

**SYSTEMATIC REVIEW: A QUALITATIVE ANALYSIS OF THE INFLUENCES AFFECTING PARENTAL
ACCEPTANCE OF ROTAVIRUS VACCINE**

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*Systematic Review:
A Qualitative Analysis of the Influences Affecting
Parental Acceptance of Rotavirus Vaccine*

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Abstract:

Objective:

To evaluate factors contributing to the rotavirus vaccine parental hesitancy. We hypothesize that the greatest cause of hesitancy is the fear of intussusception. Identifying hesitancy factors will enable physicians to address concerns and help parents make informed decisions regarding the vaccine.

Study Design:

A comprehensive search was done for key words on PubMed and OvidSP. MeSH terms were combined and filters were utilized to find relevant primary articles. Articles were screened based on titles, abstracts, conclusions, and full texts. Last search was completed on August 25, 2016. Three additional articles were found through other resources and searching references. A total of 32 articles supported the background and 4 articles supported the analysis.

Results:

This Systematic Review identified key barriers that are still causing parental rotavirus vaccine hesitancy: fear of side effects, cost of rotavirus vaccine, vaccine not included in free public programs, not protecting against all diarrhea, given in three doses, child receiving enough vaccines, vaccine is not useful, not wanting to administer a live vaccine, newness of the vaccine, narrow window of age for the vaccine, immunity achieved from acquiring the virus itself, needing to evaluate data, producing a stronger mutated virus, preventing through holistic approaches, and a perceived lack of disease threat.

Conclusion:

Identifying hesitancy factors enables advancements in parental acceptance of the rotavirus vaccine through increasing parental awareness of disease burden, removing rotavirus vaccine age limits, and educating parents on vaccine myths. Limitations include a narrow number of databases used and filtering for English-only articles.

Introduction:

Rotavirus

The Rotavirus is a dangerous virus that causes severe infantile diarrhea and dehydration.^{8, 29} Rotavirus Gastroenteritis (RVGE) is one of the major reasons for children hospitalization and outpatient visits worldwide.^{8, 11, 29, 32} It has been estimated that Rotavirus-induced diarrhea has resulted in 450,000 global childhood deaths each year, mostly in low-income and developing countries.^{8, 11}

Rotavirus Vaccine

Due to the seriousness of RVGE, there was a desperate need for a rotavirus vaccine. In 1998, the United States introduced a live and oral Rotavirus vaccine known as Rotashield (Wyeth-Lederle Vaccines).²³ The vaccine “[contained] one rhesus RV serotype and three reassortant RV serotypes derived from rhesus and human strains.”²³ Despite making great advances in disease immunity, however, in 1999, the vaccine was withdrawn from the market due to its high risk of causing intussusception, a telescoping of a bowel segment into another.⁸ The evidence “was demonstrated in a case–series study yielding an incidence rate ratio (IRR) of 29.4 (95 % CI 16.1–

53.6) for days 3–14 after the first dose and in a case–control analysis an adjusted odds ratio (aOR) of 21.7 (95 % CI 9.6–48.9), which translates into one additional [intussusception] case per 4,670–9,474 infants vaccinated (11–21 per 100,000 vaccines).”²³

In 2006, two new-generation oral Rotavirus vaccines were reintroduced into the market: monovalent Rotarix® RV1 (GlaxoSmithKline Biologicals) and pentavalent RotaTeq® RV5 (Sanofi Pasteur MSD).^{8,23,32} Rotarix® is indicated for the prevention of infantile RVGE.²³ “Rotarix® contains a live attenuated human [Rotavirus] strain.”²³ It consists of two doses, “the first dose may be administered from the age of 6 weeks. There should be an interval of at least 4 weeks between doses. The vaccination course should preferably be given before 16 weeks of age, but must be completed by the age of 24 weeks.”²³ The second vaccine RotaTeq® is also indicated for the prevention of infantile RVGE.²³ It “is a pentavalent live [Rotavirus] vaccine containing human bovine reassortant.”²³ It consists of three doses, “[the] first dose may be administered from the age of 6 weeks and no later than the age of 12 weeks. There should be intervals of at least 4 weeks between doses. It is preferable that the vaccination course of three doses should be completed by the age of 20–22 weeks. If necessary, the third (last) dose may be given up to the age of 32 weeks.”²³ After introduction of the Rotavirus vaccines to the US, Australia, Europe, and over 10 South American countries,²⁹ dramatic reductions were observed in cases of “rotavirus-associated diarrhea and dehydration leading to hospitalization, medical visits and, especially in lower income settings, death.”²⁹ Assessment of the impact of the rotavirus vaccines on the number of diarrhea-related deaths and hospitalizations in children under the age of 5 in Bolivia, El Salvador, Honduras, and Venezuela between 2002 and 2010 revealed a range of reduction in diarrhea-related deaths between 15.7%-56.8%, and a range of reduction in diarrhea-related hospitalizations between 5.6%-17.9%.⁵ The impact of the rotavirus vaccines was so great that, “[in] 2009 the World Health Organization recommended the inclusion of rotavirus vaccine in the national immunization programs of all countries.”²⁹

Rotavirus Vaccine-Induced Intussusception

The most common cause of infantile acute intestinal obstruction is intussusception.¹¹ It “involves the invagination of a bowel segment into another, and may occur in different segments of the small and large intestines.”¹¹ The main symptoms of intussusception are abdominal pain and vomiting, with an occasional abdominal mass and bloody stools. Intussusception can lead to intestinal ischemia and intestinal obstruction, which requires radiological and surgical intervention.¹¹ This condition “is a medical emergency and can be fatal if untreated.”⁸

A review of 82 studies between 2002-2012 from all World Health Organization (WHO) regions found the mean natural incidence of intussusception to be 74 per 100,000 (range: 9–328) among children <1 year of age, with peak incidence among infants 5–7 months of age.¹²

Nevertheless, there has been evidence of an increased risk of intussusception with both Rotarix (RV1) and RotaTeq (RV5) vaccines. However, results from several studies indicate that this risk is very small. Carlin et al., analyzed a total of 306 confirmed cases of intussusception in children <1 year of age from 2007-2010 with both RV1 and RV5 in Australia. Results indicated a vaccine-attributable risk of intussusception in the 1–21 days after dose 1 and 1–7 days after dose 2 to be an estimate of 7.0 (95% CI, 1.5–33.1) cases per 100,000 for RV5 and 4.3 (95% CI, 0.8–

23.3) cases per 100,000 for RV1. ³ Yih, et al., published an article in The New England Journal of Medicine that focused on potential cases of intussusception and vaccine exposure in infants age 5-36.9 weeks that participated in a Mini-Sentinel program sponsored by the FDA from 2004-2011. This study analyzed 507,874 first doses and 1,277,556 total doses of RV5, along with 53,638 first doses and 103,098 total doses of RV1. Results indicated that RV5 was associated with approximately 1.5 (95% CI, 0.2 to 3.2) excess cases of intussusception per 100,000 recipients within 21 days of the first dose. No increase in the cases of intussusception was found with RV1. ³⁶ It is important to note that “the statistical power for analysis of RV1 was lower than that for the analysis of RV5.”³⁶

When comparing the natural incidence of intussusception among children <1 year of age (74 per 100,000) to the incidence of rotavirus vaccine-induced intussusception among children <1 year of age (1.5-7.0 per 100,000 for RV5 and 0-4.3 per 100,000 for RV1), one can argue that the benefits of the rotavirus vaccine in preventing RVGE far outweigh the small increased risk of intussusception. In fact, many articles including, Carlin et al., Clark et al., Desai et al., and Escolano et al., came to the same conclusion. ^{3,4,6,8} It is also important to note that despite the small increased risk of intussusception associated with RV1 and RV5, the WHO continues to recommend the rotavirus vaccines to children. The vaccines have not been withdrawn from the market, as Rotashield was due to its high risk of causing intussusception.

Vaccine Hesitancy

The benefits of childhood vaccinations have been invaluable in preventing diseases throughout history.¹⁴ This is true even when there are small side effect risks associated with the vaccine, as is the case with the rotavirus vaccine. Some important examples of the benefits of vaccines include lowering the global incidence of polio by 99% and eradicating small-pox.¹⁴ However, because of such low incidences now, the devastations caused by such diseases are now less well known by parents, contributing to their vaccination refusal.¹⁴ Reasons for vaccine hesitancy by parents include “fear of side effects”¹⁴, “belief that the target diseases are not harmful”¹⁴, “social norms”³³, “behavior and attitude of peers”³³, “child's pain or anxiety during immunization”³³, “vaccine safety”³³, “immune system overload”³³, and the “number of vaccines received.”³³ In addition, “[nationwide], almost 25% of parents believe their children receive too many immunizations, and the administration of all the required immunizations is not healthy.”¹⁸ In 2010, Kelley et al., analyzed 379 returned surveys from central Vermont that assessed caregivers’ perspectives toward childhood vaccination in children <5 years of age. Results indicated that respondents whose children were undervaccinated listed “vaccine safety” (65%) and “too many vaccines at one time” (62%) as reasons for not vaccinating their children.¹⁴ Two demographic groups were associated with undervaccinated children.¹⁴ One included families of lower socioeconomic status.¹⁴ Interestingly, the second group included parents of higher level of education and socioeconomic status that refused to vaccinate their children.¹⁴

With regards to vaccine hesitancy, one of the most influential parties is the media. “[Widespread] media coverage of negative claims against vaccinations has led parents to question their safety despite clear evidence that such claims are false.”¹⁴ “In some areas, antivaccine campaigns are so influential that parents and health care providers (HCPs) are made to feel guilty or even intimidated for vaccinating children.”¹⁸ One potential reason for the popularity of the

antivaccine campaign is due to the false “belief by some parents that immunizations cause autism.”¹⁸ This is largely due to a research paper published in 1998 by Andrew Wakefield, a physician in the UK, with claims of a link between the Measles, Mumps, Rubella (MMR) vaccine and the occurrence of autism. However, in 2010, the article was fully retracted based on the falsification of evidence. “Despite eight review panels by the Institute of Medicine reassuring parents that there is no causal relationship between immunizations and autism, some parents continue to express uncertainty regarding safety.”¹⁸

The increasing number of parents choosing not to vaccinate their children has led to recent disease outbreaks. “The 2014–2015 measles outbreak, in which 129 people from 7 states in the US were reported to have measles linked to Disneyland in California, has highlighted the resurgence of vaccine-preventable childhood diseases previously all but eliminated in the US by the implementation of the routine child immunization schedule.”³³ “[The] resurgence of measles, with 668 cases in 2014 and 178 in 2015 as of June,”³³ truly stresses the dangers of the rise of vaccine hesitancy.

It is important to stress the fact that an infant’s immune system does not fully developed until the age of two,¹⁸ “thus reinforcing the importance of immunizations during the first 2 years of life.”¹⁸ Furthermore, “[undervaccinated] and unvaccinated children not only create risk for themselves but also pose a risk for the community. Both infants who are not yet vaccinated due to their age and immunocompromised children who are unable to be vaccinated depend on herd immunity for protection against vaccine-preventable diseases.”¹⁴ Herd immunity is the concept of indirect disease protection for unimmunized individuals due to the disease immunity of the surrounding population.

The rationale for this project is based on the fact that for the first several years after the introduction of the RV1 and RV5 vaccination, there was uncertainty of whether the vaccines increased the risk of intussusception. However, with the publication of many studies within the past two years, there has been a consistent small increase of intussusception identified among children <1 year of age within 21 days of receiving either RV1 or RV5 vaccines. Knowing the importance of childhood vaccination and understanding the evidence that supports the fact that the benefits of the rotavirus vaccine in reducing hospitalization and deaths from RVGE far outweigh the small risk of intussusception, the goal of this systematic review is to identify the factors that are still causing parental hesitancy in acceptance of the rotavirus vaccine. By identifying those factors, we can begin to address those concerns and move towards rotavirus vaccine acceptance.

Methods:

Search Strategy

A comprehensive search was done for key words including MeSH and free text terms on PubMed. After the searches on PubMed, a comprehensive search was conducted on OvidSP in an effort to locate all possible relevant articles. The charts below only outline searches on PubMed because no new articles were found on OvidSP that were not previously located on PubMed. MeSH terms were combined and filters were utilized in order to find relevant primary

articles. With articles specific to rotavirus vaccination and parental attitudes, a 10-year cutoff was utilized in order to find articles that addressed current beliefs and understandings among parents since the introduction of the RV1 and RV5 vaccines in 2006. Primary articles were screened based on titles, abstracts, and conclusions. Full texts of potentially relevant articles were read for final screening. The date of last search was August 25, 2016. Furthermore, 3 additional articles were found from other resources and through searching the references of the selected primary articles.

PubMed Search	Articles Found
Rotavirus Vaccine	3719
Intussusception	9367
Children Vaccination	33378
Children Vaccination, Rotavirus Vaccine, Intussusception	111
Filter -Publication date last 5 years	51
Filter -Human species	44
Filter -English	43
Read and Chose	19

PubMed Search	Articles Found
Ethics of Vaccination	672
Vaccination Herd Immunity	997
Ethics of Herd Immunity	29
Vaccination Parental Views	83
Ethics of Vaccination, Ethics of Herd Immunity, Vaccination Parental Views	0
Ethics of Vaccination, Ethics of Herd Immunity, Vaccination Parental Views	0
Ethics of Vaccination, Vaccination Herd Immunity, Vaccination Parental Views	0
Ethics of Vaccination, Vaccination Herd Immunity	24
Filter -Human species	22
Filter -English	20
Read and Chose	0

PubMed Search	Articles Found
School Vaccination Requirements	232
Ethics of Vaccination	672
School Vaccination Requirements, Ethics of Vaccination	7
Filter -Human species	7
Filter -English	7
Read and Chose	0

PubMed Search	Articles Found
Medical Ethics	74236

Rotavirus Vaccination	1732
Medical Ethics, Rotavirus Vaccination	3
Filter -Human species	3
Filter -English	3
Read and Chose	0

PubMed Search	Articles Found
Vaccine Hesitancy	156
Filter -Human species	79
Filter -English	79
Read and Chose	10

PubMed Search	Articles Found
Rotavirus Vaccine	3719
Parental Vaccine Attitude	1113
Rotavirus Vaccine, Parental Vaccine Attitude	17
Filter -Human species	15
Filter -English	13
Filter -Publication date last 10 years	11
Read and Chose	3

PubMed Search	Articles Found
Rotavirus Vaccine	3870
Parent Vaccine Hesitancy	82
Rotavirus Vaccine, Parent Vaccine Hesitancy	0

PubMed Search	Articles Found
Vaccine Parents Attitudes	1243
Rotavirus Vaccine	3870
Vaccine Parents Attitudes, Rotavirus Vaccine	18
Filter -Human species	17
Filter -Publication date last 10 years	15
Filter -English	11
Read and Chose	1

Inclusion Criteria

Vaccine Hesitancy – Primary articles with data on parental opinions, physician opinions, and reasons for vaccine hesitancy.

Rotavirus Vaccine, Parental Vaccine Attitude – Primary articles with data on factors influencing parental opinions towards the rotavirus vaccine.

Data Analysis

There were a total of 22 articles found that supported understanding and background for the association between intussusception and the rotavirus vaccine. These articles were not part of the qualitative analysis.

There were a total of 10 articles found that supported background and discussions regarding general vaccine hesitancy and parental attitudes. These articles were not part of the qualitative analysis.

There were a total of 4 articles found that addressed factors influencing parental opinions towards the rotavirus vaccine. These articles were part of the qualitative analysis.

Results

E. Dubé et al.⁷ published an article in 2012 that focused on men and women of at least 18 years of age who were expecting a child or were parents of a newborn age 0-6 weeks in three different Canadian cities. A Phase 1 Questionnaire, focusing on parental intentions to vaccinate, was completed by 413 parents and 394 of them (95%) completed a Phase 2 Questionnaire, focusing on the behavior of vaccinating, at 6-month follow-up. The questionnaires were based on The Theory of Planned Behavior, often used to identify major determinants of health-related behaviors. In this study, the questionnaires were used to identify determinants leading to parental acceptance or hesitancy of the rotavirus vaccine. For the analysis, a Likert-type scale was used to quantify parent's beliefs and attitudes toward rotavirus vaccination. Generally, "a score of 1 [indicated] a low probability for this item to happen or a strong disagreement with the sentence, whereas a score of 5 [indicated] a high probability or a strong agreement with the sentence."⁷ Results at Phase 1 indicated that factors significantly associated with parental intentions to vaccinate ($277/413 = 67\%$) were the "perception of the moral correctness of having their child immunized (personal normative belief)" (Mean: 3.41 ± 1.02 (SD)), "perception that significant others will approve of the immunization behavior (subjective norm)" (Mean: 3.87 ± 0.91 (SD)), "perceived capability of having their child immunized (perceived behavioral control)" (Mean: 4.44 ± 0.67 (SD)), and "household income"⁷ (Table 1). Results at Phase 2 indicated that 165 parents ($165/394 = 42\%$) "reported that their child was immunized against rotavirus," the main determinant of which was "parental intention to have their child vaccinated."⁷ Personal normative beliefs was found to influence both the intention to vaccinate and the behavior of vaccinating against the rotavirus vaccine.⁷ It is important to note that "Two of three parents had a firm intention to vaccinate their child, yet only 42% of children were effectively vaccinated at follow-up 6 months later..."⁷ At Phase 2, the main barriers identified that caused parents not to vaccinate their children against rotavirus were, "Fear of side effects" (Mean: 3.12 ± 1.29 (SD)), "Cost of the rotavirus vaccine" (Mean: 2.76 ± 1.34 (SD)), "The fact that the vaccine will not protect against all diarrhea" (Mean: 2.50 ± 1.18 (SD)), and "Having the vaccine given in three doses" (Mean: 2.22 ± 1.09 (SD)) (Table 1).⁷ Two other factors were also associated with parents' likelihood to not vaccinate against rotavirus: "More than one child in the family" and "Parent does not live with a partner."⁷ On the other hand, the main "enabling condition that was significantly higher for parents who decided to vaccinate their children against rotavirus was 'having a doctor or nurse recommend the vaccine'" (Mean: 4.30 ± 1.02 (SD)).⁷ Furthermore, parents stated that the reason they did not vaccinated their children was because "their child was receiving enough vaccines" (51%), "they believed that the vaccine was not useful" (48%), and

“they did not vaccinate their child because the vaccine was not included in the free public vaccination program” (40%).⁷ Finally, it is important to note “the association between parents’ source of information about vaccination and their decision to have their child vaccinated against rotavirus.”⁶ “Compared with parents of unvaccinated children, parents who chose to vaccinate their children against rotavirus were more likely to report being informed on vaccination by a health professional.”⁷ (Informed by a Doctor: 157/165 = 95% for vaccinated versus 192/229 = 84% for unvaccinated or informed by a Nurse: 95/165 = 58% for vaccinated versus 102/229 = 45% for unvaccinated).⁷ They were also “less likely to report using the Internet” as their source of information about vaccinations.⁷ (Internet: 28/165 = 17% for vaccinated versus 72/229 = 31% for unvaccinated).⁷

Patel et al.²⁶ published an article in 2007 that focused on the beliefs and attitudes of parents and providers towards rotavirus and the rotavirus vaccine, RotaTeq RV5. A qualitative assessment using focus groups and in-depth interviews was utilized when analyzing parental opinions (n=57) and provider opinions (n=10). Results focused on provider opinions indicated that physicians were reassured with the safety profile of RV5 and on a scale from 1-7 (1 = "absolutely not", 7 = "absolutely yes") a mean score of 5 (range = 3–6) was found for their likelihood to use RV5.²⁶ Physicians expressed two main factors that would help them adopt RV5: if RV5 was recommended by their professional organizations and if post-marketing safety data was available.²⁶ Patel et al. recommended “providing physicians with timely post-marketing surveillance data” in order to increase adoption and recommendation of the rotavirus vaccine by providers.²⁶ Similarly, results focused on parental opinions found the RV5 safety profile to be favorable. When discussing the seriousness of rotavirus disease, on a scale from 1 ("not at all serious") to 7 ("very serious"), 59% of parents considered the disease to be very serious (range 5-7), 36% considered the disease to be moderately serious (range 3-4), and 5% considered the disease to be not at all serious (range 1-2).²⁶ The average seriousness of the rotavirus disease on a scale from 1 to 7 was 4.78 (Table 1 and 2). Patel et al. recommended the increase in “parental awareness of rotavirus disease burden” in order to increase acceptance of the rotavirus vaccine.²⁶ When asked about the “likelihood of having their child vaccinated against rotavirus” on a scale from 1 to 7 (1 = "definitely not get", 7 = "definitely get"), “29% ranked 1 or 2, 36% 3 or 4, and 35% 5 to 7.”²⁶ The average likelihood of parents attaining the rotavirus vaccine for their children on a scale from 1 to 7 was 3.67 (Table 1 and 3). With this average, one can assume that there are clear concerns regarding parental acceptance of the rotavirus vaccine. Common concerns identified by Patel et al. included “the administration of a live-vaccine to ‘young, vulnerable’ infants, the newness of the vaccine, potential for adverse events as more data becomes available, and the narrow window of age when the vaccine is recommended.”²⁶ It is important to note that despite these concerns, parents expressed “...that they would rely on their physician’s recommendation on whether their child should receive the rotavirus vaccine.”²⁶

Payne et al.²⁸ published an article in 2011 that assessed the beliefs of pediatricians’ and mothers’ perspectives on rotavirus vaccine before and after knowing that DNA fragments from Porcine circovirus (PCV) were found in both RV1 and RV5 vaccines. PCV is “a virus common among pigs but not believed to cause illness in humans.”²⁸ This study conducted three focus group discussions and interviews in Seattle, WA, Cincinnati, OH, and Rochester, NY with a total of 45 pediatricians and 52 mothers.²⁸ In order to assess pediatricians’ general perspectives on the rotavirus vaccine outside of PCV, since it is beyond the focus of this project, we focused on data

exclusive to the pre-intervention group or before knowledge of DNA fragments from PCV in the vaccine. These results indicated that “Pediatricians understood firsthand the success of rotavirus vaccines in preventing severe acute gastroenteritis among infants and young children.”²⁸ In order to analyze results, a score of 1 = “Routinely recommend”, 2 = “Occasionally recommend”, 3 = “Inform but don’t recommend” and 4 = “Recommend against”.²⁸ When physicians were asked about their “current recommendation on rotavirus vaccinations for infants?” the average score was 1.1. With perceived barriers, physicians gave an average scores of: 3.4 for “Lack of insurance coverage”, 3.4 for “Lack of reimbursement”, 2.4 for “Mother’s concern with vaccine safety”, and 3.4 for “Time needed to discuss with mothers.”²⁸ It is important to note that physicians’ recommendation of the rotavirus vaccine had a high average score and it was generally “Routinely recommended”. However, with each perceived barrier, the physicians had a lower average score of recommendation. The fact that physicians are not recommending the vaccine as much with perceived barriers could be an important determinant in parental hesitancy toward acceptance of the rotavirus vaccine. This thought is strengthened by the fact that “Mothers... trusted their pediatrician’s recommendation” and hesitancy of recommendation on the part of the physicians could lead to hesitancy of vaccine acceptance on the part of the mothers.²⁸ When comparing mothers’ pre-intervention perspectives versus post-intervention perspectives on knowledge of DNA fragments from PCV found in the rotavirus vaccine, it is interesting to find that, despite the fact that “...there was no evidence that DNA or DNA fragments from PCV in rotavirus vaccines would cause harm to humans, ...”²⁸ mothers’ perspectives on the rotavirus vaccine decreased across all questions.²⁸ In order to analyze results, a score of 1 = “Strongly agree”, 2 = “Somewhat agree”, 3 = “Somewhat disagree” and 4 = “Strongly disagree”.²⁸ With the statement “Rotavirus vaccine is an important vaccine for my child,” before the intervention, mothers gave an average score of 1.5. When comparing pre-intervention to post-intervention, only 2 out of 51 mothers (4%) either somewhat disagreed or strongly disagreed with the statement before the intervention. However, after the intervention, 14 out of 51 mothers (28%) either somewhat disagreed or strongly disagreed with the statement.²⁸ With the statement “I feel confident that rotavirus vaccine works to prevent serious diarrhea,” before the intervention, mothers gave an average score of 1.7. When comparing pre-intervention to post-intervention, only 2 out of 52 mothers (4%) either somewhat disagreed or strongly disagreed with the statement before the intervention. However, after the intervention, 5 out of 52 mothers (10%) either somewhat disagreed or strongly disagreed with the statement.²⁸ With the statement “I feel confident that rotavirus vaccine is safe,” before the intervention, mothers gave an average score of 1.6. When comparing pre-intervention to post-intervention, only 5 out of 51 mothers (10%) either somewhat disagreed or strongly disagreed with the statement before the intervention. However, after the intervention, 19 out of 51 mothers (37%) either somewhat disagreed or strongly disagreed with the statement.²⁸ Lastly, With the statement “If I had another baby, I would have that baby get rotavirus vaccine,” before the intervention, mothers gave an average score of 1.4. When comparing pre-intervention to post-intervention, only 4 out of 52 mothers (8%) either somewhat disagreed or strongly disagreed with the statement before the intervention. However, after the intervention, 16 out of 52 mothers (31%) either somewhat disagreed or strongly disagreed with the statement.²⁸ This study provides a great example of a situation that caused mothers suspicion, fear, and decreased acceptance of the rotavirus vaccine based on presentation of complex scientific information. The demonstrated decreased acceptance of the rotavirus vaccine was despite the fact that there was no evidence that DNA from PCV in the vaccine would cause any harm to humans. In order to avoid this in the future, it is important

to note that “simply providing an untailed textual statement”²⁸ is unlikely to fulfill mothers’ questions and concerns regarding the safety of rotavirus vaccine, especially when presented with complex scientific information. The best way to approach this situation is through “A skillfully navigated, personalized discussion between an interested mother and pediatrician, employing sensitivity to a mother’s specific technical understanding and personal concerns on this topic, ...”²⁸

Lastly, Lugg et al.¹⁷ published an article in 2015 that assessed the attitudes and beliefs of parents in Wales and England about viral gastroenteritis (vGE) and the rotavirus vaccine.¹⁷ This study conducted a total of 28 qualitative interviews over the phone with parents whose children were less than 5 years of age at the time of illness and had experienced an acute episode of gastroenteritis within the past 3 months.¹⁷ When assessing parents’ perception of the seriousness of the vGE, the more serious that the disease was perceived, the more receptive parents were towards getting the rotavirus vaccine for their children. In contrast, if parents did not think that the disease was serious, then they believed that it was less necessary for their child to receive the rotavirus vaccine.¹⁷ When assessing the perceived benefits of a vGE vaccination programme, “Many of the participants discussed how successful and important vGE vaccine programmes would be to their community.”¹⁷ This study does note that they believe these positive views on rotavirus vaccination is linked to the parents’ views on the seriousness of vGE.¹⁷ When assessing the effectiveness and immunity of the rotavirus vaccine, there seemed to be concerns supported by the belief that acquiring the virus would result in the same immunity as receiving the rotavirus vaccine, therefore, perhaps it is not necessary to receive the vaccine.¹⁷ Finally, when assessing concerns regarding vaccination against vGE, many parents were unsupportive of the vaccine due to various reasons including a need to evaluate research data before acceptance of the vaccine, a perceived lack of disease threat, vaccination leading to virus mutation, and the belief that a holistic approach, as opposed to the vaccine, was the best way to prevent vGE.¹⁷ Based on these results, this article concludes that the acceptability of the rotavirus vaccine would be improved if parents were more aware of the seriousness and burden of vGE.¹⁷

Table 1: Summary of Results

<u>Article</u>	<u>Population</u>	<u>Barriers</u>	<u>Outcomes Per Barrier</u>	<u>General Outcomes</u>
<p>E. Dubé et al. ⁷ 2012</p>	<ul style="list-style-type: none"> - Men and Women of at least 18 years of age who were expecting a child or were parents of a newborn age 0-6 weeks. - Three Canadian cities: Vancouver, British Columbia; Quebec City, Quebec; Halifax, Nova Scotia - Phase 1 Questionnaire completed by 413 parents - Phase 2 Questionnaire completed by 394 parents at 6 months follow-up - 95% Retention 	<p>Phase 1 Intention:</p> <ul style="list-style-type: none"> - I plan to have my child vaccinated against rotavirus - I definitely intend to have my child vaccinated against rotavirus - The likelihood that I will have my child vaccinated against rotavirus is (null–very high) <p>Personal Normative Beliefs:</p> <ul style="list-style-type: none"> - My personal beliefs make me want to have my child vaccinated against rotavirus - If I did not have my child vaccinated against rotavirus, I would feel guilty - It is in my values to have my child vaccinated against rotavirus <p>Perceived Behavioral Control:</p> <ul style="list-style-type: none"> - I feel capable of having my child vaccinated against rotavirus - If I want to, I can have my child vaccinated against rotavirus <p>Subjective Norm:</p> <ul style="list-style-type: none"> - If I have my child vaccinated against rotavirus, most people who are important to me will approve 	<p>Mean ± SD:</p> <ul style="list-style-type: none"> → 3.75 ± 1.23 → 3.70 ± 1.32 → 3.88 ± 1.15 Overall: 3.77 ± 1.17 ----- → 3.75 ± 1.19 → 2.78 ± 1.28 → 3.72 ± 1.21 Overall: 3.41 ± 1.02 ----- → 4.36 ± 0.89 → 4.52 ± 0.71 Overall: 4.44 ± 0.67 ----- → 4.17 ± 0.96 	<p>Factors associated with parental intentions to vaccinate (277/413: 67%):</p> <ul style="list-style-type: none"> - Perception of the moral correctness of having their child immunized (Personal Normative Belief) - Perception that significant others will approve of the immunization behavior (Subjective Norm) - Perceived capability of having their child immunized (Perceived Behavioral Control) - Household income <p>Factors associated with parental behavior of vaccinating (165/394: 42%):</p> <ul style="list-style-type: none"> - Parental intention to have their child vaccinated - Perception of the moral correctness of having their child immunized (Personal Normative Belief)

Rate

- The people who are important to me and who have children would have their own children vaccinated against rotavirus
- Most people who are important to me would advise me to have my child vaccinated against rotavirus

Attitude:

- Having my child vaccinated against rotavirus will be useful
- Having my child vaccinated against rotavirus will be pleasant
- Having my child vaccinated against rotavirus will be valuable
- Having my child vaccinated against rotavirus will be not disturbing
- Having my child vaccinated against rotavirus will be healthy

Phase 2

Enabling Conditions:

- Having a doctor or nurse recommend it
- The fact that the vaccine is administered orally rather than by injection
- Having the vaccine given at the same time as other vaccines

→ 3.79 ± 1.09

→ 3.65 ± 1.19

Overall: 3.87 ± 0.91

→ 3.95 ± 0.84

→ 3.36 ± 0.89

→ 3.59 ± 0.73

→ 3.97 ± 0.96

→ 3.87 ± 0.76

Overall: 3.75 ± 0.57

Child 'Has'
Received Rotavirus
Vaccine (n=165)
Mean ± SD:

→ 4.30 ± 1.02

→ 3.43 ± 1.28

→ 3.77 ± 1.21

Factors associated with parents' likelihood to not vaccinate against rotavirus:

- More than one child in the family
- Parent does not live with a partner

Factors associated with parents' refusal to vaccinate children against rotavirus:

- Their child was receiving enough vaccines (51%)
- They believed that the vaccine was not useful (48%)
- They did not vaccinate their child because the vaccine was not included in the free public vaccination program (40%)

Association between parents' source of information about vaccination and their decision to vaccinate against rotavirus:

- More likely to be informed on vaccination by a health professional:
 - Doctor:** 157/165 = 95% for vaccinated vs 192/229 = 84% for unvaccinated
 - Nurse:** 95/165 = 58% for vaccinated vs 102/229 = 45% for unvaccinated
- Less likely to use the Internet as source of information about vaccinations

		<p>Vaccine Barriers:</p> <ul style="list-style-type: none"> - Difficulty in getting an appointment - The cost of the vaccine - Having the vaccine given in three doses - Having the vaccine given in two doses - Difficulty accessing the doctor's office or public health immunization clinics - Fear of side effects - The fact that the vaccine will not protect against all diarrhea 	<p>Child '<u>Has Not</u>' Received Rotavirus Vaccine (n=225) <u>Mean ± SD:</u></p> <ul style="list-style-type: none"> → 2.02 ± 1.13 → 2.76 ± 1.34 → 2.22 ± 1.09 → 2.09 ± 1.00 → 2.11 ± 1.15 → 3.12 ± 1.29 → 2.50 ± 1.18 	<p>Internet: 28/165 = 17% for vaccinated vs 72/229 = 31% for unvaccinated</p>
<p>Patel et al. ²⁶ 2007</p>	<ul style="list-style-type: none"> - Qualitative assessment using focus groups and in-depth interviews - Two Locations: Sunnyvale, California and Kansas City, Missouri - Analyzing parental (n=57) and provider (n=10) opinions 			<p><u>Parental Opinions:</u> <u>Seriousness of Rotavirus Disease:</u> (1: Not at all serious to 7: Very serious)</p> <ul style="list-style-type: none"> - 59%: very serious (range 5-7) - 36%: moderately serious (range 3-4) - 5%: not at all serious (range 1-2) - Average seriousness of the rotavirus disease on a scale from 1-7 = 4.78 <p><u>Likelihood of having child vaccinated for rotavirus:</u> (1: Definitely not get to 7: Definitely get)</p> <ul style="list-style-type: none"> - 29%: ranked 1 or 2 - 36%: ranked 3 or 4

	<p>towards rotavirus disease and rotavirus vaccine, RotaTeq RV5</p>			<ul style="list-style-type: none"> - 35%: ranked 5 to 7 - Average likelihood of parents getting the rotavirus vaccine for their children on a scale from 1-7 = 3.67 <p>Concerns regarding parental acceptance of the rotavirus vaccine:</p> <ul style="list-style-type: none"> - The administration of a live-vaccine to “young, vulnerable” infants - The newness of the vaccine - Potential for adverse events - Narrow window of age when the vaccine is recommended <p>Parental guidance for rotavirus vaccine decision:</p> <ul style="list-style-type: none"> - Physician’s Recommendation
<p>Payne et al. 28 2011</p>	<ul style="list-style-type: none"> - Pediatricians’ and Mothers’ perspectives on rotavirus vaccine Pre-Intervention & Post-Intervention - Three focus group discussions and interviews in Seattle, WA, Cincinnati, OH, and Rochester, NY - Total of 45 	<p>Pediatricians’ Pre-Intervention Analysis:</p> <p>Pediatricians’ Score Chart:</p> <ul style="list-style-type: none"> 1 = Routinely recommend 2 = Occasionally recommend 3 = Inform but don’t recommend 4 = Recommend against <ul style="list-style-type: none"> - “Current recommendation on rotavirus vaccinations for infants?” - Perceived Barrier: “Lack of insurance coverage” - Perceived Barrier: “Lack of reimbursement” - Perceived Barrier: “Mother’s concern with vaccine safety” - Perceived Barrier: “Time needed to discuss with 	<p>Average Score:</p> <ul style="list-style-type: none"> → 1.1 → 3.4 → 3.4 → 2.4 → 3.4 	<ul style="list-style-type: none"> - Physicians are not recommending the vaccine as much with perceived barriers - Mothers trust their pediatrician for vaccine recommendation

pediatricians and 52 mothers

mothers.”

Mothers’ Pre-Intervention Perspectives vs Post-Intervention Perspectives:

Mothers’ Score Chart:

- 1 = Strongly agree
- 2 = Somewhat agree
- 3 = Somewhat disagree
- 4 = Strongly disagree

“Rotavirus vaccine is an important vaccine for my child”

“Somewhat disagree” or “Strongly disagree”

“I feel confident that rotavirus vaccine works to prevent serious diarrhea”

“Somewhat disagree” or “Strongly disagree”

“I feel confident that rotavirus vaccine is safe”

Pre-Intervention Average Score:
→ 1.5

Pre-Intervention:
2/51 = 4%
Post-Intervention:
14/51 = 28%

Pre-Intervention Average Score:
→ 1.7

Pre-Intervention:
2/52 = 4%
Post-Intervention:
5/52 = 10%

Pre-Intervention

- Complex scientific information caused mothers suspicion, fear, and decreased acceptance of the rotavirus vaccine.

- “Simply providing an untailed textual statement”²⁴ is unlikely to fulfill mothers’ questions and concerns regarding the safety of rotavirus vaccine, especially when presented with complex scientific information.

- The best way to approach this situation is through “A skillfully navigated, personalized discussion between an interested mother and pediatrician, employing sensitivity to a mother’s specific technical understanding and personal concerns on this topic, ...”²⁴

		<p>“Somewhat disagree” or “Strongly disagree”</p> <p>“If I had another baby, I would have that baby get rotavirus vaccine”</p> <p>“Somewhat disagree” or “Strongly disagree”</p>	<p>Average Score: → 1.6</p> <p><u>Pre-Intervention:</u> 5/51 = 10%</p> <p><u>Post-Intervention:</u> 19/51 = 37%</p> <p>-----</p> <p>Pre-Intervention Average Score: → 1.4</p> <p><u>Pre-Intervention:</u> 4/52 = 8%</p> <p><u>Post-Intervention:</u> 16/52 = 31%</p>	
<p>Lugg et al. ¹⁷ 2015</p>	<p>- Parent’s beliefs on viral gastroenteritis and rotavirus vaccine</p> <p>- In Wales and England</p> <p>- 28 qualitative interviews over the phone with parents whose children were less than 5 years of age at the time of illness and had experienced an</p>			<p>Perception of the seriousness of vGE:</p> <p><i>“Don’t get me wrong, I’ve vaccinated my children for MMR and all those things, but they’re killers and they spread in a different way, but [not for] something like rotavirus and norovirus...There aren’t many people dying from it are there?...so then I don’t really think that there’s much point, when people can cope with it themselves.”</i></p> <p><i>“When my kids have got them they have never got them particularly badly it’s just an inconvenience so I’m not sure I’d want to put a vaccine in them for a, not</i></p>

acute episode of gastroenteritis within the past 3 months.

a serious reason ... I wouldn't be too worried about a vaccine."

"I've said no to the flu vaccination because, for myself and for her, [um] because I just kind of felt that our natural immune system would kind of, y'know, do the job really [um] but Norovirus, I don't know, I'd wanna look into it a bit more, I'd be interested in that 'cause I know so many families that it's really knocked for six [made very ill]. So, that would be a different, y'know, I'd consider that quite differently to the kind of flu jab really."

"I would be delighted if they brought out a vaccine for that, [um] purely because I feel like I spend most winters waiting for them to go down with it and it's so, so contagious [um] I mean, I know they always end up with a lot of people in the hospital with it and in the nursing homes and they keep having outbreaks like on a cruiseship, all this sort of thing [um] and it's so unpleasant to have and yeah, I'd be very happy if they brought out a vaccine, I'd be first in the queue. I hate getting D&V [diarrhea and vomiting]."

Perceived benefits of a vGE vaccination programme:

"I think if they had a vaccine that treated [rotavirus or norovirus] then I

would definitely, I think a lot of parents would welcome it without a doubt definitely because it is so common and I think this year has been pretty bad with the diarrhea and vomiting virus. I mean, every parent I talk to, you know, it is going around the schools like crazy and I don't think I have actually seen it so bad as I have seen it this year without a doubt, so I mean you know hearing of a vaccine that could prevent it or, you know, deal with it I would definitely be willing to you know give it a go once the testing has all been done you know, definitely because I think that would help a lot of parents out, you know without a doubt."

"I would jump at the chance because I don't believe vaccines are harmful in general...My children have already been vaccinated against other things so if they were going to be amongst the rare people who are sensitive to ingredients in vaccines I think that would've already [um], manifested itself...Therefore I think it's not going to be harmful to give my children vaccines, [um], and the inconvenience and misery of rotavirus, it's just horrible and if you could actually vaccinate against one of these rapidly evolving viruses...then yeah I'd do it. Definitely."

Effectiveness and immunity:

“it’s my understanding that I think once you’ve caught a certain type of norovirus or rotavirus you won’t get it again anyway and [um] I just assumed that there’s so many different types that it wouldn’t, you wouldn’t catch the same one each time.”

“I think I would always choose to vaccinate [um] yeah I think it’s a positive thing that they are being developed [um] though part of me does think you know that maybe your body with something like norovirus just does have to ride it out and [um] my little girl didn’t seem too affected by it.”

“I believe that rotavirus vaccine is already used in some of the countries, possibly in America? [um] I think, if they did bring it, if it sounds pretty safe then I’d be happy to vaccinate my children but I know rotavirus is one of the ones where you tend to get it badly the first time and as you get further episodes of it, it tends to be milder and milder and by adult you’ve generally got some immunity”

Concerns regarding vaccination against vGE:

“I don’t know about getting the other

vaccines, there would have to be quite a lot of, [um], literature or research available to me to, to have to make a decision like that, 'cause it's similar to when my eldest daughter, when she had, uh, MMR, I looked into all of that and although at the time there was lots of furore about all the links with autism and things like that, but I looked into all that and as far as I was concerned it wasn't, um, I didn't see the link that they were trying to put out there. So, like, I decided that was fine for her but there would have to be a lot of, um, research and stuff before I would give them any other kind of vaccine."

"I would definitely not give my son that. Only because I just think diarrhea and stuff is just a natural part I just think it's erm you know natural for everyone to have diarrhea at some point. So I guess. and I really, really hate putting, you know, I hate giving him needles anyway. So I don't think that I would. Unless he was obviously dangerous and then maybe I would, yeah. But not just for diarrhea and vomiting, I don't think."

"oohh: I think that if you vaccinate for anything, something new comes along doesn't it, and by allowing them to have it, they build up their own, um immunities to it, but it strengthens their

immunity. I think vaccinations can just get ridiculous and there's always side effects to these things that you discover whenever in the future... something like rotavirus and Norovirus there's always going to be another virus of some sort around the corner, and you vaccinate against one thing and it will develop into something else so no. ((laughs))."

"I'm not that keen on things like adding further things to the body and I'm not all that keen on previous things he's had to have as part of his check ups and things. But just the MMR and that kind of thing. I probably wouldn't actually know. I wouldn't unless it was life threatening things like meningitis. He had that, he had an injection for that but something which isn't life threatening as such which I don't believe that norovirus is. So probably no, I probably wouldn't tend to go for something like that all. I'm more keen on trying to manage it holistically or without medication or perhaps other ways."

Table 2: Patel et al. ²² Parental Opinion -Seriousness of Rotavirus Disease:

Scale 1-7 1 = Not at all serious 7 = Very serious	# of Participants	% of Participants	Scale (1-7) x # of Participants	Average Seriousness of Disease from 1-7:
1	0	0%	1 x 0 = 0	268/56 = 4.78
2	3	5%	2 x 3 = 6	
3	9	16%	3 x 9 = 27	
4	11	20%	4 x 11 = 44	
5	16	29%	5 x 16 = 80	
6	8	14%	6 x 8 = 48	
7	9	16%	7 x 9 = 63	
	Total = 56	Total = 100%	Total = 268	

Table 3: Patel et al. ²² Parental Opinion -Likelihood of Parental Acceptance of Rotavirus Vaccine for their Children:

Scale 1-7 1 = Definitely not get 7: Definitely get	# of Participants	% of Participants (1 Missing Data)	Scale (1-7) x # of Participants	Average Likelihood of Acceptance of Vaccine from 1-7:
1	9	16%	1 x 9 = 9	202/55 = 3.67
2	7	13%	2 x 7 = 14	
3	10	18%	3 x 10 = 30	
4	10	18%	4 x 10 = 40	
5	9	16%	5 x 9 = 45	
6	6	11%	6 x 6 = 36	
7	4	7%	7 x 4 = 28	
	Total = 55	Total = 99%	Total = 202	

Discussion

After some uncertainty, the research has now made it clear that there is in fact a small risk of intussusception associated with the rotavirus vaccines. However, it is also clear that the benefits of the rotavirus vaccine in reducing hospitalization and deaths in children from Rotavirus Gastroenteritis far outweigh the small risk of intussusception. Therefore, it is important to identify the factors that are still causing parental hesitancy in acceptance of the rotavirus vaccine. Acceptability of the vaccine and successful implementation of immunization is heavily influenced by parental opinions. The overall barriers to parental acceptance of the vaccine identified by this project include the fear of side effects, though not explicitly associated with

intussusception, the cost of rotavirus vaccine and the fact that it was not included in free public vaccination programs in some cases, the fact that the vaccine will not protect against all diarrhea, having the vaccine given in three doses, believing that the child is receiving enough vaccines, thinking that the vaccine is not useful, not wanting to administer a live vaccine to “young, vulnerable” infants, the newness of the vaccine, the narrow window of age when the vaccine is recommended, believing that the vaccine is not necessary, as immunity can be achieved from acquiring the virus itself, needing to evaluate data before accepting the vaccine, believing that vaccination will induce the development of a stronger mutated virus, believing that the holistic approach is the best way to prevent Gastroenteritis, and a perceived lack of disease threat.^{7, 17, 26, 28} Along with these barriers, two other factors were found correlated with parental vaccine hesitancy and they included having more than one child in the family and a parent that did not live with a partner.⁷ Despite the various barriers, however, it was interesting to find that if a medical provider recommended the vaccine, parents were likely to accept it for their children.^{7, 26, 28} This recommendation is likely to meet with the most success when it is accompanied with “[a] skillfully navigated, personalized discussion between an interested mother and pediatrician, employing sensitivity to a mother’s specific technical understanding and personal concerns on this topic.”²⁸

It is important to note that a key theme that was identified amongst parental rotavirus vaccine hesitancy was the lack of awareness of the seriousness and burden of viral Gastroenteritis.¹⁷ It was identified that the more serious the disease was perceived, the more receptive parents were towards getting the rotavirus vaccine for their children.¹⁷ Therefore, as it was recommended by Patel et al.²⁶ and Lugg et al.¹⁷, we too recommend an increase in parental awareness and knowledge of the burden of Gastroenteritis in order to increase the acceptance of the rotavirus vaccine.

With respect to one of the barriers identified as “the narrow window of age when the vaccine is recommended,” several researchers have suggested removal of age restrictions on the rotavirus vaccines, especially in countries with high Gastroenteritis mortality.⁴ With the removal of age restrictions on the RV1 vaccine in England, Clark et al.⁴ estimated “375 (136-1900) fewer RVGE admissions for every additional intussusception admission, and 88 (18-852) fewer RVGE deaths for every additional intussusception death.”⁴ Similarly, Flannery et al.⁹ outlined WHO’s Strategic Advisory Group of Experts on Immunization (SAGE) recommendation from 2012 for the “removal of upper age limits for administration of each dose of rotavirus vaccine.”⁹ Likewise, Patel et al.²⁵ suggested an “unrestricted schedule whereby rotavirus vaccine would be administered with DTP vaccine up to 3 years of age.”²⁵ These suggestions are all based on evidence supporting the fact that additional Gastroenteritis disease and deaths could be prevented with increased vaccine acceptance with a small increase in intussusception cases. Therefore, as it was believed by Clark et al.⁴, Flannery et al.⁹ and Patel et al.²⁵, we too believe that removal of the age limits will increase rotavirus vaccine acceptance.

Limitations identified in this Systematic Review include a literature search with a narrow number of databases for the identification of potentially eligible studies along with the possibility of missing critical information by filtering for English-only articles.

In summary, this Systematic Review was able to identify key barriers that are still causing parental rotavirus vaccine hesitancy, despite its many benefits. Now that these factors are identified, the next step is to address these concerns by increasing parental awareness of disease burden, removing rotavirus vaccine age limits, and educating parents on vaccine myths in order to increase parental acceptance of the rotavirus vaccine and decrease Gastroenteritis disease and deaths.

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