in Ghanaian children and in children in other developing nations, it is crucial to prioritize development of novel vaccines that can effectively target these emerging strains.[45] Though the Rotarix vaccine contains only a single strain, namely G1P[8], it has demonstrated its ability to protect against a variety of different rotavirus strains during multiple large-scale, multi-nation clinical trials, the review of which is published in Expert Review of Vaccines.[37] However, as the Rotarix and RotaTeq vaccines begin to decrease the incidence of the more globally common strains, there may be a global trend towards an even further increased prevalence of rare and mixed strains. This effect has been seen with mass treatment for other multi-strain viruses such as HIV.[54] It is therefore crucial to focus efforts towards designing and evaluating novel vaccine candidates that can effectively target a wide range of strains in hopes of affording maximal protection against rotavirus infection worldwide.[6,26]

## Priorities for improving vaccine delivery

Before these important recommendations can be implemented in Ghana, it is crucial to consider the most relevant improvements that must be made to Ghana's healthcare infrastructure in order to support the incorporation of this new live oral vaccine into the infant immunization program.

In September 2011, I conducted an in-person interview with the Head of Program Planning and Evaluation at Ghana's Ministry of Health. During the interview, which occurred less than a year before the rollout of the Rotarix vaccine, the representative stressed that prior to the introduction of this vaccine, a top priority for the Ministry of Health was to ensure that all aspects of vaccine transport and delivery were adequately prepared. She noted that temperature control is especially important during transport and storage of this live oral vaccine, as it must be maintained precisely between 2° and 8° C for quality assurance purposes.[40] At the time of the interview, funds were still needed to address the most relevant improvements, including improving the cold chain (vaccine transportation) system, training regional staff to properly administer the vaccine and updating the medical records systems to allow ample space to record this additional vaccine. The representative explained that the Ministry of Health was in the process of updating their cold chain system to include large, walk-in refrigerators with a reliable monitoring system that would provide alerts when appliances required maintenance or replacement. The representative seemed very hopeful that these necessary improvements would be implemented before the introduction of rotavirus vaccines to Ghana.

To date, the Ministry of Health has since successfully undergone these previously outlined revisions to their infrastructure as the rotavirus vaccination program has begun and continues to expand. Importantly, the Ministry of Health has updated their cold chain system to support massive quantities of these live oral vaccines at the required temperature of 2° to 8° C.[40] Consistent with the agenda set forth two years ago by the Head of Program Planning and Evaluation at the Ministry of Health, this agency must continue to allocate adequate funding towards closely monitoring the integrity of vaccine transport and delivery in order to ensure optimal quality and effectiveness of these vaccines.

## Update on rotavirus vaccination program in Ghana

Recently in August 2013, I conducted an interview with George Armah, Ph.D., to discuss the progress of the Rotarix vaccination program in Ghana. Dr. Armah is a specialist in rotavirus gastroenteritis and chair of the Department of Electron Microscopy and Immunohistochemistry at the University of Ghana's Noguchi Memorial Institute for Medical Research. He estimated that currently 75% of infants are being vaccinated against rotavirus in Ghana, a number that he projects will continue to rise. Importantly, he reported that as of March 2013, researchers have begun national post-licensure surveillance studies of the vaccine's performance in Ghana. This two-year-long nation-wide investigation will provide important efficacy and coverage data surrounding the performance of rotavirus vaccines, ultimately helping to inform crucial changes to rotavirus vaccine policies.

## Conclusion

In the United States and many European nations, rotavirus vaccines have demonstrated ample success at preventing severe rotavirus disease in young children. However, this is not yet the case in low-income countries around the world. Though rotavirus vaccines are now fully integrated into Ghana's infant immunization schedule, the ultimate success of these vaccines is contingent upon the adoption of immunization policies that aim to enhance performance of these vaccines in infants throughout the country.

The recommendations presented in this paper attempt to identify and overcome the most relevant challenges to the current rotavirus vaccination program in Ghana. A series of risks and benefits was weighed to take into account the specific conditions of Ghana, which differ greatly from the conditions in more affluent nations in which these vaccines have previously been used successfully. These recommendations include administering a probiotic and micronutrient supplement with the vaccine and broadening age restrictions for the vaccine up to two years old. The cost-effectiveness, however, of coupling vaccine administration with a probiotic and micronutrient supplement has yet to be examined, which would be necessary prior to introduction of this type of program.

In addition, further studies should be conducted to evaluate the risks and benefits of a neonatal dose at two weeks old, examine the potential impact of restricting breast-feeding 30 minutes before and after immunization and determine the safety and effectiveness of the vaccine in HIV-positive infants. Importantly, the investigation of new candidate vaccines may ultimately be necessary in order to provide protection against uncommon viral strains found at increasingly higher rates in children in developing nations.

I used Ghana as a case study for this paper due to the relatively well-developed healthcare infrastructure, the readiness of officials to introduce rotavirus vaccines and my personal passion for healthcare policy in this nation. Consequently, the climate, rotavirus epidemiology and access to resources in Ghana are very similar to conditions in most other developing nations around the world. Therefore, the vaccination policies suggested here could ultimately be applied to other countries in Africa, Asia and Latin America once rotavirus immunization programs have been launched in these regions. In the coming years, as rotavirus vaccine coverage continues to expand globally, it will remain crucial that officials prioritize important policy interventions surrounding vaccination that could greatly enhance the life-saving potential of these vaccines.

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