THE INTRODUCTION OF ROTAVIRUS VACCINE IN SWEDEN
- SETTING THE SCENE AND SHORT TERM OUTCOMES

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Introduction of rotavirus vaccine in Sweden – setting the scene and short term outcomes
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To Hanna, Iris and Martin

“Du blir aldrig färdig, och det är som det skall”
Tomas Tranströmer
ABSTRACT

Background
The rotavirus causes the most severe cases of viral gastroenteritis in small children worldwide, resulting in both high morbidity and mortality. The World Health Organization has recommended vaccination against the rotavirus since 2009 and the vaccine had been introduced by more than 90 countries in 2017. Since 2014, the vaccine has been offered to all newborn infants in Stockholm and Jönköping counties and it will be introduced into the national Swedish immunization program in September 2019. The aim of this thesis is to create a platform for the national implementation of the rotavirus vaccine in Sweden. It studies parental attitudes to the vaccine, examines the rare, but serious, adverse event of intussusception and looks at how the vaccine affects the burden of disease. The thesis also looks at social disparities in hospital use due to gastroenteritis.

Methods and Results
Different methods have been used to illustrate different aspects of the introduction of the rotavirus vaccine in Sweden in the five studies included in this thesis. The thesis highlights the importance of good relationships between child health care nurses and parents, sets the scene for safety surveillance, shows how paediatric care for gastroenteritis has been reduced by the rotavirus vaccine and also shows social differences in the utilization of paediatric care for gastroenteritis in small children.

Studies I and II focused on parental attitudes, conceptions and knowledge of the rotavirus vaccine during the implementation of the vaccine in Stockholm. Both studies included parents of newborn infants before the first dose of the rotavirus vaccine was offered.
Study I was a cross-sectional questionnaire study of 1,063 parents. The analyses were carried out using Pearson’s chi-square test and stepwise logistic regression in order to find the main predictors for vaccination or not. Most parents (81%) intended to vaccinate their child, 8% did not want to vaccinate and 11% were uncertain. Poor knowledge about the vaccine and the rotavirus infection, less trust in the child health care nurse, lower levels of education and having a child of up to five weeks of age were associated with being hesitant or unwilling to vaccinate.
Study II was a qualitative study of 10 in-depth interviews with parents. We identified four main categories that showed different conceptions of the rotavirus vaccine: to vaccinate without doubt, hesitant to vaccinate, risky to vaccinate and unnecessary to vaccinate.
Study III was a validation study of the diagnosis of intussusception in children under three years of age and it used data from the Swedish National Patient Register for the period 1987-2013. The aim of this study was to create a platform for further register-based follow-up studies of this rare, but serious, adverse event of the rotavirus vaccine. We manually reviewed 392 medical records that were randomly selected by The National Board of Health and Welfare from both pediatric and surgery care in Sweden, by using accepted international criteria of case definitions. A positive predictive value (PPV) of 89% was reached for the total study population and the PPV for the 240 children under one year of age was 88%.
Studies IV and V were register-based studies of national birth cohorts. In both studies the children were linked to their parents and the outcome was viral gastroenteritis for paediatric inpatient and outpatient care. In study IV the outpatient care was defined as visits at emergency departments (ED). In study V the outpatient care included both paediatric hospital care in the EDs as well as publically funded paediatric care outside of the hospital. The adjusted hazard ratios (HR) for a diagnosis of viral gastroenteritis were estimated by Cox regression.

Study IV consisted of 752,048 children below five years of age in Sweden from 2006-2012. Socioeconomic risk factors for the outcomes and national differences in geographical incidences of the outcomes were investigated. In total 3.1% children were admitted for inpatient care and 9.4% children received paediatric outpatient care at EDs. The adjusted HRs for both outcomes were increased when the mother was under 25 years of age, had a lower level of education, any parent had a psychiatric disorder, and/or when parents were born outside Europe. All these factors were associated with a lower level of health literacy. There were also considerable differences between the incidences of the outcomes between Swedish counties.

Study V consisted of 518,500 children aged two months to two years who were born alive between 1 March 2011 and 31 December 2015. The observation period ended in 31 March 2017. Children in Stockholm and Jönköping counties were compared with the rest of Sweden in order to study the effect that the rotavirus vaccine had on outcomes and on the social gradient. After adjustments for time trends and social indicators, reductions of 37% and 24% for inpatient care and 11% and 21% for outpatient care were shown in the Stockholm and Jönköping counties, respectively, compared to the rest of Sweden. The social gradient was maintained for inpatient care, but increased for paediatric outpatient care in Stockholm after the vaccine was introduced.

Conclusions
This thesis showed reductions of paediatric care of gastroenteritis in small children by the rotavirus vaccine in two Swedish counties. The thesis also showed that it is important to maintain our child health care organization built around child health care centers if we are to achieve high and socially equitable vaccine coverages for the rotavirus vaccine when it is nationally implemented. In addition, other interventions may be needed to support the introduction of the rotavirus vaccine so that we can reduce the impact that social factors have on its potential uptake. Such supportive interventions would include both targeted information and overall policy changes that focus on parents with low health literacy. The thesis also presented that the quality of the diagnosis of intussusception in children under three years of age in the Swedish Patient Register is high, as a prerequisite for further studies. A robust safety surveillance of the newly introduced rotavirus vaccine will also be important so that we can maintain the high levels of trust that the public already have in Swedish child health care nurses and the country’s preventive health care program.
LIST OF SCIENTIFIC PAPERS

I. Receiving early information and trusting Swedish child health center nurses increased parents’ willingness to vaccinate against the rotavirus infections
   Lina Schollin Ask, Anders Hjern, Ann Lindstrand, Ola Olén, Eva Sjögren, Margareta Blennow, Åke Örtqvist.
   Acta Paediatrica, 2017;106(8):1309-1316

II. Parental conceptions of the rotavirus vaccine during implementation in Stockholm: A phenomenographic study
   Eva Sjögren, Lina Schollin Ask, Åke Örtqvist, Margareta Asp.

III. Clinical presentation of intussusception in Swedish children under three years of age and the validity of diagnostic coding
   Lina Schollin Ask, Jan F Svensson, Ola Olén, Åke Örtqvist.
   Pediatric Surgery International. Online 2018 Nov 26

IV. Hospital care for viral gastroenteritis in socio-economic and geographical context in Sweden 2006–2013

V. The rotavirus vaccine effect on socioeconomic differentials of paediatric care due to gastroenteritis in Swedish infants
   Lina Schollin Ask, Can Liu, Karl Gauffin, Anders Hjern.
   Submitted manuscript
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<table>
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<th>Description</th>
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<tbody>
<tr>
<td>AGE</td>
<td>Acute gastroenteritis</td>
</tr>
<tr>
<td>CHCs</td>
<td>Child health centers</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>DTP</td>
<td>Diptheria Tetanus Pertussis (vaccine)</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency departments</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>LISA</td>
<td>Longitudinal integration database for health insurance and labour market studies</td>
</tr>
<tr>
<td>MMR</td>
<td>Measles mumps rubella (vaccine)</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>RR</td>
<td>Risk ratio, rate ratio (depending on the context)</td>
</tr>
<tr>
<td>RVGE</td>
<td>Rotavirus gastroenteritis</td>
</tr>
<tr>
<td>SAGE</td>
<td>World Health Organization Strategic Advisory Group of Experts (on immunization)</td>
</tr>
<tr>
<td>SEP</td>
<td>Socioeconomic position</td>
</tr>
<tr>
<td>SES</td>
<td>Socioeconomic status</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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1 PREFACE

The same day as this thesis was sent for print I worked as a paediatric consultant at a child health care center in the south of Stockholm. During the 15 minutes long visit I reminded myself of the challenge of these brief but important meetings with the child and the family. First, I examined the 5 weeks old child and talked to the parents in parallel. It was their first child and they had several questions about normal problems of newborns which the attending nurse and I tried to answer. I listened to the child’s heart, lungs and examined all that has to be screened for. Then, meanwhile the child health nurse weighed the child, I administered the medical record and checked that the growth curve looked good. Thereafter we had some minutes left for information of rotavirus vaccine and also about its potential adverse events. The parents were positive to the rotavirus vaccine so I prescribed it for administration the next visit.

In the end of this visit an important thought hit me: During these 15 minutes we were building trust. Trust in the preventive children’s health care, trust in the parents own capacity to take care of their child, trust in vaccines in general and that the health care and the child health care nurse will support the family when they need.

Then it was time for 12 more families the following three hours.

Illustration by Hanna Ask, 8 years old (2019)
2 INTRODUCTION

A new vaccine will be included in the Swedish national vaccine program in September 2019 to target the rotavirus infection, which is the main cause of severe diarrhea in small children. Swedish studies that focus on, preparing for, and evaluating, this vaccine are needed.

In high-income countries like Sweden, rotavirus infections are related to high morbidity, suffering of the infected children and the costs of both paediatric care and parents having to take time off work. However, deaths due to this infection are rare in these settings. In contrast, rotavirus infections can be fatal in low-income countries and are a major cause of global child mortality. The rotavirus vaccine has already been introduced into more than 90 countries and it is recommended by the World Health Organization (WHO). In 2014 it was introduced to the Swedish counties of Stockholm and Jönköping. The vaccine has been described as being cost-effective and efficient at reducing the burden of disease of gastroenteritis in small children. However, it differs from earlier vaccines introduced to Sweden in several ways. For example, the rotavirus vaccine is administered at an earlier age than the other routine vaccinations and it is administered orally instead of using intramuscular or subcutaneous routes. It can also result in a rare, but serious, side effect called intussusception. Perhaps the most important aspect of the rotavirus vaccine is that it does not target a mortal infection in settings such as Sweden.

The effect that the introduction of the vaccine will have on paediatric care and social differentials in paediatric care use due to gastroenteritis will be important. Another important factor will be the continued general trust that the public has in vaccines offered in Sweden. A number of factors will play an important role in a successful introduction of the vaccine and these will include how the vaccine is received by the parents, the safety surveillance of the vaccine and whether the vaccine will reach all socioeconomic groups. We have a robust platform for preventive child health care in Sweden, with high general trust in vaccines and high vaccination coverage overall. In addition, all socioeconomic groups can benefit from universal access to child health care. According to the United Nation’s Convention on the Rights of the Child, all children have the same rights to good and equal health. However, social gaps in children’s health have also been reported in Sweden, in common with the rest of the world.

The aim of this thesis was to create a platform for the national implementation of the rotavirus vaccine in Sweden. We have done this by studying parental attitudes about the vaccine, the adverse event of intussusception and the vaccine’s effect on the burden of disease. We also wanted to explore social disparities in the use of paediatric care due to gastroenteritis in Stockholm County where the vaccine has already been implemented.

“Give every child the best start in life”
The Marmot review 2010
3 BACKGROUND

3.1 ROTAVIRUS

Rotaviruses are very contagious and they cause gastrointestinal infections in all ages worldwide, with the most severe cases in small children.

3.1.1 The infection

The highly contagious rotaviruses affect most people during early life, leading to gastrointestinal infections with mild to severe symptoms. They sometimes result in severe complications [1, 2]. In European settings, the highest incidence and the most severe cases of rotavirus gastroenteritis (RVGE) have been described in children aged 6-24 months [2, 3]. A lower age peak occurs when RVGE is nosocomially transmitted compared to community-acquired infections [4, 5]. The peak age is also lower in low-income countries than high-income settings [6]. In the most recent Swedish study of RVGE, the median age of hospitalized children was 14 months. For community-acquired RVGE the median age was 15 months and for nosocomial infections it was nine months in the same study [5]. Other risk factors for more severe cases of RVGE, than young age, are preterm birth or a low birthweight, malnutrition, socioeconomic disadvantaged settings, impaired immunity or a co-infection with bacterial enteropathogens [7-9]. Rotavirus infections are rare in children younger than three months, probably due to transplacental maternal antibodies and/or breastfeeding. Both have been shown to be protective [10, 11]. Reinfections of rotaviruses during life are common, although the disease severity is reduced with each episode [12].

Figure 1. Summary of key symptoms and key information on rotavirus infections in Swedish infants
The main route of transmission for rotaviruses is the fecal-oral route and the virus replicates in the intestines [13]. The incubation period is 2–4 days and the duration of the infection is mostly 3–8 days, but up to eight weeks has been described in immunosuppressed children [1]. Most infected humans secrete the virus for 1–3 weeks, but about 20% can shed the virus for 4–8 weeks [14]. Diarrhea and vomiting are the dominant symptoms and fever often occurs. The infection usually starts with a short viremia and some infected children display a modest increase in transaminases [15]. The symptoms may differ from a mild infection to a life-threatening disease, with severe dehydration and extra intestinal manifestations. Swedish studies have described complications in 10-16% of hospitalized children with RVGE, such as seizures, encephalitis and severe dehydration. Studies have reported that hypertonic dehydration was the most common complication in Swedish children and, overall, complications were more common in children with community-acquired infections than those with nosocomial infections [4, 5]. Similar results have been reported from other parts of Europe [16-18]. It is rare for children to die from RVGE in high-income settings [19] but it is a major cause of child mortality in low-income settings [20]. Rinder et al reported a median duration of three days of hospitalization due to RVGE in Swedish children, but they only actually occupied hospitals beds for a median of 1.2 days, because they were often temporarily discharged after that and then followed up by phone until they were formal discharged [5].

The treatment for rotavirus infections mainly focuses on oral or intravenous fluid treatment of dehydration. Many families can manage oral treatment at home, but sometimes hospital care is needed [21].

### 3.1.2 The virus

The rotavirus is a ribonucleic acid (RNA) virus that demonstrates seasonal and geographical variations. The virus has a spherical shape and it is named after the Latin word for wheel, which is rota. It is a small, non-enveloped RNA virus of the family Reoviridae and consists of three layers: a core, an inner capsid and an external capsid [21, 22]. The genome contains 11 double stranded RNA segments that code for 12 different proteins [12]. When rotavirus infections occur, some proteins are expressed as antigens and the immune system responds to the infection by producing neutralizing antibodies of the immunoglobulin classes IgG, IgM and IgA [21, 23]. Laboratory methods to detect rotaviruses, such as enzyme-linked immunosorbent assays, reverse-transcriptase polymerase chain reaction and electron microscopy, are based on detecting the antigens of rotaviruses [24].

Some of the proteins related to the rotavirus are more important in the mechanism of the rotavirus infection, for example VP6, VP4, VP7 and NSP4. VP6 is developed from the inner capsid protein and is the most immunogenic protein. The protein NSP4 is an enterotoxin, which is important in the infectious mechanism of the symptoms of diarrhea, inducing secretory diarrhea due to excess chloride secretion through a calcium-dependent pathway [15, 25]. Figure 2 summarizes the structure of the rotavirus.
There are eight main groups of rotaviruses, named A-H and these are based on the specific antigens associated with the VP6-protein. In humans, rotavirus group A is the most common, but the groups B, C and H also occur [23, 26]. An additional ninth group “I” was recently found in dogs [27]. The nomenclature of the rotavirus is based on the surface proteins: VP4 (a P-protein, where P refers to protease sensitive) and VP7 (a G-protein, where G refers to glycoprotein). These two proteins can be combined in several ways to form different genotypes. There are currently more than 70 known G/P genotype combinations for rotavirus group A that have been shown to affect humans [22]. The five genotypes that cause 80-90% of all rotavirus infection in humans are G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8] [24, 28].

Two different kinds of immunological responses have been described. The classic immunological response of rotavirus group A is called a “homotypic response”, meaning that it provides immunological protection against the same genotype of the rotavirus infection or that is included in the rotavirus vaccine. However, reinfections by the same G or P genotypes may occur, thus corroborating the hypothesis of incomplete protection from rotavirus group A [23]. In addition, a “heterotypic response” has also been described, which is a reassorting mechanism between the 11 gene segments shown in both in vivo experiments and natural situations. This knowledge was important during the development of the rotavirus vaccine [29, 30].

There are worldwide differences in the geographic patterns and seasonal variations of the rotavirus genotypes [26]. The European Rotavirus Network is a European organization that carries out surveillance on the circulating genotypes of the rotavirus in Europe, while “GADS” is the global equivalent surveillance organization. The genotype G1P[8] has been most prevalent worldwide [31, 32]. In Sweden, G1P[8] has also been the dominating genotype in children under the age of five and the genotype G2P[4] has been the most common in children of five years and older [5, 32]. Rare genotypes driven by natural reassortment between different genotypes are described more commonly in Africa, Asia and
South America than Northern America, Europe and Oceania [31]. In addition, a seasonal epidemic pattern for rotavirus infections, with a peak during the winter months, has been shown in temperate high-income countries such as Sweden, but not to the same extent in middle- and low-income countries [33, 34]. In Sweden the peak period has been reported to occur between December and April, but yearly variations can occur [5]. In temperate countries, the peak season has often occurred simultaneously with other peaks in virus infections, such as the norovirus, influenza, respiratory syncytial viruses and other respiratory viruses. These have resulted in nosocomial transmissions and a heavy burden in general on health care during the winter period.

3.1.3 Burden of disease

Rotavirus related diarrhea is one of the leading causes of mortality in small children in low-income countries [20] and a great cause of morbidity in small children in more privileged parts of the world [5, 16, 35]. In 2008, approximately 37% of all deaths due to diarrhea in children under the age of five were attributed to rotaviruses [35]. Rotavirus vaccines have markedly decreased this burden of disease. In 2000, the global number of deaths due to RVGE in children under five years was approximately 528,000 [36]. Thirteen years later, when about 60 countries had implemented the rotavirus vaccine, RVGE deaths had fallen to 215,000 a year. [36]. Mortality due to RVGE occurs almost exclusively in low-income and middle-income countries and four countries accounted for approximately half of the deaths in 2013: India, Nigeria, the Democratic Republic of Congo and Pakistan [36]. In contrast, mortality due to rotavirus infections in high-income countries occur mostly among the elderly [37].

Deaths due to RVGE in children in high-income settings are rare [38]. In Europe the incidence of mortality in young children due to rotavirus infections, before the introduction of the rotavirus vaccine, was described as only 0.05-0.3/100,000 in the PROTECT study [3]. However, morbidity is also considerable in children living in more privileged countries, with the infection causing suffering, complications and hospitalization. The PROTECT study also stated that the incidence of children hospitalized due to RVGE was 30-1,190/100,000 people yearly and that 21% of these infections were nosocomially transmitted [3]. In Norway, Denmark and Finland the incidence of children hospitalized due to RVGE was reported to be 300-380/100,000 people before the vaccine was introduced [39-41]. In high-income settings such as Sweden, the rotavirus is responsible for about 50% of children being hospitalized due to all cause gastroenteritis (AGE) [5, 16, 35]. In 2015, the annual burden of disease in Sweden among children under the age of five was estimated to result in 2,100 children being hospitalized, 3,660 visiting emergency departments (EDs), 14,000 visiting primary care and 30,000 being treated at home [37, 42].
3.1.4 Summary

- Rotaviruses are very contagious RNA viruses that affect most people during their first three years of life, causing mild to severe gastrointestinal infections.

- Prolonged diarrhea from rotaviruses can lead to severe dehydration and other complications.

- Group A is the most common rotavirus group in humans and the genotypes G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8] cause the greatest number of human rotavirus infections.

- Rotavirus infections are a huge problem in low-income countries, as they cause both morbidity and mortality in children.

- Rotavirus infections also cause morbidity in high-income countries, but deaths due to rotavirus infections are rare in children in these settings.
3.2 ROTAVIRUS VACCINES

Rotavirus vaccines are offered in more than 90 countries worldwide, are administered from six weeks of age and have been described as being well tolerated. Most adverse events are mild, but there is a serious, but rare, adverse event called intussusception that has been described associated with the rotavirus vaccines.

3.2.1 A short history of the rotavirus vaccine

During the 1990s the first rotavirus vaccine was withdrawn and this was followed by large trials that led to the further development of the rotavirus vaccines that are now used worldwide. That first rotavirus vaccine was Rotashield® (Wyeth Lederle), which was introduced in the USA in 1998. It was withdrawn one year later because of an increased incidence in cases of intussusception (described in chapter 3.2.5) associated with the vaccine [43]. This led to the development of two new rotavirus vaccines, RotaTeq® (Merck and Co) and Rotarix® (GlaxoSmithKline). Several large safety and efficacy trials in the USA and Europe showed that these vaccines were both highly efficacious and safe [44-46]. In 2006, Rotarix® was licensed in Europe and Latin America and RotaTeq® was licensed in the USA. In 2008, Rotarix® was also licensed in the USA [47]. Figure 3 summarizes the timeline for rotavirus vaccines.

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Figure 3. Timeline as an overview of the rotavirus vaccine history.
3.2.2 Rotavirus vaccines currently in use

The monovalent Rotarix® (RV1) and the pentavalent RotaTeq® (RV5) are the most frequently used vaccines against rotavirus infections and have been reported to have the same efficacy and safety profiles. Both are oral live vaccines, attenuated through repeated passages in cell cultures (Vero cells) and should be kept at a temperature of 2-8°C. Both of these rotavirus vaccines should preferably be administered at the same time as the other vaccines in the program [48].

The two vaccines have both been used in Sweden and differ in the number of doses and number of targeted genotypes they cover. Rotarix® is produced from one human rotavirus strain that targets the genotype G1P[8] and is administered in two doses. RotaTeq® is produced from five reassortant rotaviruses from human and bovine strains that target the genotypes G1–G4 and P[8] and is administered in three doses [49, 50]. Stockholm used the RotaTeq® vaccine at first but changed to Rotarix® in July 2016. Only Rotarix® has been used in Jönköping. Both of these vaccines have been reported to provide similar protection from rotavirus infections and they have similar safety profiles [51]. Cross-protection of other genotypes than those specifically targeted by the vaccine have been described, but the exact mechanisms of these effects are not yet known [26, 29].

The age limits of the administration of the rotavirus vaccines are very important in order to avoid the natural peak age of the rare side effect of intussusception, described in Chapter 3.2.5. The time schedules for both vaccines are described below in Tables 1-2.

Table 1. Schedule for the rotavirus vaccines in Swedish child health centers [49, 50].

<table>
<thead>
<tr>
<th>Ages</th>
<th>6-8 weeks</th>
<th>3 months</th>
<th>5 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotarix®(2 doses)</td>
<td>Dose 1</td>
<td>Dose 2</td>
<td>-</td>
</tr>
<tr>
<td>Rotateq®(3 doses)</td>
<td>Dose 1</td>
<td>Dose 2</td>
<td>Dose 3</td>
</tr>
</tbody>
</table>

Table 2. Schedule for the final ages that rotavirus vaccines can be administered [49, 50].

<table>
<thead>
<tr>
<th>Ages:</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotarix®(2-doses)</td>
<td>12 weeks*</td>
<td>16 weeks**</td>
<td>-</td>
</tr>
<tr>
<td>Rotateq®(3-doses)</td>
<td>12 weeks*</td>
<td>16 weeks</td>
<td>22 weeks***</td>
</tr>
</tbody>
</table>

* The first dose must be given before 12 weeks of age
** The second dose of Rotarix® should preferably be given before 16 weeks of age and finished by 24 weeks of age.
*** The second dose of Rotateq® should preferably be given before 20-22 weeks of age. If necessary, the third dose can be administered up to 32 weeks of age.

A rotavirus vaccinated child can shed the vaccine strains in feces for several weeks and shedding is most common during the first week after the first dose. Immunosuppressed caregivers should take extra care with hygiene routines when caring for rotavirus vaccinated
infants [52]. Contraindications for the rotavirus vaccine are: a serious allergic reaction to an earlier dose of the vaccine, severe combined immunodeficiency, congenital metabolic disorders not compatible with consuming the sucrose contained in the vaccines, earlier intussusception or surgery for necrotizing enterocolitis or other congenital gastrointestinal malformations [49, 50]. Children born to women treated with tumor necrosis factor alpha inhibitors during pregnancy should not be offered the rotavirus vaccine, because these inhibitors may affect the child’s immune system. However, these changes are reversible [48]. HIV-infected children or children of HIV-infected mothers can be safely vaccinated [53]. Information on the efficacy and herd immunity of the rotavirus vaccines is available in the next chapter (Chapter 3.3). No significant differences in the impact on reductions in hospital care due to rotavirus gastroenteritis (RVGE) or acute gastroenteritis (AGE) between the two rotavirus vaccines available on the market have been shown [51, 54, 55].

Other vaccines are available in addition to the frequently used rotavirus vaccines, namely Rotarix® and Rotateq®. India introduced two indigenous rotavirus vaccines in 2016: Rotavac® (Bharat Biotech) and Rotasil® (Serum Institute of India). In addition, China and Indonesia have ongoing national development programs for new rotavirus vaccines [47]. The need to vaccinate newborn infants in high-risk areas before six weeks of age has also led to the ongoing development of a new rotavirus vaccine called RV3-BB. Birth is a great opportunity for interventions such as immunization in low-income and middle-income countries to reduce children’s mortality due to gastroenteritis [56]. For this reason, the RV3-BB vaccine is developed from an asymptomatic neonatal rotavirus strain that targets the genotype G3P[6] and the first dose is meant to be administered as soon as birth [56, 57]. However, more studies are needed before starting to use it, including whether this vaccine could also be offered to preterm children [58].

3.2.3 Rotavirus vaccines in both a global and a Swedish context

The rotavirus vaccine will be introduced in all Sweden in the near future, following the recommendations from the WHO since 2009 and the successful global implementation of the vaccine [59]. By the end of 2017, 91 countries had added the vaccine to their national immunization programs [60]. Almost half of these were low-income and middle-income countries. According to a review of the global introduction, the global coverage of the rotavirus vaccine was 89% for the first dose and 82% for the last dose, with the highest coverage (91% and 85% respectively) in countries with the lowest income levels [47]. Gavi, The Vaccine Alliance helps low-income and middle-income countries with financial resources to facilitate the introduction of this vaccine and the coverage data indicates good access to the vaccines. By the end of 2016, Gavi, The Vaccine Alliance had supported the introduction in 40 countries, with greatest efforts in African countries. The introduction has been slow in Southeast Asia and Eastern Europe, probably because those countries do not fit the criteria for financial support [47].

In high-income countries the overall rotavirus vaccine coverage was reported to be 84% for the first dose and 80% for the last dose. In comparison, the coverage in these countries for the diphtheria-tetanus-pertussis vaccines were 98% for first dose and 97% for the last dose. In low-income countries, the coverage of diphtheria tetanus pertussis vaccine (DTP), has been about the same as for the rotavirus vaccine [47].
Austria, Luxembourg and Belgium were the first European countries to introduce the vaccine in 2007. By 2017, 13 European Union countries had introduced the rotavirus vaccine [61]. France introduced the vaccine in 2013, but removed reimbursement for the vaccine in 2015 due to two cases of intussusception that led to death and were potentially related to the vaccine [62, 63]. This generated considerable media coverage and the vaccine has not been reimbursed by the French health care system since that date [62, 64]. However, the benefit-risk ratio of the rotavirus vaccination was concluded to be similar in France as in other European countries [65]. In 2009, Finland was the first Nordic country to start offering the rotavirus vaccination on a national basis, with Norway following in 2014. Both countries achieved high vaccine coverage quickly [47]. Iceland introduced the rotavirus vaccine in 2016 but Denmark has not offered it in the national immunization program yet.

In Sweden, the rotavirus vaccine was first introduced in 2014 in Stockholm County to children born after 1 March 2014 and in Jönköping County to children born after 1 July 2014. Two years after the implementation of the vaccine in Stockholm, the coverage for the first dose reached 85%. However differences were noted between socio-economic areas in Stockholm, with the lowest vaccine coverage in the most under privileged socio-economic geographic areas [66]. These socio-economic differences remained, but the gap was much narrower in the 2017 annual report when Stockholm achieved 90% coverage for the first dose of the rotavirus vaccine [67]. Jönköping reached 76% coverage in 2015 and 81% in 2017 [68]. Since 2016, several Swedish counties have also started to offer the vaccine to all newborn infants (Table 3). In 2019 the rotavirus vaccine will be included in the Swedish national immunization program.

Table 3. Swedish county councils that have introduced the rotavirus vaccine over the last five years.

<table>
<thead>
<tr>
<th>County Council</th>
<th>Date of introduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stockholm</td>
<td>2014 (born from March)</td>
</tr>
<tr>
<td>Jönköping</td>
<td>2014 (born from July)</td>
</tr>
<tr>
<td>Västra Götaland</td>
<td>2016 (born from September)</td>
</tr>
<tr>
<td>Örebro</td>
<td>2016 (born from September)</td>
</tr>
<tr>
<td>Västmanland</td>
<td>2017 (born from April)</td>
</tr>
<tr>
<td>Dalarna</td>
<td>2017 (born from May)</td>
</tr>
<tr>
<td>Gävleborg</td>
<td>2017 (born from July)</td>
</tr>
<tr>
<td>Värmland</td>
<td>2017 (born from November)</td>
</tr>
<tr>
<td>Sörmland</td>
<td>2018 (born from January)</td>
</tr>
<tr>
<td>Uppsala</td>
<td>2018 (born from January)</td>
</tr>
</tbody>
</table>
3.2.4 Prematurity and rotavirus vaccine

Preterm children are especially vulnerable to rotavirus infections and are, therefore, an important target for the vaccines [69, 70]. Rotateq® can be offered to preterm children born from gestational week 25 and Rotarix® to children born from gestational week 27. Both vaccines can be administered to preterm children six weeks after birth, according to the above mentioned schedule [49, 50]. In preterm children with increased vulnerability to apneas, the potential need for respiratory monitoring should be considered within 48-72 hours of immunization with the rotavirus vaccine [70]. There is also the risk that virus strains will be shed in the feces after immunization and this should also be taken in consideration if the child is still in the neonatal unit.

3.2.5 Adverse events, particularly intussusception

Adverse events occur with all vaccines and the most common ones for the rotavirus vaccine are mild. However, a small risk of intussusception, which is a rare but serious side effect, have been reported. The most frequent adverse events are similar to the mild symptoms of a rotavirus infection, such as diarrhea, vomiting and fever [49, 50]. Intussusception, has been described, with an increased risk of 1-6 cases per 100,000 immunized children [49, 50]. The mechanism of this association is still not clear.

Intussusception can also occur spontaneously in small children, without any association to the rotavirus vaccine and the peak age is 4-8 months. It is a condition where the bowel folds into itself, probably due to a “leading point”, causing a bowel obstruction [71]. This is illustrated in Figure 4. In countries similar to Sweden, the pre-rotavirus vaccine baseline incidence of intussusception in children of less than one year old has ranged from 27-101 cases/ 100,000 [43, 72, 73]. The condition has reportedly been more common in boys [74, 75]. A decreasing trend in the general incidence of intussusception diagnoses has been described in studies from both Denmark and USA. The reasons for this decrease is not known, but different hypotheses have been presented, such as organizational changes in health care and environmental or dietary changes affecting the incidence [73, 76, 77].

![Figure 4. Illustration of intussusception where the proximal part of the bowel is expanded because of the bowel obstruction.](image-url)
In the literature, the most frequently described symptoms of intussusception are “the classic triad” of vomiting, rectal bleeding/bloody stools and abdominal pain, although a wide range of symptoms may appear [74]. It is diagnosed by taking a medical history of symptoms, radiological techniques and/or surgery. Studies have reported that 10% of cases of intussusception are spontaneously reduced [72, 78] making the diagnostic process difficult in some cases. However, to avoid delays, and possibly surgery, it is important to come to a rapid diagnosis. Intussusception might be a life-threatening condition if hospital care is delayed or if the condition is not treated. The treatment is performed by radiological techniques, using liquid contrast enemas or air enemas, or surgery [79, 80]. About 14% of cases of intussusception required surgery in European studies [76] and 28% in the USA [78].

The WHO has pointed out the importance of performing national surveys of the diagnosis of intussusception when a country introduces the rotavirus vaccine. [81]. To standardize and facilitate the safety surveillance of the rotavirus vaccine, an international clinical case definition has been developed for the diagnosis of acute intussusception by the Brighton collaboration and this is presented in Table 4 [82, 83]. The diagnosis of intussusception has been validated in other countries, but not in Sweden. For example, in Canada 73% of diagnosed cases of intussusception fulfilled at least one of the three criteria [84], in Great Britain they fulfilled 81-86% [85] and in Switzerland it was 86% [72].

Previous surveillance studies on the relationship between intussusception and the rotavirus vaccine has been carried out using different methods, depending on resources, objectives and the timing of the study. Pre-vaccine monitoring of high-income settings has mainly been carried out using randomized controlled trials. Most of these studies have shown an increased risk of intussusception related to the rotavirus vaccine, as described above [86, 87].
**Table 4. Clinical case definition for the diagnosis of acute intussusception by Bines et al [83]**

<table>
<thead>
<tr>
<th><strong>Definite Intussusception (Level 1 of diagnostic certainty)</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgical criteria</strong></td>
<td>The demonstration of invagination of the intestine at surgery, <strong>AND/OR</strong></td>
</tr>
<tr>
<td><strong>Radiological criteria</strong></td>
<td>The demonstration of invagination of the intestine by either gas or liquid contrast enema, <strong>OR</strong></td>
</tr>
<tr>
<td>The demonstration of an intra-abdominal mass by abdominal ultrasound with specific features1 that is proven to be reduced by hydrostatic enema on post-reduction ultrasound, <strong>AND/OR</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Autopsy criteria</strong></td>
<td>The demonstration of invagination of the intestine</td>
</tr>
</tbody>
</table>

| **Probable Intussusception (Level 2 of diagnostic certainty) (Clinical criteria)** |  |
| 2 major criteria, **OR** 1 major criterion2 and 3 minor criteria |

| **Possible Intussusception (Level 3 of diagnostic certainty) (Clinical criteria)** |  |
| 4 or more minor criteria |

For any level:
- In the absence of surgical criteria with the definitive demonstration of an alternative cause of bowel obstruction or intestinal infarction at surgery (such as volvulus)

---

**Major Criteria**

1. Evidence of intestinal obstruction
   1. History of bile-stained vomiting **and either**
   2. Examination findings of abdominal distension and abnormal or absent bowel sounds, **OR**
   3. Plain abdominal radiograph showing fluid levels and dilated bowel loops

2. Features of intestinal invagination
   1. abdominal mass
   2. rectal mass
   3. intestinal prolapse
   4. plain abdominal radiograph showing a visible intussusception or soft tissue mass
   5. abdominal ultrasound showing a visible intussusception or soft tissue mass
   6. abdominal CT scan showing a visible intussusception or soft tissue mass

3. Evidence of intestinal vascular compromise or venous congestion
   1. passage of blood per rectum, **OR**
   2. passage of stool containing "red currant jelly" material, **OR**
   3. blood detected on rectal examination

**Minor criteria**

- Age 1 year and male sex
- Abdominal pain
- Vomiting3
- Lethargy4
- Pallor4
- Hypovolemic shock
- Plain abdominal radiograph showing an abnormal but non-specific bowel gas pattern

---

**Notes for Case Definition**

1 Target sign on doughnut sign on transverse section and a pseudo-kidney or sandwich sign on longitudinal section; 2 If 1 major criterion is rectal bleeding in the form of blood mixed with diarrhea then consideration should be given to infectious causes, such as E.coli, shigella or amoebiasis. In such cases 2 major criteria should be met.

**Notes for the criteria**

3 If the vomiting is bile-stained, it cannot be counted twice as a major and minor criterion;

4 Lethargy and pallor typically occur intermittently in association with acute spasms of abdominal pain. In patients with severe or prolonged intussusception, lethargy and pallor may become a constant feature associated with a deterioration in cardiovascular status and impending hypovolemic shock.

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3.2.6 Summary

- The most frequently used rotavirus vaccines are Rotarix® and Rotateq®, which are administered orally between six weeks to 24/32 weeks. They have similar profiles of safety and efficacy.

- The WHO recommends the introduction of the rotavirus vaccine and today the vaccine is offered in more than 90 countries. It will soon be offered across Sweden. In 2014 the vaccine was introduced in the Stockholm and Jönköping counties of Sweden. In September 2019 the vaccine will be included in the national immunization program.

- The most common side effects are mild, but a rare, but serious, adverse event called intussusception has been described, with an increased risk of 1-6 per 100,000 vaccinated children. National surveillance of this condition is needed when the rotavirus vaccine is implemented.
3.3 ROTAVIRUS VACCINE EFFECTIVENESS

Overall, the rotavirus vaccines have led to great reductions in child morbidity, mortality and health care costs worldwide [51]. The reductions have been larger in middle-and high-income countries than in low-income countries. Most studies of the vaccine impact have focused on laboratory-verified findings or hospitalized RVGE as the specific outcome measures, but there are also studies of the vaccines effect on AGE in general and outpatient care. The vaccine’s effect on hospital care has been reported to be most common in the youngest children and the protective effect of the vaccine has been shown to persist until at least the age of three [88].

3.3.1 The vaccine’s effect in high-income countries

The efficacy of the rotavirus vaccine has been shown to be high in high-income settings, specifically for hospital care due to RVGE and in general for AGE. [89]. According to a 2012 Cochrane review, countries similar to Sweden have reported reductions of: 80-84% of severe cases of RVGE, 70-73% of the rotavirus diarrhea of any severity, 42-51% of severe cases of AGE, 42-75% of AGE cases requiring hospitalization and 15-72% of AGE of any severity in children under the age of two [51]. Another review from 2013, with pooled data from six randomized controlled trials from both middle-income and high-income countries, reported reductions of 91-92% for hospitalized RVGE, 74% for all severities of RVGE and 41% for serious AGE [90].

Several Nordic and European countries have reported large reductions in hospital care due to RVGE and AGE after the introduction of the rotavirus vaccine. For example, just one year after the rotavirus vaccine was introduced in Finland, vaccine coverage had reached 90% and there was a decrease of 80% in RVGE hospitalizations and 54% of AGE hospitalizations in children under the age of one. The hospital outpatient care figures for the same study and age group were a reduction of 79% for RVGE and 13% for AGE [91]. Five years after the introduction of the rotavirus vaccine, there were even bigger reductions in Finland, with a reported decrease of 93% in hospitalized RVGE cases, 69% in hospitalized AGE cases and 91% in hospital outpatient RVGE cases. In contrast, another study reported a 6% increase in AGE in hospital outpatient cases five years after Finland introduced the rotavirus vaccine [92]. Another Nordic example is Norway, which achieved coverage of 82% one year after the national introduction of the rotavirus vaccination, together with a 86% decrease in RVGE and a 35% decrease of AGE in children under the age of five [93]. Belgium, one of the first European countries to offer the rotavirus vaccine, which was added to its national program in 2006, also achieved a rapid uptake like the Nordic countries. Two years later in 2008 it had achieved coverage of 91%. Belgium also reported that RVGE cases fell by 80-90% and there was a 36% fall in AGE hospitalized children. These figures were based on all children eligible for the vaccine [94, 95].
Studies from many other European countries, together with Australia, Canada and the USA, have presented consistent results that showed great reductions in both RVGE and AGE after the introduction of the rotavirus vaccine, as described above [55, 96-108]. Similar results of great reductions of RVGE have been presented in France and USA despite lower vaccine coverages in both countries. The IVANHOE study from France presented a relative risk reduction of 98% due to RVGE hospitalizations in children under the age of two in a French region, two years after the rotavirus vaccination was introduced, despite moderate vaccine coverage of only 47% [109]. The USA has reported similar results of decreased laboratory findings of rotavirus infections after vaccinations were implemented, despite low regional rotavirus vaccine coverage [110]. However, in both of these cases the follow-up period was only two years after the vaccine was introduced, meaning the results might have been affected by seasonal variations of more or less contagious rotaviruses. Both studies were also performed in rather small geographic areas.

3.3.2 The vaccine’s effect in middle-income countries

Smaller, but still large reductions, of RVGE and AGE in small children have also been shown by the rotavirus vaccine in middle-income settings [111-113]. For example, in Mexico, there was a general reduction of 30-40% in hospitalizations for diarrhea after the introduction of the vaccine. The greatest effect was in children under the age of one and the vaccine coverage for the first dose was 89% [114, 115]. Another example from other parts of Latin America showed reductions of approximately 80% in children with severe RVGE during their first year of life [116].

3.3.3 The vaccine’s effect in low-income countries

In low-income countries the effect that the rotavirus vaccine has on hospital care due to gastroenteritis has been found to be smaller than in middle-income and high-income countries [6, 117-119]. Overall, the decrease of severe RVGE in children under the age of two in low-income countries has been shown to be 41-63% and for AGE it was 15-42% [51]. However, there is a high mortality from diarrheal diseases in low-income settings and, therefore, the vaccine’s effect on mortality may be even more important than in other parts of the world [111, 120-123]. Sub-Saharan Africa has particular issues with deaths from diarrheal diseases [120]. The smaller vaccine effect on hospital care due to gastrointestinal infections in low-income countries than middle-income and high-income countries is probably related to several factors and different measurement methods of the outcomes. Important factors that affect a lower vaccine effect in such settings in general can include: limited access to healthcare and oral dehydration during gastrointestinal infections, a malnutrition status of children, different genetic susceptibility to the vaccine and reactions by different distribution of rotavirus genotypes. Low-income countries have a greater burden of disease in general and reactions to rotavirus infection may be accompanied by infections caused by other pathogens and exacerbated by bad sanitary conditions, [6, 124-126].

3.3.4 Indirect benefits of the rotavirus vaccine

In addition to the rotavirus vaccine’s direct effects on reducing the hospital care needed for RVGE and AGE in small children eligible for vaccinations, additional indirect protection in older children and adults has also been shown, called herd immunity [127]. This has been
described in all types of income settings [88, 94-97, 108, 112, 128-131]. In high-income countries, mortality from rotavirus infections is seen in older age groups and this means that they benefit from the introduction of the rotavirus vaccine [37]. For example, an American study showed a 50% decline in laboratory-verified rotavirus infections in adults during the peak rotavirus season in 2008-2010 [132].

### 3.3.5 Extra-intestinal benefits of the rotavirus vaccine

The extra intestinal impact of the rotavirus vaccine, which is called the “rotavolution”, has recently become a growing field of debate and research [133]. It has been suggested that the effect of rotavirus infections depend on host susceptibility, host genetics and the interaction with the intestinal microbiota. The effects has been suggested going far beyond the classic gastrointestinal symptoms which are just the top of an iceberg, shown in Figure 5. A review from 2019 stated that the currently known rotavirus infection pathology is just the tip of an iceberg and that new questions about the impact of the rotavirus vaccine impact have emerged. For example, it has been suggested that rotavirus infections can trigger autoimmune diseases. Therefore, rotavirus vaccines might lead to decreased incidences of autoimmune related conditions such as diabetes mellitus and coeliac disease, due to immunological susceptibility and mechanisms. These hypotheses need to be explored further [133].

![Figure 5](image.png)

Figure 5. The “iceberg” model of rotavirus infections according to Gomez-Rial et al [133]. Printed with permission from Dove Medical Press

Another example of the extra intestinal effects by the rotavirus vaccine is the decreased reduction in the incidences of seizures and seizure-related hospitalizations in vaccinated children, as presented in observational studies [134, 135]. However, these results were questioned in a recent population-based study from the UK that used more robust statistical methods and did not find any evidence of a decrease in seizures [136]. There has also been speculations about a broader protection from infections in general, through a so-called “non-specific vaccine effect” by the rotavirus vaccine, similar to what has been described for the Bacillus Calmette-Guérin vaccine. This “non-specific effect” is thought to be caused by the
live attenuated form of the virus in the vaccine and how it stimulates the innate immune system in the child. Further research is needed on this [137].

3.3.6 Cost effectiveness of the vaccine

The rotavirus vaccine has been described as being cost-effective in all settings, due to its direct and indirect effects [42, 89, 92, 138-147]. Sweden’s public health agency performed a cost-effective analysis as a platform for the future national implementation of the vaccine, based on a model from England and Wales. This model based its calculations on a vaccine coverage of 95% and a time-period of six years after the implementation of the rotavirus vaccine in Sweden. It concluded that the introduction of the vaccine could generate savings of 120 million Swedish crowns per year [148].

3.3.7 Effects on seasonal patterns and a potential shift in genotypes

The rotavirus vaccine has been described as being cost-effective in all settings, due to its direct and indirect effects [42, 89, 92, 138-147]. Sweden’s public health agency performed a cost-effective analysis as a platform for the future national implementation of the vaccine, based on a model from England and Wales. This model based its calculations on vaccine coverage of 95% and a time-period of six years after the implementation of the rotavirus vaccine in Sweden. It concluded that the introduction of the vaccine could generate savings of 120 million Swedish crowns per year [148].

A reduced and delayed season for rotavirus infections [110, 149, 150], disruption of the epidemiological pattern with seasonal peaks [151] and a potential shift of genotypes [98, 152, 153] have been reported. Studies from the USA and Belgium have shown that the rotavirus season was delayed and that the peak was shorter [102, 149, 154].

Several countries have reported an increase in the genotypes associated with G12 (mainly G12P[6] and G12P[8]) [26, 32], and in Canada an unexpected increase of the proportion of rotavirus group A G10 was reported when the post-vaccine period of 2012-2013 was compared with the pre-vaccine years of 2010-2011 [155]. These findings suggest that the introduction of the vaccine has the potential to shift the rotavirus genotypes. On the other hand, a natural variation of the genotypes through genetic reassortment and interspecies transmission could be a possible explanation for these short-term findings of changes in the genotype distribution. Long-term follow-up studies are needed [32, 156-158]. The latest report from the European Rotavirus Network did not present any evidence of emerging strains and it stated that the circulating rotavirus genotypes and the seasonality of the rotavirus infections were similar to observations prior to the vaccine’s introduction [158].
3.3.8 Summary

- The rotavirus vaccine has led to great reductions in child morbidity, mortality and health care costs worldwide due to rotavirus gastroenteritis and all cause gastroenteritis.

- Reductions in hospital care have been reported to be larger in middle-income and high-income countries than low-income countries. However, the vaccine has had remarkable effects on reducing mortality rates in low-income countries.

- Herd immunity has been described among older age groups who are not eligible for the vaccine. This has been achieved through indirect protection, due to a reduced spread of rotavirus infections after the introduction of the rotavirus vaccines.

- The rotavirus vaccines have been shown to be cost-effective in all income settings.

- A seasonal shift, and a reduced seasonal duration of rotavirus infections, has been described, following the introduction of the rotavirus vaccine. However, there is no evidence yet of changing genotypes of rotaviruses following that introduction.

- Several extra intestinal benefits from the rotavirus vaccine has been described and these are subjects for further research.
3.4 THE SWEDISH CONTEXT
The Swedish population have a unique trust in the preventive child health care system, in vaccines in general and have a universal access and utilization of the preventive child health care. When a new vaccine is due to be introduced, it goes through a very thorough process, which includes groups of experts carrying out detailed analyses of mandatory criteria that must be met. The vaccine has to be efficient with regard to reducing the burden of disease and it must be cost-effective and sustainable from an ethical and humanitarian point of view.

3.4.1 Public trust in the Swedish child health care system
Sweden is unique as it has achieved high vaccine coverage, enjoys the general public’s trust in vaccines and provides universal access to child health care, with frequent visits during early childhood within all socioeconomic groups. Since the 1930s, Swedish child health centers (CHCs) have been responsible for providing preventive child health care for children aged 0-6 years and the child health care nurse plays a key role. These visits are free of charge and 99% of the children in Sweden attend [159]. It has been reported that children attend a mean of 14 face-to-face appointments with the child health care nurse during the first 18 months of life in Sweden [160, 161]. These frequent visits form the platform for close relationships between the family and the child health care nurse. In Sweden both pediatric and district nurses work in the CHCs. In addition, children see pediatricians and family doctors for the 3-4 physical examinations carried out during the preschool years [159]. Pediatric nurses usually work for so-called focused CHCs, while district nurses sometimes work with patients of all ages and these organizations are called mixed CHCs. The focused CHC model has shown greater benefits for both families and nurses than the mixed CHC model [162, 163].

The universal program of child health care that has been developed in Sweden during recent years is similar to the UK’s Healthy Child Program [164] and it comprises three levels of child health care [165]. The first level is universal and basic and meant for all children. The next two levels also include child health care and support for children with extra needs. None of the levels are fixed, as families and their children may have different needs during different times of their lives. Extra support needs can for example include additional home visits for vulnerable families. Figure 6 illustrates the Swedish national child health program.

<table>
<thead>
<tr>
<th>Health monitoring - to follow children's health, development and living conditions</th>
<th>Calls, guidance and support as needed</th>
<th>Additional guidance and support in collaboration with other health care providers and social services.</th>
</tr>
</thead>
</table>

Figure 6. Schematic illustration by Schollin Ask, of the three levels of the Swedish national child health program [165].
Vaccine coverage is high all over Sweden. For example, in 2017, 96% of two-year-old children were vaccinated against measles, mumps and rubella (MMR) and 97% had received the *Haemophilus influenza* type B vaccine, the Polio vaccine and three doses of the diphtheria, tetanus, bordetella pertussis vaccine [166]. The Swedish national immunization program includes 10 vaccine-preventable diseases so far (2017): diphtheria, tetanus, bordetella pertussis, polio, *haemophilus influenza* type b, invasive pneumococcal disease, measles, mumps, rubella and the human papillomavirus vaccine for girls. It is also recommended that children at risk are vaccinated against tuberculosis, hepatitis B and influenzae [166]. Decisions about the national immunization program are made by the Government. The Swedish national immunization program is shown in Table 5 [166]. Recently, the hepatitis B vaccine has been offered to all children at three, five and 12 months of age, following additional decisions taken by the county councils.

**Table 5.** The Swedish national immunization program [166]

<table>
<thead>
<tr>
<th>Vaccine against:</th>
<th>Child health care</th>
<th>School health</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>5 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 1</td>
<td>Dose 2</td>
<td>Dose 3</td>
</tr>
<tr>
<td>Dose 1</td>
<td>Dose 2</td>
<td>Dose 3</td>
</tr>
<tr>
<td>MMR</td>
<td></td>
<td>Dose 1</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6, below, presents the reported overall coverage for each vaccine in Sweden during the years 2013-2017 [166]. All the diseases included in the national program are severe, and potentially fatal, for small children.

**Table 6.** Overall coverage for each vaccine in Sweden during from 2013-2017 [166]

<table>
<thead>
<tr>
<th>Vaccine against:</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTP and Polio</td>
<td>98.4</td>
<td>98.2</td>
<td>98.1</td>
<td>97.5</td>
<td>97.3</td>
</tr>
<tr>
<td><em>Haemophilus influenza</em> type b</td>
<td>98.3</td>
<td>98.1</td>
<td>98.0</td>
<td>97.4</td>
<td>97.2</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>97.6</td>
<td>97.5</td>
<td>97.4</td>
<td>96.6</td>
<td>96.5</td>
</tr>
<tr>
<td>MMR</td>
<td>97.4</td>
<td>97.3</td>
<td>97.5</td>
<td>96.7</td>
<td>96.7</td>
</tr>
<tr>
<td>Hepatitis B*</td>
<td>34.8</td>
<td>41.7</td>
<td>52.9</td>
<td>67.4</td>
<td>75.8</td>
</tr>
<tr>
<td>Tuberculosis**</td>
<td>24.9</td>
<td>25.8</td>
<td>23.6</td>
<td>26.4</td>
<td>24.8</td>
</tr>
</tbody>
</table>

*Hepatitis B is offered to risk groups. Since 2016 it has been included in the six-valent vaccine (diphtheria, tetanus, pertussis, polio, *haemophilus influenza* type b and hepatitis B.

**Offered to risk groups.
The actors involved in the distribution and surveillance of vaccines in Sweden are the child health care, school health, the county medical officers, the Public Health Agency of Sweden, the Swedish Medical Products Agency, the National Board of Health and Welfare and the Government.

3.4.2 How a new vaccine is introduced to the Swedish program

When a new child vaccine is about to be included into the Swedish national immunization program, a process of routine preparatory work and decision-making is mandatory. First, the Public Health Agency of Sweden considers if the vaccine fulfills the three necessary criteria in the Swedish Communicable Diseases Act (2004:168) [167]:

1. The vaccine should efficiently prevent the spread or reduce the disease burden of a communicable disease in the population or specified groups.
2. The vaccine should be cost-effective from a societal perspective.
3. The vaccine should be sustainable from an ethical and humanitarian point of view.

These three criteria are based upon 13 factors that need to be examined, which are also described in the legislation [167]:

1. The burden of disease in society, for health care and for individuals.
2. The expected vaccine impact on burden of disease, based on the epidemiology of the infection.
3. The number of vaccine doses needed to achieve a desired vaccine effect.
4. The targeted groups that will be offered the vaccine.
5. The safety of the vaccine.
6. The vaccine influence of county councils, counties and private care givers.
7. The vaccine’s suitability of combining it with other vaccines, already included in the national vaccination program.
8. The public’s possibility to accept the vaccine and its impact on attitudes of vaccines in general.
9. What other alternative preventive actions or treatments to the vaccine are available.
10. The cost-effectiveness of the vaccine according to costs and saved costs for society, county councils and municipalities.
11. The possibilities of surveillance of the vaccine effects according to point 1-10 above and estimated costs for this surveillance.
12. The need of information to the public in general and care givers in specific, and the estimated costs for these information actions.
13. Medical ethical and humanitarian considerations.

All these factors and criteria were explored and fulfilled with regard to the rotavirus vaccine in 2016-2017. In 2017 the Swedish Government decided that the rotavirus vaccine would be included in the national immunization program. The start date will be September 2019.

When a vaccine is included in the national immunization program in Sweden, all will be offered the vaccine, it will be free of charge and it will be registered in national vaccine registers [167].
3.4.3 Child health care in Stockholm and Jönköping

Stockholm and Jönköping county councils were first to offer the rotavirus vaccine in Sweden in 2014 and the child health care is organized similarly in both county councils. In Stockholm County there were 122 CHCs, 483 child health nurses and every child health nurse was responsible for an average of 69 newborn infants and 423 children per full-time equivalent post in 2017 [67]. In comparison, Jönköping County had 25 CHCs, 90 child health nurses and every child health nurse was responsible for an average of 58 newborn infants and 352 children per full-time equivalent post in the same year. All CHCs are focused CHCs in Jönköping. In Stockholm five CHCs are mixed CHCs and the rest are focused CHCs. Data on geographic differences in the health care burden was only available from Stockholm and this showed wide variations within the county council area, affecting the results of both vaccine coverage and preventive interventions [67]. The health care burden was also in accordance with a socioeconomic index in Stockholm. Figure 7 presents the variety of health care burden in Stockholm County in 2017.

Figure 7. Health care burden index of Stockholm’s municipalities. 1.0 indicates the mean of Stockholm County [67].
3.4.4 Summary

- The Swedish population has unique trust in the organization of child health care and vaccines in general

- In Sweden coverage of childhood vaccine is generally high

- There is a universal access to preventive child health care in Sweden. Most families visit the child health care centers frequently, regardless of socio-economic status.

- When Sweden is considering adding a new vaccine to the national vaccine program it goes through a thorough process that includes expert groups examining the mandatory criteria that must be met. The vaccine has to be efficient enough to reduce the burden of disease, cost-effective and sustainable from an ethical and humanitarian point of view.

- Stockholm and Jönköping counties organize their child health care in similar ways. In Stockholm County there are considerable geographical differences in the health
3.5 SOCIO-ECONOMIC DIFFERENTIALS OF CHILD HEALTH

"Addressing inequities is an ongoing process rather than an end that can be achieved."

The Swedish Commission for Equity in Health

3.5.1 Social determinants of health in children and the life course

Social inequity in health may begin as early as before birth, depends on differences in health status and is related to an unequal distribution of social determinants. Social determinants of health were defined by the WHO Commission on Social Determinants of Health as [168].

“The social determinants of health are the conditions in which people are born, grow, live, work and age. These circumstances are shaped by the distribution of money, power and resources at global, national and local levels.”

These differences are systematic, socially produced, unfair and often socially graded [169-171].

Early childhood is one of the most vulnerable periods in life in terms of the development of health inequities. A platform for future health is created during early childhood [168, 172-174] and less privileged parental socioeconomic status (SES) has been described as the most significant risk factor associated with poor health outcomes during childhood and later on in life [168, 175]. Even during intrauterine life, before birth, social determinants are important.

These include prematurity and low birth weight and socially graded patterns of these outcomes have been described [176]. Other examples of health inequities in child health related to family SES have been described for many different conditions during childhood, such as injuries and for chronic conditions with asthma as an example [177].

The socio-ecological model in Figure 8 by Bronfenbrenner explains the human development, starting with early childhood, and is divided into five socially organized subsystems [178]. The inner core environment for the child is the individual system with the surrounding microsystem. These two layers are the most important for the very early childhood. The individual system consists of, for example, age, health and gender-fixed factors that are difficult to change. The microsystem consists of, for example, the child’s immediate family members and other relatives, friends, their school and health services. The three outer layers consist of the so-called mesosystem, exosystem and macrosystem and they may all impact on each other and the inner layers. The mesosystem connects two or more systems where the child lives, for example it connects their school to their parents. The exosystem consists of greater systems, such as parental working schedules, the family’s social network, the neighborhood context and local politics. These all indirectly affect the child’s prerequisites. This system can buffer the child’s environment and development. It can also be degrading as, for example, parental work-related stress can affect the child. The outer layers are called the macrosystem and they consist of the cultural and social contexts and overall ideologies and decisions that influence all the underlying layers [178].
3.5.2 Preventive health care and the Swedish example

Preventive health care has the potential to buffer social gradients of health in children, but paradoxically they may also increase health inequity if they are not equitable accessible or distributed. There is an important difference between health care and preventive health care with regard to how they affect social disparities of health. Health care takes care of sick people, but has no important role in reducing social differences, unlike preventive health care. The Swedish CHCs are a good example of how preventive health care can buffer social disadvantaged groups [179, 180]. This results in a child health care system that provides higher and more equitable screening prevention and uptake of vaccines than other countries. In contrast, in Denmark preventive child health care is organized by primary care, which has other responsibilities than child health care and this is probably one reason for the lower uptake of preventive actions and vaccine coverage for MMR, compared to the other three Nordic countries of Sweden, Finland and Iceland, which provided dedicated child health services [160, 179, 181]. The key role and the gate keeper function that child health nurses play in preschool children’s health in countries with CHCs, such as Sweden, Belgium, Finland, Iceland, Netherlands and Norway, seems to be important for minimizing social gradients in health by providing preventive care [179]. A recent systematic literature review from 2019 of European and Australian structural and organizational differences of the preventive child health care stated that this issue matters when studying equity in vaccine
uptake. The Swedish structure with CHCs (also called well baby clinics) was obviously beneficial for lower levels of inequities of primary care and social differentials of vaccine uptake of MMR and DTP, compared to other regions with other structures of the preventive child health care [180]

3.5.3 Strategies for reducing social inequities in child health

Policy changes, legislation and a redistribution of resources are the most important focuses for interventions to reduce inequities of health, but interventions on an individual level are also needed. These two types of actions are referred to as directly and indirectly or individual or universal. Direct action targets social determinants, focusing on better health in social groups. Indirect action is the overall way of intervening on a policy level [182, 183]

A Swedish example of an intervention at a higher level than an individual one, with positive outcomes, was a recently extended home visiting program by public child health care nurses to a socioeconomic vulnerable geographic area with a lot of vaccine hesitant inhabitants in Rinkeby and Tensta, Stockholm [184]. This program improved the vaccine coverage for the MMR in this area [184-186]. The model was based on the concept of “proportionate universalism”, which means an acess and delivery of universal services proportionate to the degree of need. [187] The WHO’s Commission on Social Determinants of Health advocates the approach of proportionate universalism and the Swedish government has recently decided to apply this extended home visiting program to disadvantaged geographic areas across the country. Another example of proportionate universalism were the policy changes carried out in the UK from 2001-2011. Resources were redistributed with a focus on more disadvantaged areas, resulting in reduced health inequalities between different geographic areas [188]. A further example was the reduction of Swedish infant mortality during the first half of the 20th century. Political decisions drove through a more equitable redistribution of economic resources and universal social and health policies that targeted the most disadvantaged families in society [189].

Disparities in health related to social determinants are a global priority. [168, 190]. The WHO’s Commission of Social Determinants of Health reinforces the need for action to close the existing social gaps in children’s health worldwide, both between countries and within countries [168]. In 2016, the Swedish Commission for Equity in Health concluded that Sweden had come a long way towards equal health, but there was still a lot of work to do. They suggested establishing a Council for Good and Equitable Health in Sweden, which would promote research and evaluate health initiatives and establish a closer dialogue between research, policy and the health professions [191].

In summary, both overall policy changes and individual interventions are needed if equity of health is to be achieved and improved by preventive health care. Figure 9 by Bo Burström presents action points and the potential buffering interventions in grey circles and squares [192].
3.5.4 The importance of health literacy

An important factor in the development of disparities in child health and differences in health care seeking behaviors is parental health literacy. Health literacy is defined as an individual’s “capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions” [193]. The WHO has stated that [194]: “Health literacy is linked to literacy and entails people’s knowledge, motivation and competences to access, understand, appraise and apply health-related information in order to make judgement and take decisions in everyday life concerning health care, disease prevention and health promotion to maintain or improve quality of life during the life course.”

Mostly, health literacy is associated with education levels and the ability to read health information. However, it has been reported that the way health information is presented is too complex [195, 196]. Low literacy in caregivers has been shown to be associated with poor preventive care behavior and poor child health outcomes [195, 196]. The WHO has declared that we have a “health literacy crisis” in Europe and beyond. A European health literacy survey showed that nearly half of the adults from eight European countries had problematic health literacy skills [194]. The WHO has stated that: “Addressing health literacy requires a whole-of-society approach – many sectors, settings and actors need to work together to improve the health literacy of individuals and communities and to make environments easier to navigate in support of health and well-being.”

If we are to achieve the goal of equitable health related behaviors we need to improve health literacy and how we measure interventions that aim to enhance health literacy [194].
3.5.5 Summary

- Social inequity in health depends on differences in health status between different socioeconomic groups, related to an unequal distribution of social determinants.

- Early childhood is a vulnerable period in this context. The model by Bronfenbrenner explains human development, starting with early childhood by summarizing five socially organized subsytems.

- A less privileged parental SES has been described as the most significant risk factor associated with poor health outcomes during childhood and later on in life.

- Access to, and the use of, preventive health care, is important for inequity of health and equitable vaccine coverages in children. Swedish child health care is a good example in this context.

- Both overall policy changes and individual interventions are needed if equatable child health is to be achieved. A good example of proportionate universalism was targeting vaccine hesitant Somali communities in Rinkeby and Tensta.

- Health literacy is closely associated to health care behaviors and the unequal distribution of health.
3.6 VACCINES IN THE SOCIODEMOGRAPHIC CONTEXT

Worldwide there are vaccine coverage gaps and differences in vaccine effect between different socio-economic groups, both within and between countries. This also applies to the rotavirus vaccine and is an emerging question that needs to be dealt with.

3.6.1 Vaccines in general

Vaccines can be a powerful tool in reducing inequity of health in children, but only if they reach all groups of children to the same extent. Worldwide, childhood vaccines have made the greatest contribution to reducing childhood mortality, along with safe water, and have saved millions of lives. However, even though vaccines have improved public health and saved lives, we still need to close vaccine gaps, both between and within countries [168]. Differences in vaccine coverage have often been related to different attitudes and levels of vaccine hesitancy during recent years. The WHO has now stated that the reasons for suboptimal vaccine coverage and differentials in vaccine coverage are probably more complex and multifactorial. Its view is that vaccine coverage differences are also driven by social determinants in the same way as differences in health outcomes in children (described in Chapter 3.5), even in countries such as Sweden [197]. The WHO’s conclusions point to the need for all countries to further improve how they measure social determinants related to vaccine coverage. Boyce et al recently suggested that each country should analyze vaccine uptake data in relation to the following key determinants of inequities [197]:

1) Socioeconomic status
2) Geographical location
3) Education level of the parents
4) Ethnicity and migration status.

If the equity lens of vaccines is not applied, there is a risk of a widening health gap, with regard to the availability of vaccines and gaps in vaccine coverages in the future [198-201]. As Boyce et al declares [197]:

“The first step of understanding inequities in immunization is making inequities visible” and “To understand who not vaccinated helps to understand why.”

Groups who face extra risks for suboptimal vaccine coverage, incomplete vaccine status and therefore outbreaks of vaccine preventable diseases have been described globally. Migrant and refugee children are the groups at greatest risk [202]. Another marginalized group is the Roma population, who have lower rates of childhood vaccinations compared to other populations [203].

Globally, vaccine coverage tend to be higher in groups with a higher SES compared to groups with lower SES in all income settings. However, the contrary has also been shown for specific vaccines or in particular geographic regions or in groups within a similar context [204, 205]. In Europe, Denmark, Austria, Belgium and France have been described as regions with lower vaccine coverage, generally below 90% in preschool children, compared to other
European countries with vaccine coverage above this level [206]. In Austria, lower vaccine coverage has been shown to be more common when children are born to parents with lower levels of education, compared to parents with higher education. The same is true in England, Scotland, Belgium and Sweden, but to a lower extent. In England and Germany, lower vaccination rates have been reported in children who live with a single parent rather than cohabiting parents. In comparison, the same was not true in Ireland, Sweden and Spain. Compared to the most common pattern of lower vaccine coverage within groups of lower SES compared to groups of higher SES, the opposite was found for the measles vaccine in a study from Germany. In Germany regional differences has also been shown, with higher vaccine coverage for measles in children born in former East Germany than former West Germany [206].

Different factors are important for the social differentials of vaccine coverage in different settings [204, 205]. In all types of income settings combined parental education levels and income are important factors when it comes to vaccine coverage gaps. In low-income settings, an additional number of others factors have been associated with lower vaccine coverage compared to higher income settings, such as: poor household living conditions, being part of religious or minority groups, the presence of war and civil unrest, having migration status and having decreased social support [205]. However, the coverage gaps in those settings are slowly decreasing, due to support from organizations like Gavi, The Vaccine Alliance [207-209]. Factors affecting the social differentials of vaccine coverage in middle-income and high-income settings, compared to low income countries have additionally been described as concerns about vaccine safety, philosophical considerations, religious beliefs and rural living compared to urban living [205]. Parental beliefs, attitudes and ethical concerns have also been described as important factors in the middle- and high income settings [204, 205].

As mentioned in chapter 3.5.2, the structure and organization of the preventive child health care is of great importance for preventing inequitable vaccine coverages, where the Swedish organization and structure of well-baby clinics is a good example of smaller socioeconomic differences in vaccine coverage compared to other countries without well baby clinics [180]

### 3.6.2 Rotavirus vaccine in particular

There have been a few studies of differences in rotavirus vaccine coverage related to sociodemographic variables and the impact of the rotavirus vaccine on social gradients of health in children. These few studies have presented diverged results. In the UK, Hungerford et al reported that the largest effect from the rotavirus vaccine on hospitalized children due to AGE was in the most socially deprived communities, despite lower vaccine coverage in the same groups [210]. Meanwhile, in Belgium higher vaccination coverage in children of families with high SES compared to families with low SES have been reported [211]. However, an important factor in the Belgium study was that the rotavirus vaccine was not fully reimbursed by the Government. In contrast, studies from Israel and Canada presented a lower vaccine effect on hospitalization of AGE and RVGE of rotavirus vaccine in groups of lower SES compared to groups of higher SES [212, 213]. In a recent study from Canada, factors associated with whether the rotavirus vaccination schedule was completed were: High continuity of care, Receiving the maternal influenza vaccination (as a proxy for attitudes of
vaccines). Maternal immigration to Canada in the last five years and that The child had no siblings. The same study presented stepwise increased rotavirus vaccine coverage alongside the implementation of the vaccine [104]. This increase in rotavirus vaccine coverage has also been shown in both Stockholm and Jönköping counties. In Stockholm County, the total vaccine coverage of the rotavirus vaccine was 85% in 2016, but there was an obvious coverage gap between different socio-economic areas, with the lowest coverage reported from geographic areas with low socio-economic indexes (see Figure 10) [66]. In 2017 the overall coverage of the rotavirus vaccine in Stockholm was 90% and the gap had narrowed between the social groups and was more similar [67]. We do not have data on the differences in vaccine coverage by SES in Jönköping County. In Jönköping County the rotavirus vaccine coverage was 76% in 2015 with an increase to 81% in [68].

A recent study from the USA presented an opposite image, with low odds of initiating the rotavirus vaccine in groups with a higher SES. This could have been due to the fact that American health care is based on a health insurance system, but Sweden provides free health care for children. The odds for initiating the rotavirus vaccine in the USA were lower for preterm children, if the children were older age than 15 weeks when they started the DTP, if they were born to highly educated mothers and if they came from families with higher income levels. The odds for completing the rotavirus vaccination were higher in children born to highly educated mothers and lower in preterm children and children from families with no health insurance. There were also ethnic and regional differences when it came to completing the rotavirus vaccine [214].
3.6.3 Summary

- There are worldwide vaccine coverage gaps both within and between countries.

- The WHO has highlighted the importance of understanding these differences, depending on social determinants.

- Minority groups like migrant children or refugee children face extra risks for suboptimal vaccine coverage.

- Globally, vaccine coverage tends to be higher in higher SES groups than lower SES groups, but the opposite effect has also been shown for specific vaccines, in particular in geographic regions or in groups within a similar context.

- In Stockholm, geographical differences between the rotavirus vaccine have been shown, with lower vaccine uptake in areas with lower levels of SES. This has also been shown in other parts of the world. In America, which has a different health system, based on insurance, the opposite was shown.
3.7 PARENTAL VACCINE ACCEPTANCE

Whether parents decide to vaccinate their child is a multifactorial and complex process. Lately, we have seen reductions in public trust in vaccines worldwide. This has been referred to as a “vaccination backlash” or a “crisis of public confidence”. This emphasizes the need to understand the underlying determinants for parental vaccine decisions and how to build public trust through transparency in communicating the facts about childhood vaccines.

3.7.1 Different aspects of parental vaccine acceptance

Most parents accept vaccines for their children [215] with different underlying arguments and degree of acceptance. In addition, it is not always as easy as saying that parents are for or against vaccines [215-219]. Figure 10 by Julie Leask (reproduced with the kind permission of the author) summarizes and describes different parental ways of accepting vaccines. This pyramid of vaccine acceptance is based on a 2016 paper by Benin et al and a literature review from 2012 [216, 218]. The pyramid shows that while most parents accept fully vaccines, a smaller proportion partially accept vaccines and a minority of only 1-2% refuse vaccines. The accepting group ranges from unquestioning acceptors to cautious and hesitant acceptors. Cautious and hesitant acceptors have expressed many concerns, but still completed the vaccine schedule [216, 218]. The parents that partially accepted vaccines were also called “cherry-pickers” in the review, because they commonly accepted some, but not all, of the vaccines in the program. They also searched for a lot of additional vaccine information. Lastly, the smallest group was described as “the decliners” and they were hard to reach with information. This group included the small group of anti-vaccination activists [216, 218].

Figure 10. Illustration by Julie Leask of the different ways that parents accept vaccines, with reference to Leask et al BMC Pediatrics 2012 and Benin et al Pediatrics 2006 [216, 218].
3.7.2 Vaccine hesitancy

The concept of vaccine hesitancy is a relatively new term. We need to explore this further to understand the underlying parental factors that drive the decision making process for vaccination and to be able to communicate about vaccines [219-222]. The WHO’s Strategic Advisory Group of Experts (SAGE) on Immunization, established a working group to focus on determinants of vaccine acceptance. This group has defined the term vaccine hesitancy as [215]: “A behavior, influenced by a number of factors including issues of confidence (do not trust vaccine or provider), complacency (do not perceive a need for a vaccine, do not value the vaccine), and convenience (access). Vaccine-hesitant individuals are a heterogeneous group who hold varying degrees of indecision about specific vaccines or vaccination in general. Vaccine-hesitant individuals may accept all vaccines but remain concerned about vaccines, some may refuse or delay some vaccines, but accept others; some individuals may refuse all vaccines.”

The WHO SAGE Working Group on Vaccine Hesitancy has summarized determinants of vaccine hesitancy in a model, shown in Figure 11 [215, 222]. This model has three key domains: 1) Contextual influences, 2) individual/ group influences and 3) vaccine and vaccination specific issues [215].

Figure 11. The key determinants of vaccine hesitancy by SAGE. Printed with permission from Elsevier [215, 222].
In addition, Larsen et al described the three key domains more specifically in a review from 2014 on global vaccine hesitancy [222]. The **contextual influences** were described as levels of SES, levels of education and influences from media. All these contextual influences acted as both barriers and promotors for vaccines, depending on the setting and the context. The **vaccine specific issues** were described as costs, knowledge and access to vaccines. All three had different influences, depending on if partial or full vaccination were considered. For the key domain of **individual/group specific influences**, social norms were described as important factors for vaccination decisions, such as levels of health knowledge and health behaviors. Knowledge of the preventable disease that the vaccine targeted, and believing that the targeted disease was severe, were identified as factors that promoted vaccination within the third domain of individual and group specific influences [222]. Specific parental factors that have been associated with vaccine hesitancy in previous studies are: safety concerns, concerns about giving a child too many vaccines at the same time and believing that the targeted disease was harmless and therefore it was unnecessary to vaccinate [222-230]. Studies have also shown that parents who refused to vaccinate their children tended to cluster geographically, possibly due to shared cultural beliefs [231-233].

In anti-vaccination groups, earlier concerns about vaccines have been described as questions related to mandatory vaccines, while current drivers for objecting to vaccines have been described as more multifactorial. For example, anti-vaccination groups have expressed concerns about the financial benefits derived by the vaccine industry, skepticism about scientific truths and concerns about giving vaccines to healthy people instead of treating people who were ill. They have also attributed adverse events to vaccines, even though the events were only coincidental. There have also been reports of groups of people who think it is unnecessary to vaccinate their own child, because other children have been vaccinated, and they can rely on herd immunity. These are just some of the issues that have decreased public confidence in vaccines [234].

### 3.7.3 Understanding vaccine hesitancy

Understanding vaccine hesitancy, and the complexity of underlying determinants of vaccine acceptance that have been described, is an emerging issue. Research on this subject has so far presented wide-ranging results by using various study designs and describing different outcomes and conclusions [222]. In addition, determinants of vaccine hesitancy often depend on the context where the studies have been performed. In Europe, the most important parental concerns have been described as concerns about vaccine safety [235, 236]. These concerns are probably more common when vaccine preventable diseases have already been eradicated through vaccination and there is more room to focus on the vaccines themselves instead of the targeted infections [234]. MacDonald et al stated that the decision process for vaccination was often intuitive and depended on beliefs and emotions in addition to facts. They pointed out that there is no single strategy to address vaccine hesitancy [237]. In the same paper they presented evidence for informed strategies for addressing vaccine hesitancy and improving vaccine uptake (see Table 7).
Table 7. Evidence informed strategies for addressing vaccine hesitancy and improving vaccine uptake. Printed with permission from Taylor and Francis group [237].

<table>
<thead>
<tr>
<th>Immunization Program Focus</th>
<th>Individual Patient Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Detect and address hesitancy in the population/subgroups</td>
<td>-Ensure health care professionals are aware of their impact on vaccine decision making</td>
</tr>
<tr>
<td>-Ensure all health care professionals know and use best immunization practices</td>
<td>-Don’t dismiss hesitant or vaccine refuser</td>
</tr>
<tr>
<td>-Use specific evidence-based strategies known to increase uptake</td>
<td>-Use effective parental discussion techniques</td>
</tr>
<tr>
<td>-Effective communication</td>
<td>-Use clear language and be aware of the effects of framing questions??</td>
</tr>
<tr>
<td>-Educate children on the importance immunization for health</td>
<td>-Reinforce the important role of community protection</td>
</tr>
<tr>
<td>-Work collaboratively</td>
<td>-Address pain at immunization</td>
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3.7.4 Information on vaccines

Even though there is a challenging new media landscape today, with the potential for global sharing of both information and concerns about vaccines [234], health care workers are still the most trusted advisors and influencers when it comes to vaccine-related questions [215]. Previous studies have shown that a good relationship between parents and healthcare workers promotes vaccinations [216, 218, 229, 238]. A recent Cochrane review highlighted the importance of communicating with parents about vaccines and discussed the different needs for information by different groups of parents. The same review also stated that the vaccine hesitant group needed more information than other groups [239]. It has been pointed out that hesitant parents often use additional information sources rather than health care professionals when making their decisions [223, 239]. Peters et al described three key main factors that were needed in order to trust the information about vaccines provided by individual health care professionals or institutions and regard them as credible: 1) perceptions of knowledge and expertise, 2) perceptions of openness and honesty and 3) perceptions of concern and care [240]. Other studies have also emphasized the importance of understanding what factors promote public trust in each context in order to build public confidence in vaccines [241-244]

New media sources have created new communication routes about vaccines. Previously there was only vertical communication between the expert and the consumer of the vaccine and coverage by traditional media, such as newspapers and TV news channels. Today, the communication is mostly horizontal, non-hierarchical and dialogue-based and it has been facilitated by the emergence of new media tools, mostly the Internet and social media. [234]. New media channels create opportunities for groups to be misinformed by possible anti-vaccine messaging. However they also provide the opportunity for health care institutions to reach people with serious and evidence-based information.
3.7.5 Historical examples of a decreased public confidence in vaccines

History has shown examples of decreased public confidence in vaccines ever since vaccines started to exist. There are many specific historical examples of events, misinformation or policy changes that have negatively affected public trust in vaccines. Two previous examples focused on suspected associations between vaccines and autism. One was a connection between vaccines in general and thiomersal, as organic quicksilver has been included in some vaccines to prevent bacterial contamination since the 1930s. The second was a connection to the MMR vaccine. However, both of these concerns were subsequently disproved [245, 246]. The suggestion by Wakefield in 1998 that autism was connected to the MMR vaccine still influences some anti-vaccine groups and are used in discussions about vaccines against the measles, even though the results were proved to be false and the published paper was retracted [247, 248]. Other examples of false historical rumors were statements by religious groups that the tetanus vaccine caused infertility during the 1990s and a 2003 rumor in Nigeria that the oral polio vaccine also caused infertility and was contaminated with the human immunodeficiency virus [234].

There are also examples of policy changes at a higher level and differences in vaccine schedules that have prompted the public to ask questions about vaccines [242, 249]. For example, the hepatitis B vaccine was withdrawn in France in 1998, because of suspected associations with multiple sclerosis, even though the WHO recommended that it should be included in vaccine programs [250]. This resulted in remaining low hepatitis B vaccine coverage for 10 years [251]. Another similar example was when the USA withdrew vaccines that included thiomersal, before evidence showed that this ingredient was not related to an increased incidence of autism [234]. This affected public trust in vaccines and lowered vaccine coverage and prompted a number of disease outbreaks at the time of the withdrawal and afterwards. It also created tension between the USA and global vaccine programs. The withdrawal of vaccines containing thiomersal also caused an unexpected temporary decline in vaccination against hepatitis B, which did not include thiomersal, in the USA around the time of the withdrawal [234].

In Sweden there have recently been debates and concerns expressed about the vaccine used against the H1N1 seasonal influenza in 2009 and the relation to developing narcolepsy in adolescents afterwards [252-254]. In addition, the introduction of the human papilloma virus vaccine for young girls has been questioned [255]. Discussions about vaccinating against measles in hesitant groups are also ongoing in Sweden [253, 256, 257].

3.7.6 Parental attitudes on the rotavirus vaccine in particular

Previous studies have mostly focused on barriers to childhood vaccine uptake or hesitancy among parents to vaccines other than the rotavirus vaccine. However, a few studies have been carried out in countries where the rotavirus vaccine has been included in the immunization program. These studies have shown that knowledge of rotavirus infections and belief in vaccines in general were associated with an intention to vaccinate [258-263]. Qualitative studies from the Netherlands and USA have raised concerns adding more vaccines, such as the rotavirus vaccine, into immunization schedules [259, 264]
3.7.7 Summary

- The way that parents decide whether to vaccinate their child is a multifactorial and complex process. It is important for health care professionals to understand their concerns in order to build trust and communicate with parents about vaccines.

- Loss of public trust in vaccines has taken place at various times since vaccines were introduced and there are plenty of historical examples of how public confidence in vaccines has affected the public trust.

- The WHO SAGE Working Group on Vaccine Hesitancy has summarized determinants of vaccine hesitancy and identified three key domains: 1) contextual influences, 2) individual/group influences and 3) vaccine and vaccination specific issues.

- Understanding vaccine hesitancy is crucial so that we can provide balanced information on vaccines. Evidence-based strategies for addressing vaccine hesitancy are presented above.

- The few studies that have explored parental attitudes to the rotavirus vaccine have shown that knowledge of rotavirus infections, and belief in vaccines in general, have been associated with an intention to vaccinate against the rotavirus infection.
4 AIMS

4.1 OVERALL AIM
To investigate the short-term effects of the introduction of the rotavirus vaccine in Sweden and to create prerequisites for a long-term evaluation of the vaccine’s impact in Sweden.

4.2 SPECIFIC AIMS
1) To investigate parental attitudes towards the rotavirus vaccine, during the implementation of the rotavirus vaccine in Stockholm County.

2) To evaluate the quality of the diagnosis of intussusception in children < 3 years of age in the Swedish National Patient Register.

3) To study socioeconomic risk factors for viral gastroenteritis in small children and present Swedish geographic differences on the incidence of the infection.

4) To study the effect of the introduction of the rotavirus vaccine on paediatric inpatient and outpatient care in Stockholm and Jönköping counties, due to viral gastroenteritis in small children.

5) To study if, and how, the introduction of the rotavirus vaccine affects the socioeconomic gradient of paediatric care due to viral gastroenteritis in small children.
### 5 SUMMARY OF THE STUDIES

<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Study design</th>
<th>a) Study population and b) Study period</th>
<th>Method/ Statistics</th>
</tr>
</thead>
</table>
| I     | Receiving early information and trusting Swedish child health center nurses increased parents’ willingness to vaccinate against rotavirus infections *(Published 2017 Acta Paediatrica)* **First author** | Observational cross-sectional study | a) N=1063 Parents of newborn babies under 12 weeks of age before they received their first dose of the rotavirus vaccine in Stockholm  
| II    | Parental conceptions of the rotavirus vaccine during implementation in Stockholm: A phenomenographic study *(Published 2017 Journal of Child Health Care)* **Second author** | Qualitative study                  | a) N=10 Parents of newborn babies of 4-6 weeks of age, before their first dose rotavirus vaccine in Stockholm  
| III   | Reliability of acute intussusception diagnosis coding is high among small children in the Swedish national patient register, a validation study *(Published 2018 Pediatric Surgery International)* **First author** | Population-based validation study. | a) N=392 Random sample of all children under 36 months in Sweden with their first diagnosis of intussusception  
  b) 1987-2013 | Descriptive statistics. PPV. |
| IV    | Hospital care for gastroenteritis in 0-5 year olds in socio-economic and geographic context: A Swedish national cohort study *(Published 2018, Acta Paediatrica)* **Second author** | National register-based birth cohort study. | a) N=752 078 Children under five years of age, born in Sweden from 2006-2012  
  b) 2006-2013 (pre rotavirus vaccine) | Multivariate Cox regression analysis. |
| V     | The rotavirus vaccine effect on socioeconomic differentials of paediatric care due to gastroenteritis in Swedish infants *(Submitted manuscript)* **First author** | National register-based birth cohort study. | a) N=537,479 Children from two months to two years of age, born 1st March 2011-31st December 2015  
6 MATERIAL AND METHODS

This section presents an overview of the methods used in each study. More detailed information is included in the respective paper. The text of study II below is more informative as it provides additional information to the paper.

6.1 STUDY I

This cross-sectional study was based on 1,063 questionnaires completed by the parents of newborn infants in September 2014. The questionnaire was distributed to all 133 CHCs in Stockholm County Council. The child health nurses distributed the questionnaire to the parents of newborn babies before the first dose of the rotavirus vaccine was offered. The questionnaire was based on one used in a Canadian study [258] and was used with the permission of the authors. Pearson’s chi-square test was initially used to determine the univariate analysis of associations between the questions, as exposure variables, and the outcome of “intention to vaccinate”. Then a stepwise logistic regression (N= 936) was used to identify the main predictors.

6.2 STUDY II

The study followed a descriptive, qualitative design with a phenomenographic approach [265]. This approach was chosen to study the width of parental perceptions of vaccinating their child against the rotavirus. The study aimed to investigate how parents expressed their conceptions of the phenomenon of the rotavirus vaccination. A purposeful sampling was used, with the intention of including parents who were positive to attend the study and were prepared to share their views. In order to optimize and expand the knowledge of the parents’ perceptions of the rotavirus vaccination, the participants were chosen consciously and deliberately. They were included by five different child health care centers, two families from each. All participants were interviewed before the first dose of the rotavirus vaccine was offered and when their baby was between four and six weeks of age. The number of study participants was limited to 10 for practical reasons. A pilot interview was performed to test the interview guide (presented in the paper), but this was not included in the total analysis because the baby was born before 1 March and its birth date was before the qualifying date for the rotavirus vaccine. The interviews were conducted in Stockholm County during spring 2014 and were preceded by written and oral informed consent. The interviews were then transcribed by the first author and analyzed by the first and last authors to describe the qualitatively different conceptions of rotavirus infections and vaccination. The co-authors were informed during the process. Partial analysis of the first transcribed interviews were performed, as the first interviews may have affected the subsequent ones, according to the phenomenographic approach. The first author’s preconception was consisting of experience of working as a child health nurse for many years including introducing new vaccines and vaccinating children but she had no experience of rotavirus vaccine in specific.
6.3 STUDY III

This was a validation study of the concordance between the diagnosis intussusception coded in the Swedish Patient Registry in children under three year of age and accepted international criteria of case definitions (Brighton collaboration criteria) [83]. The National Board of Health and Welfare selected a random sample of 500 cases diagnosed with intussusception from 1987-2003 by using codes in the ninth revision of the International Classification of Diseases (ICD-9) (560A) from 1987-1996 and the tenth revision (ICD-10) (K56.1) from 1997-2013. The cases that were included were randomly selected from both pediatric and pediatric surgery departments all over Sweden. This resulted in 392 medical records included in the analysis. A manual review of the 392 medical admission records was conducted based on the international criteria of case definitions in order to result in a positive predictive value (PPV). The procedure and main results are presented in Figure 16, in the result part of the thesis.

6.4 STUDY IV AND V

Both studies were register based cohort studies of national birth cohorts. Outcomes in both studies were viral gastroenteritis for paediatric inpatient and outpatient care. In study IV the outpatient care was set as ED visits but in study V paediatric outpatient care included both paediatric hospital care in the ED as well as publically funded paediatric care outside of the hospital. Viral gastroenteritis was defined by a main or a complimentary ICD-10 discharge diagnosis of A08-A09 in the Swedish National Patient Register, excluding the presence of a diagnosis of A04-A07. All of the socio-demographic register variables used in study IV and V are described in table 8. Children in both studies were linked to their parents through their personal identity number by linkage through the Multi Generation Register to further retrieve parental and familial characteristics.

In both study IV and V, estimated adjusted hazard ratios (HR) of person-time by Cox regression for a viral gastroenteritis inpatient care and outpatient ED care were performed.

In study V, the effect of the vaccination program was estimated by comparing children born in counties that had implemented the program in 2014 with those that had not. Furthermore, the effect of the program on the social gradients in rotavirus hospitalization within Stockholm was estimated by comparing before and after rotavirus vaccine introduction. The estimator “Difference-in Difference” (DiD) was used to estimate the effect of rotavirus vaccination program on paediatric inpatient and outpatient care for viral gastroenteritis and on the social gradients of the paediatric care, adjusting for the overall decreasing trend of hospital care in Sweden [266]. Sensitivity analyses were also performed in order to test if the results were affected by herd immunity.
Table 8. Overview of the covariates used in studies IV and V and national registers that were used

<table>
<thead>
<tr>
<th>Variables</th>
<th>National Register</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of birth</td>
<td>The Medical Birth Register</td>
<td>IV, V</td>
</tr>
<tr>
<td>Gender</td>
<td>The Medical Birth Register</td>
<td>IV, V</td>
</tr>
<tr>
<td>Prematurity/ gestational age at birth</td>
<td>The Medical Birth Register</td>
<td>IV, V</td>
</tr>
<tr>
<td>Birth order</td>
<td>The Medical Birth Register</td>
<td>IV</td>
</tr>
<tr>
<td>Maternal age at birth</td>
<td>The Medical Birth Register</td>
<td>IV, V</td>
</tr>
<tr>
<td>Maternal smoking during pregnancy</td>
<td>The Medical Birth Register</td>
<td>IV</td>
</tr>
<tr>
<td>Cohabitation or not during pregnancy</td>
<td>The Medical Birth Register</td>
<td>IV, V</td>
</tr>
<tr>
<td>Maternal and paternal country of birth¹</td>
<td>The Register of Total Population</td>
<td>IV, V</td>
</tr>
<tr>
<td>Linkage between children and their parents</td>
<td>The Multi-generation register</td>
<td>IV, V</td>
</tr>
<tr>
<td>Households receiving social welfare benefits</td>
<td>LISA²</td>
<td>V</td>
</tr>
<tr>
<td>Disposable Income of the household³</td>
<td>LISA</td>
<td>IV</td>
</tr>
<tr>
<td>Parental level of education⁴</td>
<td>LISA</td>
<td>IV, V</td>
</tr>
<tr>
<td>Place of Residency⁵ (the year before the child was born)</td>
<td>LISA</td>
<td>IV</td>
</tr>
<tr>
<td>Parental Psychiatric disorder</td>
<td>National Patient Register</td>
<td>IV</td>
</tr>
<tr>
<td>Parental disorder related to substance abuse</td>
<td>National Patient Register</td>
<td>IV</td>
</tr>
<tr>
<td>Outcome: viral gastroenteritis inpatient and outpatient emergency care</td>
<td>National Patient Register</td>
<td>IV, V</td>
</tr>
</tbody>
</table>

¹ Non-European (both parents born outside Sweden and at least one outside Europe), European (both parents born in Europe outside Sweden), mixed (one parent from Sweden and the other from outside Europe), Swedish (both born in Sweden)
²LISA=Longitudinal Integration Database for Health Insurance and Labour Market Studies
³Quintiles according to Statistics Sweden
⁴0-9 years (Swedish primary school), 10-12 years (upper secondary school), 13-14 years (short post-secondary education), >15 years (university degree)
⁵Major cities (Stockholm, Gothenburg, Malmö), other (predominately urban municipalities), rural

6.5 EPIDEMIOLOGICAL CONCEPTS AND STATISTICAL METHODS

Cross sectional study (study I): An observational study of a specific time period. Exposure and outcome are measured at the same time, no time variable is included [267].

Cohort study design (study IV and V): An observational study where time is included. A defined cohort is studied retrospectively or prospectively. The exposure is predefined and the association to the outcome is then compared between exposed and non exposed groups. This method is suitable for relatively common outcomes but also for rare exposures [272].

Stepwise regression model (Study I) A multivariate regression model, which automatically selects which variables to be included in the final model [267].

Cox proportional hazard regression (study IV and V): Cox regression model is also called proportional hazard regression model and is a survival analysis of the risk of acquiring the outcome, expressed as hazard function. This model takes time into account and estimates the ratio between hazard rates, which means the time to a specific outcome between two or more groups. The Hazard ratio (HR) is the risk ratio between an exposed and an unexposed population (hazard for the exposed/ hazard for the unexposed). Through the cox regression model other variables can be adjusted for in the
analysis (confounding factors), as for this and other so called multivariate regression models. This method requires that the hazards for both exposed and unexposed are reasonably proportionate to each other over time. This assumption can be tested using for example “Schonefeld residuals.” Unlike other regression models, this model does not build on any assumptions about the distribution of the outcome [268].

**Difference in Difference (DiD) design (Study V):** DiD is a quasi-experimental design that has long been used in economy to evaluate the effect of a policy [266]. The same principle can be used for evaluating the effect of public health interventions. In a simple DiD design, two groups (treated and untreated) at two time points (before and after the treatment) are observed (Figure 12). Based on the parallel trend assumption, which means there were no other factors that changed the difference between the two groups, the effect of the treatment can be estimated by comparing the differences between the two groups in the time after treatment to the differences before the treatment, i.e. difference in differences. In a regression framework, the effect of treatment can be estimated by the interaction term of treatment status and time.

![Figure 12. Illustration by Can Liu of the interaction analysis method difference in difference [266].](image-url)
6.6 SUMMARY OF QUALITATIVE CONCEPTS, RELEVANT FOR THE THESIS

Qualitative versus quantitative research

Different research questions are best answered by different research methods. For example, quantitative methods are needed when we want to know if one treatment is more efficient than another, if there are significant differences between the outcomes of different groups or how often an outcome occurs. In comparison, qualitative methods enable us to answer other kinds of questions, such as what something is, what a result means and how something happens. Qualitative methods are preferable when the aim is to understand variations in the perspectives of a phenomenon or to explain different experiences or values. Qualitative research focuses on understanding, rather than explaining, and could be used as both a hypothesis generating method for further quantitative testing of the hypothesis and a continuation of quantitative research by developing a deeper understanding of the results.

The researcher plays in a way a bigger individual role in qualitative than quantitative methods. The understanding of the subject before the research starts, and the interpretation of the results, are individual and have to be described and included in the process, in order to inform the reader’s understanding of the results and conclusions. This is a kind of bias in one way and is often called reflexivity (in Swedish: reflexivitet). In the majority of cases, there are many different possible ways of interpreting qualitative results. It becomes more difficult to reflect on findings critically if the researcher has a close relationship to the material and the subject and qualitative researchers need to be aware of this during the whole process. It is not a question of whether the researcher affects the results but how? The aim of qualitative research is to describe the opinions of the participants as clearly as possible. [269-271]

In qualitative research, the number of participants are often much smaller than in quantitative research and cohorts of 10-25 subjects are common. Quantitative research usually requires large numbers of data units, in order to find significant differences and in order to generalize the results to similar populations. In qualitative research, a large number of participants might result in superficial conclusions and an ability to understand the research questions deeply enough [269]

Figure 13 illustrates the qualitative research process and the important role that the researcher plays in this process.
Figure 13 presents the qualitative research process. Illustration by Schollin Ask with reference to Malterud Family practice 1993. Permission to use in the thesis from Universitetsforlaget [269].

**Preconceptions and confirmability**
The researcher has to be aware of the preconceptions (in Swedish: förförståelse) and stay as neutral as possible during the process in order to achieve confirmability (in Swedish: objektivitet, bekräftelsebarhet). The preconceptions consist of “the researcher’s backpack”, which includes the professional role of the researcher, the researcher’s knowledge of the subject, earlier experiences and the chosen theoretical framework. The preconceptions affect the data collection and the interpretations of the results. Therefore, the researcher has to describe this and be aware of this during the whole process. The preconceptions can be both a strength and a limitation for the research project. [269, 271].

**Theoretical framework and phenomenography**
The theoretical framework is the chosen perspective when collecting, analyzing, interpreting and presenting the data and a qualitative researchers need to choose which framework will work best for their study [269]. We chose the framework of phenomenography during our process. Phenomenography aims to describe different conceptions of a phenomenon and the goal is to be able to describe the variety of existing perceptions that the participants hold.

This is mostly described in descriptive categories (in Swedish: beskrivningskategorier). How these are related to each other are thereafter described in different sample spaces (in Swedish: utfallsrum). The descriptive categories gather conceptions of statements with similar meanings and the sample spaces are used to explore the relationships between the descriptive categories [272, 273].
The data collection
The data collection for qualitative research can be performed in a number of ways, including person to person interviews, focus group interviews or surveys that are filled in by the participants. The interviews are mostly recorded and then transcribed, preferably by the researcher themselves. In study II the first author performed in-depth interviews, also called semi-structured interviews. The interviews were based on themes that were developed by the research group and these were used as a memorandum, rather than a strict protocol, during the interview. The research group followed the data collection. The guide could be revised during the process and the interviews could be based on open questions, with the researcher adopting a flexible approach [269].

Systematic text condensation
The interpretation of the results has to be transparent and systematically analyzed. In study II we adopted systematic text condensation, which can be based on collected data or on the intuitive assessment of the researcher themselves. In our paper on study II the main author and the last author reported systematic text condensation that involved decontextualization and recontextualization based on four procedures [269]. These procedures were:

1) Getting an overall impression of the results: Reading the transcribed material and finding possible overall themes, trying to put the preconceptions and the theoretical framework alongside. Preferable more than one researcher should be involved in this process.
2) Identifying meaning units: Sorting out the text and separating irrelevant text from relevant text. A meaning unit is a piece of text and it can be short or long. The next step is coding, which is sorting out the meaning units related to the different themes in step 1. One meaning unit can fall into several codes. This step is a decontextualization of the results.
3) Condensation: The codes from step two are divided into subgroups of different aspects of the content of each code. Thereafter a condensate is created for each subgroup. A condensate is an artificial quote that includes the content of the subgroup.
4) Recontextualization: Categories are created as summaries of the condensed subgroups and are all given a suitable heading.

Reliability, validity and relevance
In qualitative research, reliability and validity are important when it comes to describing honest and systematic data collection and the research process. Reliability, or dependability (in Swedish: pålitligthet/rimlighet), is about whether the instruments that are used (the researcher and the technical equipment) are reliable. The validity (in Swedish: validitet), is about how to use the results. If the results are generalizable outside the context of the study, then the results are valid. Validity is divided in internal and external validity in both qualitative and quantitative research, but are not exactly the same in these two different research methods. Internal validity is fulfilled if we measure what we want to measure and are able to present the existing diverged perceptions and thereby a comprehensive picture of what we aim to measure. Another word for internal validity is credibility (in Swedish: trovärdighet). This has to be achieved in order to fulfil external validity. We can achieve external validity if we can generalize the results from the study to another context than the measured one. The sample of the participants (in Swedish: urval) is crucial for external validity in both quantitative and qualitative research. Another word for external validity is transferability (In Swedish: överförbarhet/tillämpning). However, in qualitative research the
results are not generalizable, compared to, for example, population-based quantitative
research. But the results may be discussed in the term of transferability instead.
*Relevance* is fulfilled if the results add something to the existing knowledge base. If the
results present any information that is not already known, it is seen as relevant [269, 271].

**Sampling and saturation**

To be able to describe the variety of perceptions that a study aims for, the sampling of the
participants is important and the number of participants is often decided by an achieved
saturation. So-called *purposive sampling* (in Swedish: *strategiskt urval*) provides enough
depth and width of data and results and is important for internal validity. In order to achieve
such a sample, it is important to have knowledge of the context of the purposed sample. At
the start it is not obvious how many participants are needed for the purpose and therefor a
flexible study design in qualitative research is important. When perceptions start to be similar
to the prior perceptions during the process, the total number of participants has been reached
and the sampling process is finished. This is called “achieving *saturation*” (in Swedish:
*mättnad*). When saturation is achieved, perceptions are repeated and this indicates that the
research has covered the variety of perceptions in the study cohort. In contrast, epidemiologic
research often requires a high number of participants so that the results can be generalized. In
qualitative research, it is not always possible to carry out purposive sampling due to
organizational or logistic problems and this is then called a *convenience sample* (in Swedish:
*tillgängligt urval*) or a *purposeful sample* (in Swedish: *ändamålsenligt urval*) [269, 271].
7 METHODOLOGICAL CONSIDERATIONS

Confounding: Confounders are factors that covariates with both exposure and outcome and may not be an intermediate link in the causal pathway. Confounding factors can introduce both over and underestimations of an effect and these can be adjusted by, for example, multivariate regression models or stratification. Study designs can also take care of confounding by randomized study designs or matched cohort or case-control studies. Residual confounding is persistent confounding despite trying to adjust for confounding factors [267]. In studies I, IV and V we tried to adjust for confounding factors. In studies IV and V the social variables, which have often been viewed as confounders in other studies, were the variables of interest.

Bias: Bias can be systematic or random, in other words by chance. Systematic bias is more serious for results and may lead to wrong conclusions. This can be due to the study design, the data collection or the analysis of the results. Random bias can be adjusted for by using big sample sizes. Systematic bias is independent of the sample size of the study population and may consist of information bias (misclassification), selection bias or confounding [267]. In study I there might have been a selection bias due to the administration of the questionnaires. The majority of the responders were highly educated mothers and the sample contained fewer mothers of foreign birth than the local population. In study III we might have missed spontaneously reduced cases of intussusception, as there was no diagnostic code for intussusception in such potential cases.

Effect mediators: One or more variable modifies the association between exposure and outcome and therefore modifies the outcome. In comparison, a confounder interacts with both exposure and outcome. One way of addressing effect mediators is to test the homogeneity between stratified groups [267]. In study IV, we adjusted for the potential effect mediators (gestational age, parental psychiatric disorder, substance abuse, maternal smoking during pregnancy) for the social gradients of paediatric care due to gastroenteritis.

Study I: The original questionnaire was from a Canadian study, developed by experts and reviews of the literature. They had pretested the questionnaire with a sample of 20 people and had content and face validity in their expert groups. Our questionnaire was adapted to the Swedish context and piloted with 13 parents of newborn infants in order to increase the internal validity.

Study II: We could have described the sampling of the participants in study II more carefully, as well as the preconceptions of the first and last researchers who were responsible for the interviews and the data analysis. Sampling is important for transferability and the number of participants in our study might have been too small to achieve transferability. One reason is that the manuscript started as a Master’s thesis. In addition, the homogenous socio-demographics of the participants might have resulted in transferability only to similar groups as the participants. Due to this homogeneity we may have missed several shades of perceptions in other socioeconomic contexts [271]. However, the aim of qualitative research is not to generalize and our results may still, in some way, contribute to the whole picture of parental conceptions of the rotavirus vaccine. Studies I and II tended to enrich each other, as quantitative and qualitative methods can do [270].
**Study III:** One methodological consideration in this study was the dependency on what and how carefully symptoms and treatment were reported in the collected medical records. This was related to the retrospective study design. Another question to be aware of was that the missing information in the medical records was analyzed as negative and this means that a possible dilution of the PPV may have occurred. The first author’s interpretation of the text in the medical records may also have been a methodological consideration when validating the cases, due to the Brighton case criteria. However, when there was any doubt about a symptom or the results from radiological procedures, for example, these were discussed with a co-author, who is an experienced pediatric surgeon, and a consensus was reached. In addition, in **study III** we had no access to procedural codes or evaluations for the radiological procedures that were performed.

**Studies IV and V**
The use of high-quality national registers with multiple demographic and socio-economic indicators was a strength of **studies IV and V**. These two studies were population-based studies with minimal attrition, which means that it is possible to generalize the results. However, the lack of data on the prevalence of viral gastroenteritis in Sweden by social context was a limitation. Northern Sweden had a lower incidence of viral gastroenteritis in outpatient care. This may indicate a lower prevalence of viral gastroenteritis due to that part of the country being less densely populated, and with less opportunities for contagion, than the Southern parts of Sweden, which tend to be more urban and densely populated. Another limitation for both studies, was that the information on the universal education of immigrants in Sweden was not very good [274]. The registered ED outpatient care visits may have been confounded by reported cases from outpatient care outside hospital but we have tried to minimize this risk through the used patient register and by selection of acute visits at emergency departments. Additionally the study period of study IV was before the choice reform in Stockholm. Organizational differences between counties we could not adjust for.

In **study V**, the population of Jönköping County was too small to allow for meaningful analyses of the effect of the rotavirus program by socioeconomic variables, resulting in broad confidence intervals. Therefore, the effect of the vaccine effect on social gradients, and the sensitivity analysis, were only studied for Stockholm County. In the sensitivity analysis, the change in the use of hospital care after the introduction of the rotavirus vaccine was compared with an older cohort born in 2009-2012, to avoid the influence of herd immunity. All the results were consistent with the main analysis. Compared to previous studies from other countries we presented lower reductions of paediatric care of gastroenteritis in Stockholm and Jönköping counties after the rotavirus vaccine introduction. This was probably a result of our adjustment of the time-trend of an overall decrease of paediatric care of gastroenteritis in children in all Sweden. The increased social gradient of paediatric outpatient care in Stockholm could have been confounded by the introduction of the choice reform in Stockholm in 2014, parallel to the rotavirus introduction. This might have led to an increased access of paediatric care for children with acute gastroenteritis and has to be studied further.
8 ETHICAL CONSIDERATIONS

All the studies included in the thesis were approved by the Regional Ethical Review Board in Stockholm, with the following dnr:

**Study I:** 2013/2041-31/5 and 2014/912-32  
**Study II:** 2013/2041-31/5  
**Study III:** 2014/2121-31/4  
**Study IV:** 2015/2113-31/5 and 2016/2380-32  
**Study V:** 2015/2113-31/5 and 2016/2380-32 and 2017/732-32

In studies I and II an ethical consideration was that the responders might have felt valued due to their opinions during the surveys or interviews. The only thing we could really do to address this was by keeping an objective approach during the interviews and making sure that informed consent was provided. We concluded that the benefits from the results of these two studies outweighed the risks. In the analysis process all the data in study I was anonymized.

In study III only two researchers had access to the 392 medical records of children with suspected intussusception besides the current caregivers. This could be perceived as an infringement of privacy. Since many believe that intussusception is not a particularly sensitive condition, we concluded that the benefits of the manual reviews of the medical records was a justifiable infringement of privacy. There was no other possible way that we could have determined if the diagnosis was reliable in the registers. Unfortunately, we could not seek consent due to the fact that the patients were randomly selected as a part of the validation of the study design. If we had sought consent, we could have introduced a selection bias and the results would not have been able to be generalizable.

We considered that the benefit of collecting new information on this rare, but serious, adverse event in a Swedish context outweighed the described risks.

The register-based design of studies IV and V posed several ethical considerations. Consent could not be obtained due to the register-based design. That would have introduced a possible selection bias and the number of patients included in such studies was too high to make collecting informed consent feasible. To minimize the risk of infringements of privacy, all data was anonymized during the process. The researchers had no access of any personal identity numbers when analyzing the data for both studies. There might also be a risk that anyone reading the study would feel stigmatized due to the socioeconomic variables, which included education level, parental age, birth country, disorder and income level. We nevertheless considered that the benefits of these studies outweighed such risk. Collecting information on vulnerable socioeconomic groups may make it possible to develop interventions that improve the conditions and outcomes of these groups.

We also had to consider that children under the age of 18 relied on parental decisions in many situations.
9 RESULTS OF EACH STUDY

9.1 STUDY I AND II

Most parents (81%) said that they intended to vaccinate their child against the rotavirus. We found that 11% were uncertain about vaccination and 8% were unwilling to vaccinate. Parents of children who were younger than five weeks or with lower levels of education were more likely to be uncertain or unwilling about vaccinating their child. Other factors associated with an unwillingness or uncertainty were: a) Paying little heed to the child health nurses’ recommendations, b) Thinking that rotavirus infections were not serious illnesses, c) Not believing that the vaccine provided protection against serious forms of gastroenteritis and d) Not having enough information about the vaccine. The same group of parents had no intention of accepting other vaccines either. Table 9 from the paper describes these results in detail.

Table 9. Forward stepwise logistic regression analysis of significant predictors (p<0.05) from Table 1 and 2 in paper I. No intention and uncertain intention to vaccinate versus positive intention to vaccinate, (n=936).

<table>
<thead>
<tr>
<th></th>
<th>Model 1*</th>
<th>Model 2**</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have not enough information to make a decision about rotavirus vaccination</td>
<td>6.0 (4.3-8.3)</td>
<td>3.7 (2.5-5.8)</td>
</tr>
<tr>
<td>My child will not receive all the vaccines that are offered by the child health center (or Don’t know).</td>
<td>9.6 (6.5-14.1)</td>
<td>7.1 (4.4-11.6)</td>
</tr>
<tr>
<td>The rotavirus infection provides better immunity response than the vaccine itself (or Don’t know).</td>
<td>3.6 (2.0-6.4)</td>
<td>4.0 (1.6-9.0)</td>
</tr>
<tr>
<td>In my decision regarding vaccination against the rotavirus, I give little importance to the fact that…</td>
<td></td>
<td></td>
</tr>
<tr>
<td>…the vaccine is recommended by the child health nurse.</td>
<td>5.3 (3.6-7.8)</td>
<td>3.7 (2.2-6.3)</td>
</tr>
<tr>
<td>…the rotavirus infection can make my child seriously ill.</td>
<td>7.2 (4.4-11.6)</td>
<td>2.4 (1.1-5.1)</td>
</tr>
<tr>
<td>…the vaccine protects against the most serious forms of gastroenteritis.</td>
<td>9.0 (5.7-14.2)</td>
<td>3.1 (1.5-6.4)</td>
</tr>
</tbody>
</table>

* Unadjusted, univariate analysis of each factor that remained in Model 2
** Forward stepwise logistic regression analysis

In study II, four main categories were identified as: a) To vaccinate without doubt, b) Hesitant to vaccinate, c) Risky to vaccinate and d) Unnecessary to vaccinate. All ten participant parents wanted to protect their children from suffering, either by vaccinating their child to avoid a rotavirus infection or by not vaccinating their child because of concerns about the side effects. The four main categories are presented in figure 14 on the next side.
Figure 14. The four main categories of study II. Illustration by Eva Sjögren.
9.2 STUDY III

The total PPV was 89%, meaning that 89% of the 392 admissions fulfilled any level of the international criteria of diagnostic certainty of acute intussusception during the study period, namely level 1-3. The PPV for a definite diagnosis (level 1) was 84% and the total PPV for any level among the children under one year of age (N=240) was 88%. High reliability of the diagnosis coding was shown in the study population. Figure 15 from the paper presents the process for the different levels of 1-3.

Figure 15. The study process and main results of study III.
9.3 STUDY IV

In total, 23,113 (3.1%) children from the study population were admitted at least once with a discharge diagnosis of viral gastroenteritis and 70,422 (9.4%) of the children were treated in outpatient ED care with this diagnosis. The adjusted HRs for hospital admission with a diagnosis of viral gastroenteritis were increased when: a) The mother was under 25 years, b) The mother had a short education, c) Any of the parents had a psychiatric disorder and/or d) When both parents were born outside Europe. The pattern of HRs for outpatient ED hospital care was similar. Table 10 summarizes the main results from this study and the significant associations relevant for the conclusions are circled. It is important to note that the disposable income of the family was only marginally associated with paediatric hospital care for viral gastroenteritis when adjusted for the included covariates.

Table 10. Cox regression models of determinants of hospital care due to gastroenteritis, study IV. (N=751,646)

<table>
<thead>
<tr>
<th>Mother’s highest education</th>
<th>Model 1 (HR)</th>
<th>Model 2 (HR)</th>
<th>Model 3 (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9 yrs</td>
<td>1.42 (1.37-1.48)</td>
<td>1.24 (1.18-1.30)</td>
<td>1.18 (1.12-1.23)</td>
</tr>
<tr>
<td>10-12 yrs</td>
<td>1.14 (1.11-1.18)</td>
<td>1.10 (1.06-1.13)</td>
<td>1.06 (1.04-1.11)</td>
</tr>
<tr>
<td>13-14 yrs</td>
<td>1.07 (1.02-1.11)</td>
<td>1.04 (0.99-1.09)</td>
<td>1.02 (0.97-1.07)</td>
</tr>
<tr>
<td>15 +</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disposable income of the household</th>
</tr>
</thead>
<tbody>
<tr>
<td>First quintile</td>
</tr>
<tr>
<td>Second quintile</td>
</tr>
<tr>
<td>Third quintile</td>
</tr>
<tr>
<td>Fourth quintile</td>
</tr>
<tr>
<td>Fifth quintile</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cohabitation of parents during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parental country of birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-European</td>
</tr>
<tr>
<td>European</td>
</tr>
<tr>
<td>One Swedish born</td>
</tr>
<tr>
<td>Two Swedish born</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parental psychiatric disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
</tr>
<tr>
<td>Father</td>
</tr>
</tbody>
</table>

Significant associations relevant for the conclusions are circled. Note that the disposable income of the family was only marginally associated with paediatric hospital care for viral gastroenteritis when adjusted for the included covariates, thereby the cross-over sign.

**Model 1**: each variable adjusted for gender and year of birth separately.
**Model 2**: adjusted for socio-demographic variables.
**Model 3**: adjusted for all variables.
There were great differences in the hospital care incidences for viral gastroenteritis between Swedish counties, as presented in Table 11. The wide-ranging relationship between outpatient ED care and inpatient care were shown, for example, by a quota of almost 10 in Uppsala County compared to 1.5 in the northern regions of Sweden.

**Table 11.** Incidence and HRs of Swedish hospital care for viral gastroenteritis for children aged 0-5 years by county. HRs are adjusted for year of birth, parental country of birth, maternal age and education.

<table>
<thead>
<tr>
<th>County</th>
<th>Inpatient care 1/100 person years</th>
<th>ED outpatient care 1/100 person years</th>
<th>Inpatient care HR (95% C.I.)</th>
<th>ED outpatient care HR (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stockholm</td>
<td>0.91</td>
<td>3.15</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Västra Götaland</td>
<td>0.72</td>
<td>2.07</td>
<td>0.79 (0.75-0.82)</td>
<td>0.65 (0.64-0.67)</td>
</tr>
<tr>
<td>Skåne</td>
<td>0.77</td>
<td>2.91</td>
<td>0.82 (0.79-0.86)</td>
<td>0.89 (0.87-0.91)</td>
</tr>
<tr>
<td>Jönköping</td>
<td>0.82</td>
<td>1.72</td>
<td>0.88 (0.82-0.94)</td>
<td>0.53 (0.51-0.56)</td>
</tr>
<tr>
<td>Uppsala</td>
<td>0.35</td>
<td>3.49</td>
<td>0.39 (0.35-0.46)</td>
<td>1.12 (1.08-1.16)</td>
</tr>
<tr>
<td>Örebro</td>
<td>0.79</td>
<td>2.56</td>
<td>0.85 (0.78-0.92)</td>
<td>0.79 (0.75-0.82)</td>
</tr>
<tr>
<td>Södermanland</td>
<td>1.06</td>
<td>2.75</td>
<td>1.11 (1.04-1.20)</td>
<td>0.84 (0.80-0.87)</td>
</tr>
<tr>
<td>Dalarna</td>
<td>0.70</td>
<td>1.88</td>
<td>0.75 (0.68-0.82)</td>
<td>0.59 (0.56-0.62)</td>
</tr>
<tr>
<td>Västmanland</td>
<td>0.76</td>
<td>2.86</td>
<td>0.81 (0.74-0.88)</td>
<td>0.87 (0.83-0.91)</td>
</tr>
<tr>
<td>Halland</td>
<td>0.86</td>
<td>1.87</td>
<td>0.91 (0.83-0.99)</td>
<td>0.61 (0.58-0.64)</td>
</tr>
<tr>
<td>Västerbotten</td>
<td>1.16</td>
<td>1.75</td>
<td>1.29 (1.21-1.40)</td>
<td>0.58 (0.54-0.61)</td>
</tr>
<tr>
<td>Västernorrland</td>
<td>0.87</td>
<td>1.32</td>
<td>0.95 (0.87-1.04)</td>
<td>0.43 (0.40-0.46)</td>
</tr>
<tr>
<td>Gävelöborg</td>
<td>0.68</td>
<td>1.50</td>
<td>0.73 (0.67-0.79)</td>
<td>0.47 (0.44-0.50)</td>
</tr>
<tr>
<td>Värmland</td>
<td>0.82</td>
<td>1.95</td>
<td>0.91 (0.83-0.99)</td>
<td>0.64 (0.61-0.68)</td>
</tr>
<tr>
<td>Kalmar</td>
<td>1.08</td>
<td>1.91</td>
<td>1.17 (1.08-1.26)</td>
<td>0.60 (0.57-0.65)</td>
</tr>
<tr>
<td>Norrbotten</td>
<td>1.00</td>
<td>1.11</td>
<td>1.09 (1.01-1.01)</td>
<td>0.36 (0.34-0.39)</td>
</tr>
<tr>
<td>Blekinge</td>
<td>0.75</td>
<td>1.91</td>
<td>0.82 (0.73-0.91)</td>
<td>0.61 (0.57-0.65)</td>
</tr>
<tr>
<td>Kronoberg</td>
<td>0.45</td>
<td>2.61</td>
<td>0.49 (0.43-0.55)</td>
<td>0.86 (0.82-0.91)</td>
</tr>
<tr>
<td>Jämtland</td>
<td>1.16</td>
<td>1.70</td>
<td>1.28 (1.16-1.42)</td>
<td>0.56 (0.52-0.61)</td>
</tr>
<tr>
<td>Gotland</td>
<td>0.94</td>
<td>1.94</td>
<td>1.04 (0.88-1.23)</td>
<td>0.64 (0.57-0.72)</td>
</tr>
</tbody>
</table>
9.4 STUDY V

There was an overall reduction in paediatric care due to viral gastroenteritis in the whole of Sweden during the study period. Table 12 and Figures 16 and 17 show a steeper reduction of 37% in Stockholm County and 24% in Jönköping County for paediatric inpatient care and 11% in Stockholm County and 21% in Jönköping County for paediatric outpatient care visits compared to the rest of Sweden, after adjustment for time trends and social indicators.

Table 12. Cox regression of paediatric care due to gastroenteritis. Study V.

<table>
<thead>
<tr>
<th></th>
<th>Difference in difference estimate of HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>After versus before vaccine start:</td>
</tr>
<tr>
<td></td>
<td><em>(reference in italic)</em></td>
</tr>
<tr>
<td><strong>Inpatient care for gastroenteritis</strong></td>
<td></td>
</tr>
<tr>
<td>Stockholm versus <em>rest of Sweden</em> (Jönköping excluded)</td>
<td><strong>0.63</strong> (0.56-0.70)</td>
</tr>
<tr>
<td>Jönköping versus <em>rest of Sweden</em> (Stockholm excluded)</td>
<td><strong>0.76</strong> (0.58-0.99)</td>
</tr>
<tr>
<td><strong>Outpatient care for gastroenteritis</strong></td>
<td></td>
</tr>
<tr>
<td>Stockholm versus <em>rest of Sweden</em> (Jönköping excluded)</td>
<td><strong>0.89</strong> (0.85-0.93)</td>
</tr>
<tr>
<td>Jönköping versus <em>rest of Sweden</em> (Stockholm excluded)</td>
<td><strong>0.79</strong> (0.69-0.90)</td>
</tr>
</tbody>
</table>

Figure 16. Inpatient care incidence of viral gastroenteritis in children 12-24 months
Table 13 presents the groups of children in Stockholm County with parents with shorter education, low maternal age, use of social welfare and where both parents were foreign born. These groups demonstrated a smaller reduction in paediatric outpatient care than the comparatively more socially privileged groups. When it came to inpatient care, there were no social differences in hospital care use for gastroenteritis in Stockholm County after the rotavirus vaccine was introduced.

**Table 13.** Cox regression of the socioeconomic covariates related to paediatric outpatient care due to gastroenteritis in Stockholm County.

<table>
<thead>
<tr>
<th>Socioeconomic covariates:</th>
<th>Stockholm County</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference in difference estimate of HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Inpatient care for gastroenteritis</td>
</tr>
<tr>
<td>Maternal primary education versus tertiary education</td>
<td>0.99 (0.74-1.31)</td>
</tr>
<tr>
<td>Maternal secondary education versus tertiary education</td>
<td>1.15 (0.84-1.57)</td>
</tr>
<tr>
<td>Paternal primary education versus tertiary education</td>
<td>0.99 (0.77-1.25)</td>
</tr>
<tr>
<td>Paternal secondary education versus tertiary education</td>
<td>0.81 (0.59-1.12)</td>
</tr>
<tr>
<td>Maternal age under 25 at birth versus other</td>
<td>0.88 (0.62-1.24)</td>
</tr>
<tr>
<td>Use social welfare benefit versus other</td>
<td>0.90 (0.58-1.39)</td>
</tr>
<tr>
<td>Both parents foreign born versus at least one Swedish-born parent</td>
<td>0.96 (0.77-1.20)</td>
</tr>
<tr>
<td>Single parent household versus cohabitation</td>
<td>0.98 (0.76-1.27)</td>
</tr>
</tbody>
</table>

Bold text indicates statistical significant associations at p <0.05 level.
10 DISCUSSION

Major findings
This thesis aims to set the scene for the national introduction of the rotavirus vaccine in Sweden. Five studies that used diverse methods and studied different aspects of the introduction of the rotavirus vaccine in Sweden are presented.

In studies I and II, parental attitudes and the various conceptions of the rotavirus vaccines were described by both quantitative and qualitative methods. Both studies highlighted the importance of a good relationship and a responsive dialog between the family and the child health nurse. We also concluded that early information and extra information for parents with a lower level of education were important factors to reach high rates of rotavirus vaccine.

In the diagnostic validation study III, the diagnosis of intussusception was validated in the Swedish National Patient Register, resulting in a high PPV of 89% in children under the age of three and 88% in children under the age of one, according to international criteria for the diagnosis. Studies IV and V were national register-based cohort studies of paediatric care and the social gradient due to viral gastroenteritis in Swedish children and also covered the rotavirus vaccine’s effect in this context in two Swedish counties. Study IV presented factors associated with lower levels of parental health literacy related to an increased use of paediatric care due to viral gastroenteritis in children in the Swedish pre rotavirus vaccine era. The same study also presented geographical differences between the incidences of paediatric care of viral gastroenteritis in young children by Swedish counties. Study V showed significant reductions in paediatric care for viral gastroenteritis in young children after the rotavirus vaccine was introduced in both Stockholm and Jönköping counties, compared with the rest of Sweden. The social gradient in paediatric inpatient care remained unaffected three years after the rotavirus vaccine was introduced in Stockholm. On the contrary, the social differences were increased in lower social groups who received paediatric outpatient care.

The importance of parental trust and a good relationship with the child health nurse
The first two studies in this thesis stressed the importance of maintaining the unique trust that most Swedish parents have in the child health preventive care, in order to achieve high coverage for the new rotavirus vaccine. Those who responded to study I said that the main source of information about the rotavirus vaccine was the child health care nurse. Being able to trust the knowledge and recommendations of health care professionals may be crucial for the introduction of any new vaccines and for the rotavirus vaccine in particular [216, 218 229, 238]. In study I, the responders who were skeptical or hesitant about the rotavirus vaccine were also skeptical or hesitant about other program vaccines. This confirmed previous literature [258, 263, 275, 276]. The same responders did not follow the nurse’s recommendations as much as the parents who intended to vaccinate their child.

The introduction of a vaccine for a comparatively mild disorder, such as the rotavirus infection, could test the acceptance of vaccines by the Swedish population. Trust may be maintained by ensuring that health care professionals and robust health care systems provide
carefully designed information, grounded knowledge and recommendations on the vaccine [258, 260, 261]. A recent systematic review also highlighted the Swedish structure and organization of well-baby clinics as beneficial for equity in vaccine uptake for previous vaccines [180].

In a fast developing media landscape, with political vulnerability and in a world where vaccines have eradicated the most dangerous infections it is more important to ensure that trust is maintained in health care professionals and vaccines. A risk of forgetting about the infections that vaccines eradicate and target both health care professionals and parents with more focus on potential risks with the vaccines has been described [234]. Thereby a foundation for changing attitudes of vaccines and an increased vaccine hesitancy may be created, with results of suboptimal vaccine coverages and outbreaks of diseases [277].

Safety surveillance, and how we inform parents about the adverse events of intussusception, are also matters of trust [223]. When the rotavirus vaccine is offered, the child health care professional needs to inform parents about the rare, but serious, adverse events of intussusception. The Swedish state medical ethical advisers have pointed out the need to provide balanced, but accurate, information about intussusception to parents when the rotavirus vaccine is implemented nationally [167]. Implementing robust safety surveillance and providing clear information to parents of this adverse event will probably be crucial if we are to maintain continued trust in the rotavirus vaccine.

**Safety surveillance on intussusception as an adverse event.**

The results of study III will hopefully provide a platform for the safety surveillance of intussusception as a potential adverse event of the rotavirus vaccine in Sweden. This will inform future follow-up studies based on national registers. The high PPV of 89% that was demonstrated in children under three years of age in the Swedish Patient Register was in accordance with other validation studies of the same diagnosis and criteria from other countries [72, 84, 85]. The PPV of 88% that was reported for children under one year of age would be applicable for children who face the risk of intussusception due to the rotavirus vaccine. While we were working on study III and reading the literature it became obvious how important it is to provide careful descriptions in the medical records when intussusception is suspected and also to perform radiologic procedures to confirm the diagnosis. If this is done it would enable further retrospective studies to be carried out on potential cases of intussusceptions to find out whether they are related to the rotavirus or not, based on the international criteria and evaluation. Because intussusception is a relatively rare condition, it may be difficult to make the wider medical community aware of the symptoms to look out for. The symptoms of intussusception may obviously be diffuse and within a wide range. For example, abdominal pain was described as the most common symptom (88%) but the classic triad of symptoms was only present in 24% of the cases in our study, in line with previous studies [74, 76, 81, 278]. Abdominal pain has been shown to be a symptom with high sensitivity (91%) but low specificity (19%) for intussusception, according to the Brighton case definitions [278]. In comparison, the PPV of 84% for the level 1 case definitions in our study showed that the objective methods of
diagnosing the patient by using radiological procedures or surgical intervention is preferred in high-income settings when they are applicable and available. Enema therapy has demonstrated a high success rate [279, 280] when it comes to resolving intussusception. In the diagnostic procedure, using abdominal ultrasound has been reported to have a specificity of 78-100% and a sensitivity of 100% [281, 282]. Of course, there are different prerequisites for diagnosing cases of intussusception, depending on the setting. Because there are greater distances to hospitals in low-income countries, there are often delays in diagnosing intussusception. This can result in more severe cases of intussusception and lead to a higher related rates of surgery and mortality [283]. In such settings, it is probably more important to use the case definitions to diagnose level 2 and 3 than the radiologic procedures and treatments and to use the surgical criteria to diagnose level 1.

**Tailored information on vaccines, policy changes or proportionate universalism?**

A combination of both individually designed information and overall policy changes of interventions of information about the rotavirus infection and the rotavirus vaccine are needed to achieve a high rotavirus vaccine coverage in all groups of SES.

**Studies I, II, IV and V** presented results that highlighted the need for targeted information to be provided on different levels and that different groups of parents have different information needs. However, according to the literature, interventions need to be carried out at a higher level than only individual interventions if equitable health outcomes and equitable vaccine coverage are to be achieved [182]. Both approaches are suitable in our Swedish setting and would result in more tailored information. Proportionate universalism has been shown as a good example in the Swedish context of intervening on social gradients of vaccine coverage and children’s health and is a combination of a targeted and universal approach with resources and delivery of the preventive health care according to the level of need [184, 187].

The individual meetings between the families and the child health nurses are important and challenging. It has been shown that parental decisions about vaccines are often connected to how the health care professionals communicate with them about vaccines [218, 239, 284]. Furthermore, health care professionals need to be provided with education and tools to guide parents during the individual meetings and to determine the level of information that the family needs. This could for example include motivating interviews, which are already used extensively [277].

Understanding vaccine hesitancy will become increasingly more important and we need to be able to provide tailored information in addition to policy changes [222].
The importance of health literacy
Studies IV and V showed that interventions that target health literacy will be important if we are to bridge the social gap in paediatric care due to gastroenteritis and differences in rotavirus vaccine coverage. In study IV, factors associated with low levels of health literacy were related to increased usage of paediatric care of gastroenteritis. Thereby, increased efforts to target low SES groups with information so that they can manage their children’s health issues more effectively, may be even more important than the rotavirus vaccine when it comes to reducing the social gap of paediatric care [196, 285, 286]. Secondly, efforts to reach all socioeconomic groups to the same extent with information of the rotavirus vaccine in specific when introducing the new rotavirus vaccine will be important in order to prevent socially patterned rotavirus vaccine coverage gaps. The best way to tackle these two issues is a delicate question. The extended home visiting program that was put in place in Stockholm to tackle a vaccine hesitancy in the Somali community is also in the context of information a good example of improved health literacy through targeted and designed information in a specific vulnerable region by “proportionate universalism” [184]. Another example of a campaign that increased health literacy was a media campaign by the Danish health authorities in 2017. This followed a considerable decrease in the uptake of the human papillomavirus vaccine in a particular cohort of girls due to false and negative media reports. The aim of the campaign was to increase public confidence in the human papillomavirus vaccine for girls by using social media and focusing on balanced facts and personal stories. As a result of this campaign the coverage for the human papillomavirus vaccine increased [287].

The equity lens on immunization
Studies I and V focused on the suggestion that social determinants were related to differences in vaccine coverage in the same way as they are for health outcomes in children [168, 197]. The WHO has encouraged researchers to focus the equity lens on the future of immunization in all countries in order to explore the pathways of different levels of vaccine coverage related to social determinants [169, 288]. Interventions to reduce the differentials of vaccine coverages depend on the context. In some countries, the main issue is the need to focus on equal delivery or equal access to vaccines by the population [197, 289]. In some countries it is easier to measure social determinants than others. Sweden is an example of a country that has high-quality robust registers that make it possible to measure social determinants on an individual level [290, 291]. Study V may be seen as a starting point for measuring social determinants related to vaccines in the Swedish context. Most of the studies in the thesis stresses the benefits of our system with well-baby clinics in Sweden and that this organization need to persist in order to maintain our high vaccine coverages overall and the small social differentials in vaccine coverage that we have compared to other countries with other preventive health care structures [180].
The rotavirus vaccine’s effect on the the social gradient and the utilization of paediatric care for gastroenteritis

In study V the vaccine reduced paediatric inpatient care due to viral gastroenteritis (ICD-codes A08-A09) by 34% in Stockholm county and 24% in Jönköping County. These levels were lower than previous studies [51] and may have been related to an underestimation of the effects of the vaccine due to the short period of follow up and due to the low vaccine coverage at the beginning of the study period [66, 186]. However the used method of comparing two counties with the rest of Sweden probably explains our results of these moderate reductions and is probably a more precise estimate of the real vaccine effect compared to regional studies. With the used methods we have adjusted for the overall decreasing trend of the utilization of paediatric care for gastroenteritis in all Sweden, in comparison with regional results from Jönköping and the northern parts of Stockholm. Oldin et al recently presented data from Jönköping County for 2013-2018, which showed a decrease of 60% for paediatric inpatient admissions for viral gastroenteritis for children under the age of five, four years after the rotavirus vaccine was introduced, in comparison [68]. Similar preliminary results, namely a reduction of almost 50% for cases of children under the age of five admitted for gastroenteritis, have been reported from the Northern part of Stockholm County for the years 2008-2016 [292].

The rotavirus vaccine reached all socioeconomic groups equitably for the more severe cases of viral gastroenteritis, i.e. inpatient care, according to the results of study V. However, the increased social gradient for paediatric outpatient care in Stockholm was a bit surprising. This may partly be explained by the parallel implementation of a choice market reform in the Stockholm County since 2014. This reform included paediatric outpatient care and may have confounded the results due to an increased access to paediatric inpatient care for gastroenteritis after 2014. This has to be studied further.

Hospital care of gastroenteritis versus gastrointestinal infections in the community

The incidence of rotavirus infections and gastroenteritis in the community are more difficult to measure than reductions in hospital care. Studies of hospital care are mostly based on register data and are therefore easier to measure. Using pediatric care indicates more severe cases or cases where the family is not able to handle the infection at home. It is probable that incidences of gastroenteritis will be reduced by the rotavirus vaccine and that this will result in a parallel reduction in paediatric care. However, data on gastrointestinal infections in the community will have to be collected in other ways. These could include surveys or questionnaires, data from telephone advice companies such as “1177” in Sweden, by logbooks from preschools or by information on parental work absences. In these examples, selection bias could easily be introduced and it would be more difficult to generalize the results. A 2018 review of gastrointestinal infections showed that transmission of gastrointestinal viruses from person to person in the community was more common in children from low SES families than children of high SES families [293]. These findings were in accordance with our results of hospitalized children with gastroenteritis.
Will gastroenteritis be rare in Swedish children after the rotavirus vaccine?
Gastroenteritis may still be caused by less severe forms of the rotavirus than the ones that the vaccine targets and also by other viruses, bacteria or parasites after the national rotavirus vaccine introduction. Studies have shown that noroviruses are becoming the leading common cause of gastroenteritis when the rotavirus vaccine has been implemented [294, 295]. Also, the role of the sapovirus and astroviruses have been more common causes of acute gastroenteritis in children in the post rotavirus vaccine era [296, 297].

For or against the rotavirus vaccine in high-income settings?
There are motives for both being for and against the rotavirus vaccine in settings such as Sweden. People who do not believe there is a need for the rotavirus vaccine in high-income settings could claim that this is the case in Sweden, because we have a welfare state that provides high-quality health care. They may also be afraid of the potential side-effect of intussusception or state that the rotavirus infection is not lethal, and that the vaccine is only being introduced to reduce costs. On the other hand, many pediatricians will agree that children can be severely dehydrated by a rotavirus infection, even in Sweden, and can be close to shock in the emergency room. In addition, the complications of the infection can be severe and the number of children who suffer could be avoided by using the vaccination to reduce the more severe cases of rotavirus infections [5]. Additional indirect effects of the introduction of the rotavirus vaccine could include herd immunity and a reduced impact on older adults and children with chronic disabilities who could die from a rotavirus infection [167]. These are arguments that people who believe in rotavirus vaccination will accept. The results of the interviews in study II showed that it is not always as easy as being for or against the vaccine and that is an important point that health care professionals need to understand when they are communicating with parents [218, 219].

Does the rotavirus vaccine provide an eye-opener for the wider vaccine debate?
Introducing the rotavirus vaccine in a country like Sweden that already has a robust healthcare system could be an eye-opener for the vaccine debate in general. Before the rotavirus vaccine was introduced, the pneumococcal disease vaccine was included in the program in Sweden. It quickly achieved high vaccine coverage and resulted in large reductions in morbidity [298, 299]. The national introduction of the rotavirus vaccine can be seen as an opportunity for further discussions on the important issue of equity of health in children and how a public health intervention, such as a new vaccine, may affect public trust and raise questions about safety surveillance. That fact that the rotavirus vaccine differs in many ways from other national preschool vaccines that are already included in the national program is a potential vulnerable factor when it comes to trust. On the other hand, if the implementation is seriously and carefully handled it could also open up opportunities for the future introduction of new vaccines into the Swedish program.
What does this thesis add to prior knowledge?
All five studies included in the thesis presented results that may be valuable for the national implementation of the rotavirus vaccine into Sweden in the near future. A number of factors relevant to the introduction of the rotavirus vaccine had not been studied in Sweden prior to this thesis.

The results from study V are probably important for further cost effective studies of the national introduction and the focus of vaccine as a public health intervention and the studying of the effect on health equity is an important further issue globally.

Figure 18. Summary of the main findings and important factors of this thesis
Strengths and limitations

A strength of all five studies that were included in this thesis was that the results were new to the Swedish context. Another strength, which might also be considered as a limitation, was the use of different methods to illustrate the different objectives included in the thesis.

In study I, the high response rate was a strength, although there were some limitations, namely the cross-sectional design, the fact that most of the mothers were highly educated and the lower percentage of foreign born mothers than in the local population. This may mean that the results are not generalizable. However, the distribution of parents who stated that they intended to vaccinate their child against rotavirus infections was similar to the coverage reported in Stockholm at the time and we have concluded that it was unlikely that these demographic differences changed the conclusions of the study. Study II had a qualitative approach and this means that the results could provide some helpful tools when communicating with parents about the rotavirus vaccine, as it presented the diverged spectra of conceptions within the same parents and between different parents from an urban area. Study I and II could be seen as siblings, supporting each other by their results of parental attitudes, conceptions and knowledge of rotavirus vaccine by the usage of various methods.

The generalizability of studies III, IV and V, with their population-based designs and use of reliable patient registers in Sweden, was a strength [290]. In addition, the fact that study III was based on a random sample of medical records from all over Sweden, and the use of standardized international case definitions [83], strengthened the generalizability. The results of study III could facilitate further Swedish safety surveillance register-based studies of intussusception associated with the rotavirus vaccine. The limitations of study III included the retrospective design and the fact that we had to rely on the records created by the doctor who discharged the patient. Another limitation of study III was the long study period that was needed to capture enough cases of intussusception, as various diagnostic techniques may have been used during that time. For example, radiological techniques and treatments have improved over the years. Performing an ultrasound is much more common these days for diagnosing cases of intussusception in children. Also, study III presented results for children 0-3 years which is a limitation due to that the youngest children could display different symptoms of intussusception due to rotavirus vaccine [300]. However, that is why we presented data for infants aged 0-1 years of age separately in order to deal with this potential limitation.

As studies I and II could be considered as sibling studies this could also be true of studies IV and V. Study IV acted as a baseline for study V, mostly to present the existing social gradient of paediatric care for viral gastroenteritis covering all of Sweden, but also as a prerequisite for presenting diverged incidences by Swedish counties. The outcome of paediatric outpatient care differed between the two studies. In study IV the outcome was ED outpatient care visits of gastroenteritis. However a limitation was that the results of ED outpatient care might have been confounded by reported cases from outpatient care outside
hospital but we have tried to minimize this risk through the used patient register and by a selection of acute visits at emergency departments. That is a limitation.

The main strength of study V was the unique opportunity of comparing counties that did not offer the rotavirus vaccine free in comparison with previous studies about the rotavirus vaccine’s effect. The used method has not been performed in many other previous studies and may be one cause of the lower reductions of hospital care of gastroenteritis compared to other countries. Seasonal variations were also taken into consideration by including three winter seasons during the study period. Also, the data on individual SES variables was a strength in study V. The use of multiple indicators of SES made the estimates in study V more precise than earlier studies of social gradients, which used neighborhood variables of SES [210, 212, 213]. However a limitation of study V was the absence of the individual rotavirus vaccine status of the children, since the vaccine was not nationally implemented and therefore not included in the national vaccine registry. Another potential limitation of study V was the eventually confounding factor of the new choice reform in Stockholm 2014, parallel to the introduction of the rotavirus vaccine in Stockholm County which might could have affected the results of paediatric outpatient care in Stockholm.
11 CONCLUSIONS AND IMPLICATIONS

This thesis underlines the importance of maintaining the trust of the general public in the organizations that deliver Swedish child health care and to maintain our child health centers in order to achieve high and equal rates of coverage for the rotavirus vaccine when it is nationally implemented. In addition, other interventions than the rotavirus vaccine may also be needed to decrease the social gradient of patients using paediatric care for viral gastroenteritis in parallel with the introduction of the vaccine. Supportive interventions with focus on parents with low health literacy could focus on providing information about oral rehydration when gastroenteritis occurs and also providing information about the rotavirus vaccine. In addition to this information, we will also need robust safety surveillance information to maintain the Swedish population’s unique trust in the child health care nurses and vaccines in general.

Studies I and II: Parental attitudes and perceptions of the rotavirus vaccines varied within a wide range of themes, from accepting the vaccine without question to believing it was unnecessary. The relationship between the family and the child health care nurse is of great importance to maintain the general trust parents have in child health care and vaccines when a new vaccine is implemented. To target parents of additional needs of information is a challenge but important due to the social differences of beliefs and decision making of vaccinating a child. The results could hopefully be helpful tools when communicating with parents about rotavirus vaccine, and perhaps in the future, for other similar vaccines.

Study III: The quality of the diagnosis of intussusception in children under three years of age in the Swedish Patient Register is high. We also found a high PPV for children under one year of age. This evaluation will create a platform for further register based studies of safety surveillance of rotavirus vaccine in Sweden.

Study IV: In the Swedish pre rotavirus vaccine era, parental indicators associated with a lower level of health literacy increased the risk for paediatric care due to gastroenteritis in young children. Therefore, providing tailored information about oral rehydration to these groups of parents is suggested.

Study V: The rotavirus vaccine targeted similar over social groups for inpatient care due to viral gastroenteritis in small children, whereas the social gradient increased for paediatric outpatient care. Data from Stockholm and Jönköping counties, compared to the rest of Sweden, showed significant reductions in both paediatric inpatient and outpatient care for viral gastroenteritis after the introduction of the rotavirus vaccine. If we are to decrease the social gradient for paediatric care use for viral gastroenteritis then other types of interventions than the rotavirus vaccine are probably also needed. The results of the overall reductions achieved in Stockholm and Jönköping counties may provide helpful data for cost analyses to guide the future national implementation of the rotavirus vaccine in Sweden.
12 FUTURE PERSPECTIVES

During the work on this thesis, several questions and thoughts for future studies have emerged. These are to:

- study the cost-effectiveness of the rotavirus vaccine based on the results of study V.
- further study differences in rotavirus vaccine coverage related to SES and also related to uptake of other vaccines. This will be possible when the rotavirus vaccine is introduced in all Sweden and thereby data of individual vaccine status will be available.
- further follow up the reductions of paediatric care due to viral gastroenteritis with geographical comparisons.
- follow organizational changes in paediatric care and how inequity in health may be affected.
- create a baseline for the diagnosis of intussusception, based on the PPV in this thesis. A future follow up of how the incidence varies after the introduction of the vaccine would be important as it would form part of the safety surveillance for the rotavirus vaccine.
- validate every reported case of intussusception in Sweden and their possible relationship to the rotavirus vaccine.
- study knowledge and attitudes towards the rotavirus vaccine in particular, and vaccines in general, among child health care professionals and assess how their beliefs and knowledge affect how parents make decisions about vaccines.
- identify and study vulnerable socioeconomic groups of parents, including those living in more vulnerable geographic areas, to gauge their attitudes and knowledge of vaccines in general and the rotavirus vaccine in particular.
- carry out intervention studies to increase health literacy in targeted groups.
- study social differentials related to other vaccines than the rotavirus vaccine in Sweden.
- study if new genotypes of the rotavirus emerge in Sweden after the national introduction of the rotavirus vaccine.
- study extra intestinal benefits from the rotavirus vaccine in Sweden.
- study the paediatric outpatient care further, also including outpatient visits to general practitioners, to estimate the broader effects of the rotavirus vaccine on outpatient care for gastroenteritis.
13 POPULÄRVETENSKAPLIG SAMMANFATTNING

Bakgrund

Det finns vaccin mot de svårare formerna av rotavirusinfektion som nu erbjuds i över 90 länder. Detta vaccin har visats vara effektivt i att minska sjukvårdskonsumtionen för rotavirusinfektion och magsjuka och därmed relaterade samhällskostnader. Alla barn som söker sjukvård för diarré och kräkningar provtas inte för just rotavirus, därför har man studerat vaccinets effekt avseende både rotavirusinfektion och magsjuka världen över.


I Sverige skiljer sig vacciner mot rotavirusinfektion mot andra vacciner inkluderade i det nationella programmet gällande flera faktorer. Exempel på detta är att vaccin mot rotavirus ges tidigare än de andra vaccinerna, det ges i munnen, det kan leda till en allvarlig men ovanlig biverkan kallad invagination, men framför allt skiljer det sig från de andra vaccinerna genom att det är ett vaccin riktat mot en icke dödlig sjukdom i ett svenskt sammanhang. Invagination är ett livshotande tillstånd som utan relation till rotavirus vaccin förekommer bland barn där tarmen hakar upp sig i sig själv. Riskökningen för invagination på grund av rotavirusvaccination är beskriven som 1-6 extra fall per 100 000 vaccinerade barn där mekanismen för detta är okänd.

Syfte med studierna
Syftet med de fem studierna som ingår i avhandlingen var att i ett svenskt sammanhang belysa och studera olika områden av rotavirus vaccinets införande inför det nationella införandet med hjälp av olika metoder.

Metod
De två första studierna handlade om föräldrars attityder kring och uppfattningar om rotavirus vaccin i Stockholm. Den tredje studien handlade om diagnosen invagination och de två sista
studierna fokuserade på ojämlig hälsa avseende sjukvårdsanvändande för magsjuka hos små barn i Sverige och rotavirusvaccinets effekt i de två landsting där vaccinet infördes 2014 jämfört med övriga Sverige.

**Studie I** baserades på en enkät för nyblivna föräldrar under fyra veckors tid i september 2014. Antalet svarande var 1063 stycken. Avsikten var att se vilka faktorer som skilde de föräldrar som tänkte vaccinera sitt barn mot rotavirus infektion från de som var osäkra och de som tänkte tacka nej. Alla tillfrågades innan första dosen av vaccinet skulle erbjudas.

**I studie II** intervjuades 10 nyblivna föräldrar med syftet att förstå olika uppfattningar om rotavirus vaccinationen.

**Studie III** bestod av en genomgång av 394 slumpvis utvalda journaler från hela Sverige under 1987-2013 av barn < 3 år med diagnosen invagination. Journalerna granskades utifrån internationellt definerade och accepterade kriterier av diagnosen. Därefter räknades ett positivt prediktivt värde (PPV) fram, d.v.s. hur stor andel (%) av de genomgångna journalerna som överensstämde med kriterierna. Antalet journaler var tillräckligt för att kunna överföra resultaten i en svensk befolkning yngre än 3 år.

De två sista studierna var större registerbaserade kohortstudier där barnens personnummer kopplades till föräldrarnas personnummer och andra relaterade register.

**Studie IV** bestod av 752 048 barn < 5 år under perioden 2006-2012 före införandet av rotavirus vaccin. Geografiska skillnader och skillnader mellan olika grupper baserat på sociala faktorer (t.ex. inkomst, utbildning, födelseland, psykisk sjukdom) för användande av barnsjukvård (inneliggande sjukhusvård och öppen vårdsbesök på akutmottagning till barnläkare) för magsjuka hos små barn studerades.


**Resultat**

**I studie I** avsåg 81 % att vaccinera sitt barn mot rotavirus vaccination medan 11 % var osäkra och 8 % tänkte tacka nej. Faktorer som var relaterade till att vara osäker eller att tacka nej var: 1) Att anse sig ha o tillräckligt med information om vaccinet. 2) Att man ej tänkt låta sitt barn vaccineras mot andra sjukdomar. 3) Att inte tycka att BHV-sjuksköterskans rekommendationer var så viktiga. 4) Att tycka att rotavirus infektion inte är en allvarlig sjukdom. 5) Att inte tro att vaccinet skyddar mot de allvarligaste formerna av rotavirus. 6) Att barnet var yngre än 6 veckor. 7) Att förälderns utbildning var kortare än 12 år.

**I studie II** presenterades fyra huvudsakliga kategorier över uppfattningar kring rotavirus vaccinet som visade på den bredd föräldrars tankar sträcker sig inom: 1) Att vaccinera utan tvekan 2) Tveksamhet att vaccinera. 3) Riskabelt att vaccinera. 4) Onödigt att vaccinera. **I studie III** var PPV hög, nämligen 89 % av journalerna för diagnosen invagination av barn <
3 år i svenska patientregistret uppfyllde de internationella kriterierna för diagnosen. För gruppen av barn < 1 år var PPV 88 %.

**I studie IV** sågs stora geografiska skillnader inom Sverige avseende sjukhusvård för magsjuka hos små barn och ett ökat användande av både inneliggande vård och öppenvårdsbesök för barn till: 1) Mödrar yngre än 25 år. 2) Mödrar med lägre nivå av utbildning. 3) Föräldrar med psykisk sjukdom. 4) Föräldrar där båda två var födda utanför Europa. Alla dessa faktorer tolkades vara associerade med lägre nivåer av "health literacy" dvs förmågan att söka, tillgodogöra sig och använda sig av information om vård av det sjuka barnet.


**Slutsats:**
Införande av rotavirusvaccin i ett svenskt sammanhang minskade användandet av barnläkarvård relaterat till magsjuka hos små barn. Dock kommer andra interventioner än bara vaccin mot rotavirus sannolikt också behövas för att också minska de sociala skillnader som finns i användandet av sjukvård för magsjuka hos små barn i Sverige. Specialinriktad information och övergripande policyförändringar för föräldrar med lägre förmåga att tillgodogöra sig information om egenvård och vaccin skulle kunna vara sådana stödjande insatser. Att underhålla och bibehålla förtroendet för den svenska barnhälsovårdsorganisationen kommer också att vara viktigt framöver för att uppnå hög och jämligt vaccinationstäckning av rotavirusvaccin när det införs i hela Sverige. Viktiga delar i detta är en trygg relation mellan familjen och BVC-sjuksköterskan samt robusta övervakningssystem av vaccinets säkerhet. De fem studierna i denna avhandling ska kunna fungera som en förberedelse inför den svenska introduktionen av rotavirusvaccin och uppföljningen av detta.
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Illustration by Iris Ask, 9 years old (2019)
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