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Vaccines against Rotavirus, Data Based on a Study for Safety and Efficacy

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Abstract

In the history of vaccination, we have savings of lives of people of different ages from children aged 0 days and the very old people.

Before using the rotavirus vaccine in USA 4 or 5 children had symptomatic rotavirus gastroenteritis (RVGE) [1], 1 in 7 children required a clinic or emergency department visit, 1 in 70 cases was hospitalized, one case in 200,000 would die from this disease within age 5 years old [2]. The cost of this situation was estimated approximately $ 1 billion [3]. The situation in developing countries related to rotavirus gastroenteritis continues to be a major cause of severe childhood morbidity, with approximately half a million deaths per year among children aged < 5 years [4].

Of the estimated 8.795 million deaths in children younger than 5 years worldwide in 2008, infectious diseases caused 68% (5.970 million), with the largest percentages due to pneumonia (18%, 1.575 million, uncertainty range [UR] 1.046 million - 1.874 million), diarrhea (15%, 1.336 million, 0.822 million - 2.004 million), and malaria (8%, 0.732 million, 0.601 million - 0.851 million). 41% (3.575 million) of deaths occurred in neonates, and the most important single causes were preterm birth complications (12%, 1.033 million, UR 0.717 million - 1.216 million), birth asphyxia (9%, 0.814 million, 0.563 million - 0.997 million), sepsis (6%, 0.521 million, 0.356 million - 0.735 million), and pneumonia (4%, 0.386 million, 0.264 million-0.545 million). 49% (4.294 million) of child deaths occurred in five countries: India, Nigeria, the Democratic Republic of the Congo, Pakistan, and China [5].

Keywords: *Rotavirus Vaccine; Infection; Intussusception; Safety; Countries; Case*

Introduction

The transmission of rotavirus infectious is a fecal-oral route, through close person to person contact and through fomites [6].

Rotavirus infection is spread not only in low income countries but and in middle and high income countries. This very high spreading is the reason which all of us to pay a lot of attention to measures to prevent this infection, which has not only economic costs but also high health costs. Rotavirus is a virus from the Reoviridae family and is a 70 nm non-enveloped RNA virus, genome with 11 segment double-strained RNA, surrounded by a triple -layered capsid and every fragment encoded the protein in different function.

In year 1969 for the first time was discovered the Rota Virus (RS) in cattle, which was the same the virus causes the diarrhea in mice, calves and also in rectal swab of healthy monkey. 4 years later on may year 1973 Bishop, Davidson, Holmes, and Ruck by electron micros-

copy (EM) which during the examination founded abundant viral particles in the epithelial cell linings of the upper villous surface which were similar in appearance to the RVs discovered in animals (Figure 1).

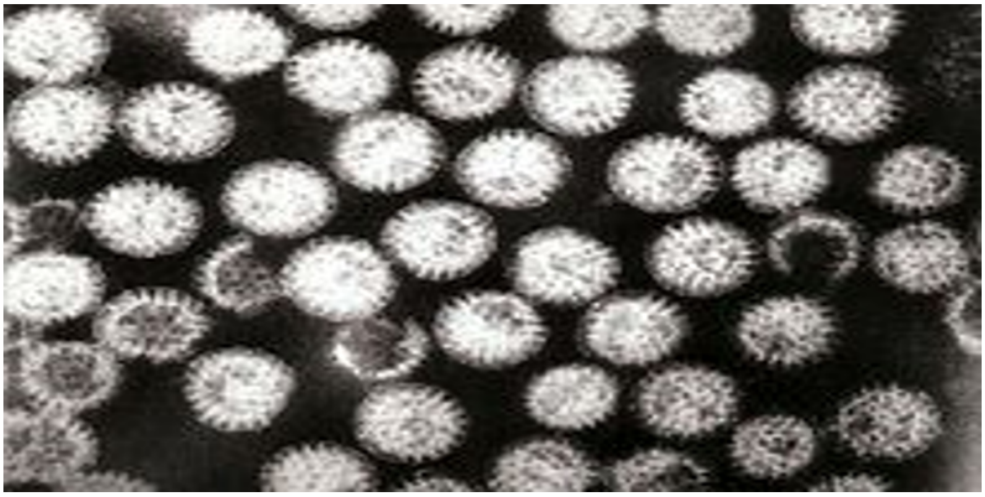

Figure 1: *Rotaviruses in the faeces of an infected child [7].*

Proteins produced in cells infected by rotavirus are show in figure 2.

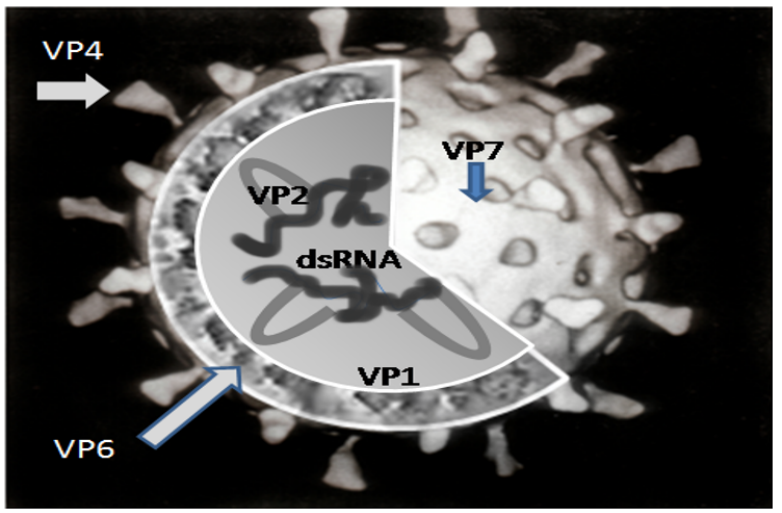

Figure 2: *A simplified diagram of the location of rotavirus structural proteins.*

The proteins produced in cells infected by rotavirus are 6 and called nonstructural proteins NSP1, NSP2, NSP3, NSP4, NSP5 and NSP6, forming virus particle- virion and their role is not clearly understood. The functions are thought to be related to:

1. RNA (ribonucleic acid) synthesis and packaging in the virion,
2. mRNA (messenger ribonucleic acid) transport to the site of genome replication and
3. mRNA translation and regulation of gene expression.

There are 6 viral structural proteins:

1. VP1- is located in core of the virus particle and is RNA dependent RNA polymerase.
2. VP2-forms the core layer of the virion and binds the RNA genome.
3. VP3-is part of the inner core of the virion and is an enzyme called guanylyl transferase.
4. VP4-is on the surface of the virion that protrudes as a spike, binds to molecules on the surface of cells called receptors and drives the entry of the virus into the cell, modified from the protease enzyme trypsin found in the gut, into VP5* and VP8* before the virus is infectious.VP4 determines the virulence of virus and the P-type of the virus.
5. VP6-form the bulk of capsid, highly toxic and used for identification of species of rotavirus.
6. VP7- is glycoprotein in outer surface and determines the G- types and strain and together with VP4 involved in immunity of infection [8,9].

Materials and Methods

The study is performed based in literature for situation in different countries in world for cases of infection from rotavirus. This manuscript include the reported cases of infection before and after vaccination. Situation in countries after vaccination, impact of vaccination with the rotavirus vaccines in decreasing of the number of rotavirus infection. An important point is the safety and efficacy of vaccines, number of Adverse Event Following Immunization (AEFI) in countries.

Results and Discussion

Genotypes of rotavirus and spreading in host

In humans and animals are identified 51 types P and 36 types G.

The differentiate of RV species made with immunofluorescence techniques targeting VP6 and currently are at least 9 species designated from A to I and is in tentative tenth species. Lestari., *et al*. classified the RV according to the genotypes and host spreading in humans and animals. The ten groups of rotavirus A, B, C, D, E, F, G, H, I, J are spread in different hosts as table 1.

Host	Group of Rotavirus
Human	A, B, C, H
Pig	A, B, C, E, F, H
Cattle	A, B
Horse	A
Rabbit	A
Alpaca	A
Turkey	A, G
Pheasant	A

Bat	A, H, J
Sugar Glider	A
Camel	A
Vicugna	A
Velvet Scoter	A
Fox	A
Common Gull	A
Chicken	A, F, G
Shrew	A
Roccoon	A
Mouse	A
Sheep	A
Partridge	A, G
Panda	A
Monkey	A
Mussel	A
Oyster	A
Shellfish	A
Salmon	A
Shark	A
Trout	A
Deer	A
Mosquito	A
Cormorant	A
Fly	A
Moth	A
Tick	A
Tasmanian Devil	A
Leafhopper	A
Buffalo	A
Antelope	A
Dog	A, C, I
Civet	A
Cat	A, I
Giraffe	A
Pigeon	A, D, G
Guanaco	A
Macaques	A

Table 1: *Classification of RV according to the genotypes and host spreading.*

All mammals are infected from rotavirus group A, but more sensitive from infections with more one group of rotavirus are pig with A, B, C, E, F, H, human with A, B, C, H, bat with A, H, J, chicken with A, F, G, dog with A, C, I and Pigeon with A, D, G group.

Cases of infection reported in different countries

The situation of rotavirus infection before vaccination with rotavirus vaccine in different countries in world.

Southeast Asia infection situation: Lestari., *et al*. study the situation of infection caused by RV infection reported 40.78% of all diarrheal disease in children smaller than 5 years old. Today, the infection of RV cause the morbidity and mortality for the children under 5 years, especially from distribution predominant genotype which changed form G1P [8] and G2P [4] into G3P [8], G8P [8] and G9P [8], which are rare and unusual transformation. RV infection season does not changed while ascendant strain changed. The infection with RV can decreased using of vaccination with effective vaccines [9].

Rotavirus in Albania

In the current condition, considering the important contribution of Rotaviruses in the overall rate of diarrheal disease in the pediatric population of the city of Tirana, Albania and its surroundings, the specific vaccine would certainly be an important contribution, able to prevent at least two thirds of the burden of cases of diarrhea in all clinical forms, both clinical and morbidity, and cases of hospitalization and deaths related to Rotaviruses, which continue to heavily affect the country's pediatric population [10].

The vaccination against Rotavirus infection in Albania started on October 1, 2019 and administered orally [11].

The vaccination with Rotavirus vaccines is in Albania in age 2, 4 and 6 months based in the calendar of the National Program of vaccination [12].

Rotavirus situation in Europe

In European countries approximately hospitalized 300-600 children per 100,000 under 5 years old from Rota Virus Gastro Enteric (RVGE) every year. Between European countries occurs different genomes of RV at different times. In EU/EEA countries with approximately five million births per year has approximately 75,000 to 150,000 hospitalizations of children in age under 5 years old. The higher number 2 to 4 times more children appear in emergency rooms or other health facilities for medical services for health assessment. The rate of mortality was low according to 2 study performed for children the age under 5 years old were:

- The first study mortality rates were 0.1/100,000.
- The second study mortality rates were 0.2/100,000.

Factors which impact for severe of RVGE are some as hygiene, feeding and weight of birth. If the children live in bed condition of hygiene have malnutrition and the birth weight was low these children are more exposed from the risk of rotavirus infection [13].

Situation of rotavirus USA

USA situation of infection with RV before implementation of vaccination were 2,7 million rotavirus infections every year and 95% of children at least has experienced one rotavirus infection by age 5 years. The infection of rotavirus in the case studied from Margaret M. Cortese., *et al*. resulted a high physician visits around 410,000 and 200,000 emergency visits and 55,000 - 70,000 hospitalizations and 20 to 60 deaths annually in children age under 5 years old.

The higher incidence of clinical illness was for children 3 to 35 months in case of 30% to 50% of all hospitalizations for gastroenteritis children under 5 years old [14].

Monitoring of safety of vaccine from CDC (Center for diseases control and prevention)

The vaccine approved from FDA and CDC, and if the problem occur during the implementation of vaccination both of institutions will inform officially all health institutions, health care providers and public about the concern.

The way of monitoring the safety of vaccine in USA are 3 systems:

- First system of monitoring safety of vaccines from CDC is vaccines adverse event reporting system (VAERS), with co-managed both institutions where detect the serious problem officially inform all health institutions and public.
- Second system is vaccine safety datalink (VSD), CDC and 9 healthcare organizations conduct the monitoring of vaccines safety
- Third system is clinical immunization safety assessment (CISA) project. CDC and research center in partnership give the expert consultation and arrange the clinical research for safety of vaccines related for the risk of health.

CISA is national network of vaccine safety in collaboration with CDC immunization safety office arrange with 7 medical research centers and other partners the study for safety of vaccines in generally [15].

Common side effects reported for rotavirus vaccines are irritability, mild and temporary diarrhea or vomiting.

Intussusception which happen in some infants every year in USA. This is a small risk from vaccination with rotavirus and is estimated in USA 1/20,000 to 2/100,000 infants who gets rotavirus vaccine. The intussusception treated in hospital and sometimes require and surgery.

Happen and for medicines and the chance is for vaccines to have AEFI serious, severe or death. The parents should advised in case of intussusception to look for sign of stomach pain during the severe crying, episode which can be for few minutes but repeat sometime an hour.

Safety of vaccine

Babies vomit sometimes, move the legs up the chest, have blood in the stool, is weak and irritable. These can happen the first week of the first or second dose of vaccination with rotavirus vaccine. In case of intussusception should contact the health care provider or the hospital.

In case of allergic reaction the parents should be careful to check if the baby after vaccination have hives, swelling of the face and throat, difficulty breathing, a fast heartbeat, dizziness or weakness, case is serious and should contact health care providers or go to the hospital and the reported of AEFI should make in VAERS VAERS websiteexternal icon[16].

Adverse event were collected from the clinical trial for RV vaccines 5 Valente, for 42 days after the vaccination of each dose from the recipients table 2.

Adverse events reported	Vaccine group	Placebo group
Diarrhea	18.1%	15.3%
Vomiting	11.6%	9.9%

Table 2: *The results of investigation in the first week after every dose of vaccination with RV5.*

The adverse events resulted from the group of the children vaccinated with RV5 rotavirus vaccine five Valente show close results of the adverse events with the children in placebo group. The results are to close but statistically are significant and the results should be considered.

All period of investigation 42 days the results for any dose of vaccination of RV5 show vomiting, otitis media, nasopharyngitis, bronchospasm statistically greater than in placebo recipients.

Flatulence are reported 2.2% in RV1 group and 1.3% in placebo group.

Serious AEFI including and death the investigation show the same results between RV1 and placebo recipients except cough or runny nose which are higher in RV1 recipient vaccine (grade 3) 3,6% and 3,2% in placebo group.

USA and other countries during the post-marketing strain surveillance in stool sample of children with diarrhea detected rotavirus vaccine with reassortant strains, virus which think is the cause of diarrhea in this group.

The evaluation of phase III clinical trial were involved more than 60,000 infants for each RV5 and RV1 vaccine for intussusception after vaccination show no increased risk after vaccination.

In USA the case of intussusception 1 week after vaccination with first or second dose RV are evaluated 1 case per 20,000 to 100,000 recipients of vaccine, but this can happen and up 21 days after the first dose. In some middle or low income countries are reported the case of intussusception of RV5 or RV1 which request the monitoring of AEFI and after the detailed the information from the clinical trial. Related to the serious adverse events following immunization, include and deaths, the results were the same between placebo and RV5 for any dose of vaccination.

The period of investigation show that the rate of gastroenteritis after every dose of vaccination was 0.2% after RV5 and 0.3% in placebo recipient, as see the results are almost same.

Clinical trial results for RV1 vaccine

The participants were monitored for 31 days for AEFI after vaccination. The results of investigation were:

Irritability: 11.4% in RV1 vaccinated and 8.7% in placebo group which statistically is high incidence.

Immunogenicity and vaccine efficacy

Infection from the rotavirus caused very high any gastroenteritis: 74% - 87% and severe gastroenteritis: 85% - 98%. The vaccines against rotavirus has high impact in reducing the number of infection with rotavirus and the hospitalization of patients. A clinical study were performed in USA and Finland for the phase III of efficacy of rotavirus vaccines. The results of the study during the first full rotavirus season for 3 doses series against G1- G4 rotavirus gastroenteritis of any severity was 74%, and 98% for severe G1-G4 rotavirus gastroenteritis. The vaccination RV5 reduced the infection of children in the first 2 years of life the incidence of office visits for G1-G4 rotavirus gastroenteritis by 86%, emergency department visits for that outcome by 94%, and hospitalizations for that outcome by 96%.

The clinical trial phase III for the efficacy of RV1 in Latin America 2 doses series against severe gastroenteritis to age 1 was 85% and in European study 96% was the efficacy of severe rotavirus gastroenteritis the first rotavirus season, 87% efficacy for any rotavirus gastroenteritis infection and 96% efficacy of vaccines for gastroenteritis through the second season after vaccination.

RV5 introduced in 2006 and RV1 introduced in 2008 in USA and time after time are conducted case control for RV5 and RV1 vaccines especially for children 2 or 3 years old. On 2017 published the data for effectiveness of vaccines against rotavirus and meta- analysis re-

sulted 84% for RV5 vaccines and 83% for RV 1 vaccine for a full series against rotavirus. This results were compared with the emergency department visit or hospitalization for rotavirus diseases. The effectiveness of vaccines tend increase depend from the rotavirus disease severity, across rotavirus genotypes.

The effectiveness of rotavirus vaccines is different in countries. In USA the effectiveness is higher than in low -income countries, which is lower in second year of life than the first year of life.

Study in EU for safety of rotavirus vaccine

As the rotavirus are administered orally are very tolerated with the AEFI as: vomiting, diarrhea, fever and the conclusion achieved from the study injected rotavirus vaccines and placebo in infants, but important issue is intussusception risk.

The study performed for intussusception show that the infants of age 4 to 10 months are more vulnerable from intussusception. The incidence of intussusception in worldwide is 74 cases for 100,000 children under 1 year old and 9 to 328 cases for 100,000 in different countries for infants 4 to 6 months old. On 1998 was licensed tetravalent rhesus-human reassortant vaccines Rotashield, (RRV-TV) safety profile has been studied in detail.

The clinical trial phase III involved 60,000 infants for HRV (human rotavirus) and HBRV (human bovine rotavirus) and the results did not have any increased of intussusception cases compare with placebo group. The ratio was 6 per 100,000 cases of intussusception 7 days after vaccination with HRV and HBRV and the background of incidence 25 - 101 per 100,000 per year. The evidence is limited for risk following the second dose.

Meta-analysis show the similar results during the evaluation of studies of HRV and HBRV conducted in England intussusception cases were 4,53/100,000 doses which mean 21 cases annually and should be considered in the context of 50,000 AGE hospitalizations prevented seasonally the herd effects, and Finland 1,04 per 100,000 vaccine doses to prevent 80-90% of rotavirus disease and hospitalization and Spain with not significant number of intussusception risk, with low coverage <50% and low number cases during the study period.

The studies in three countries for the risk of intussusception with rotavirus vaccines after vaccination resulted the highest number after the first dose of vaccines and increased risk was after the second dose only in England.

The risk of intussusception during the first 7 days post-vaccination is very low. The benefit-risk profile of rotavirus vaccines remains favorable. However, vaccination should be accompanied by parental advice for the close monitoring of infants and the signs and symptoms of intussusception, with instructions to seek medical advice early. To this end, healthcare professionals need to be educated and encouraged to systematically inform parents about the risk of intussusception and the benefits of early medical attention [17].

Rotavirus vaccines as other vaccines or medicines in generally can cause side effect which can be mild and no long time.

The vaccines against rotavirus can cause:

1. **Common side effects**
   a) Restless or irritable babies
   b) Mild diarrhea
2. **Rare side effects**
   a) Allergic reaction and the possibility to cause the severe allergic reaction anaphylaxis were 1 in 1 million. This side effects happen quickly and vaccinators are trained how to act in case of anaphylactic reactions. Children can covered completely with right treatment.

3. **Very rare side effects**

a) Blocked intestine, is very rare side effect has possibility between 1 and 6 per 100.000 babies which can blocked the intestine of baby, intussusception with the symptoms:

i. Tummy ache

ii. Being sick

iii. Stool that looks like redcurrant jelly in the baby's nappy.

In case of intussusception side effects the parents should go in healthcare center or hospital for treatment of child [18].

Safety of rotavirus vaccine in Japan

Japan launched the rotavirus vaccines RV1in November 2011 and RV5 in July 2012 as voluntary vaccination. The coverage of RV vaccination in Japan increased from 30.0% in 2017 to 78.4% in 2019. Japan after RV vaccination decreased the number of rotavirus gastroenteritis infection in 2014. October 2020 Japan introduce the RV vaccines in National Program of immunization which expected to decrease more the infection of rotavirus gastroenteritis infection in country. The period 2007 - 2011 before the vaccination with RV vaccines the incidence of intussusception were 102,8 and 94,0 respectively per 100,000 per year in children smaller than 1 year old. The period 2012 - September 2014 introducing the vaccines in Japan the number of intussusception decreased. The first dose of vaccination with rotavirus vaccines in Japan implemented at age smaller 15 weeks, preferable 2 months to reduce the intussusception risk after vaccination. The strain spread in country are DS-1 like G1P [8], G3, and G8P [8]. The study conducted in Japan analysis all 11 RV genome segments for genetic characteristics of prevalent RV strains and the influence of vaccination on genetic changes of RV strains and the new genotypes [19].

Safety of rotavirus vaccines in China

China has a large birth cohort of approximately 16 million live births per year. As the number of the birth is high and the hospitalization with rotavirus associated diarrhea is high from 30% to 50%. The national immunization plan for rotavirus vaccine will help to decrease the rate of gastroenteritis in China, to save the health and financial cost. Study performed in China for rotavirus vaccination with the cost- effective are vaccines LLR, Rotarix and Rotateq 7 with 79% efficacy against moderate to severe rotavirus gastroenteritis. Studies performed for the benefit of rotavirus vaccination performed from Fu., *et al*. achieved the conclusion than vaccination against rotavirus should schedule in the programme according to the recommendation of WHO. Burret., *et al*. analysis estimated 50% reduction of hospitalization from rotavirus infections and 40% reduction of death associated to rotavirus infection in Asia if the vaccine should use widely in this region.

Safety of ROTAVAC in India

Rotavirus disease burden globally and in India

Children < 5 years old are risked of rotavirus infection. According to Rao TS., *et al*. vaccine, 2014 [20] 1 in 260 children die, and in worldwide 453.0000 deaths, 2,5 million hospitalizations which means 1 in 58 children and 24 million outpatient visit 1 in 5 children.

The vaccines used against rotavirus infectious

Rotavac (a G9, P [11] reassortant) licensed in India

Efficacy vs. severe RV gastroenteritis by serotype

Every year in India estimated 11,37 million illness episodes, 3,27 million outpatient visits and 872,000 inpatient causes from RV gastroenteritis based on the cohort of birth 2011. This situation cost USD 172,8 millions/year.

The infection of RV in India cause:

a) 39% of gastroenteritis hospitalizations

b) 78,000 deaths in children under 5 years old.

ROTAVAC introduced in India in 2016 for 4 states and in 2017 in other 5 states. The ROTAVAC is live attenuated, oral virus vaccines and contain 116E strain (G9P [11]) and the results of clinical trial of Rotavac vaccine are in table 3.

	ROTAVAC® **N = 4354**	**Placebo** **N = 2187**	**Vaccine Efficacy** **% (95%CI)**
All	93 (2,1%)	102 (4,7%)	55.1% (39.9, 66.4)
G_1 P [8]	40 (40%)	34 (1,6%)	42.0% (5.6, 64.2)
G_2 P [4]	26 (0,6%)	35 (1,6%)	63.4% (37.4, 78.8)
G_{12} P [6]	8 (0,2%)	13 (0,6%)	
G_{12} P [8]	5 (0,1%)	8 (0,4%)	
Others	8 (0,2%)	12 (0,5%)	

Table 3: *Results of clinical trial of Rotavac vaccine.*

The clinical trial on efficacy of ROTAVAC did not detect an increased risk of intussusception, but the trial was not large enough to detect a small risk. This protocol paper describes the establishment and implementation of a surveillance system to monitor the safety of rotavirus vaccine and investigate the potential infectious etiologies of intussusception.

Has not enough data to detect the cases with intussusception after rotavirus vaccination [21,22].

Report for Kawasaki diseases

Jahangir John., *et al*. study the intussusception in southern India. The study of clinical trial phase III involved 1500 infants age 6 week in ration 2 vaccines/1 placebo resulted intestinal vascular compromise assessed by the passage of blood in stool or red currant jelly stools for 55 infants approximately 93,2% [23].

Based on the study of Felicetti., *et al*. the reports of AEFI with Kawasaki Diseases (KD) 20% of reports are from rotavirus vaccines [24].

The efficacy and safety of rotavirus vaccines in countries in Africa and Asia with high child mortality

The safety of rotavirus vaccines related to IS risk any case is reported during the analysis performed observational self-controlled. The evidence are limited for IS risk for the three rotavirus vaccines evaluated Rotavac™, Rotarix™, Rotateq™ and Rotasiil™ has no self-controlled for IS. The benefit of Rotarix™ and Rotateq™ is evaluated from GACVS (the Global Advisory Committee on Vaccine Safety) was greater than risk from IS support the evaluation in the study. The IS risk of Rotateq™ vaccines in sub- Saharan Africa and Rotavac™ in India had no any indication post- vaccination surveillance compare with the risk from clinical trial results, the review of safety made from GACVS in meeting on December 2019.WHO (World Health Organization), GACVS and SAGE (Strategic Advisory Group of Experts on Immunization) from systematic review of safety and effectivity of rotavirus vaccines prequalified Rotarix™, RotaTeq™, Rotavac® and Rotasiil™ concluded in October 2020 that for vaccines can use as are safe and effective. The post vaccination surveillance should be in country for safety of rotavirus vaccines. Data from the different countries show the decreasing of the number of infection of children with rotavirus infection, reducing diarrheal morbidity and mortality for children in countries Africa and Asia with high number of infection [25].

Safety of vaccines in Latin America and Caribbean countries

RV1 did not result to have the IS risk or death according to the study and evaluation of the investigations of AEFI.

According the reports Rotavirus vaccination did not increase the risk of death, IS or other severe adverse events in children. 3 Clinical trials with RV5 involved 71,690 children the relative risk of IS was 1.34; 95% CI: 0.92-1.96; compare with 3 cases in placebo group. Clinical trial in Jamaica with RV5, 1 infants vaccinated and 3 recipients of placebo the four death were not related to the vaccine. 3 Clinical trial study conducted in pre-licensure RV1, involved 71,690 children, immunized children with RV1 relative risk 0.89; 95% CI: 0.83-0.95. Severe adverse event were reported for RV5 vaccinated in 3.5% (31/898) and placebo recipients 4.8% (43/904):

- 1 case reported of febrile infection and gastroenteritis related to RV5
- Effectiveness and impact assessment
- Study selection in region of Valencia with 48,000 birth/year among a total population 5 million inhabitants [26].

Australian surveillance

The Australian surveillance include the reports for AEFI for vaccines administered on year 2020 and trends of AEFI for 21 years from January 2000 to December 2020 reported in Therapeutic Goods Administration (TGA). The surveillance is spontaneous reporting.

According to the TGA the reporting of AEFI of vaccine does not necessarily have a causal relationship with the vaccine, because may be any unfavorable or intended sign, abnormal laboratory finding, symptom or disease or may be coincidental.

Other explanation is that AEFI occur following the incorrect handling and/ or administration of vaccine/s.

The cause of AEFI are different and cannot detected all during the registration of vaccines (clinical trial study) and it is important the post- marketing surveillance of vaccines, for detection of rare and very rare cases of AEFI in rate per 100,000 population (Figure 3).

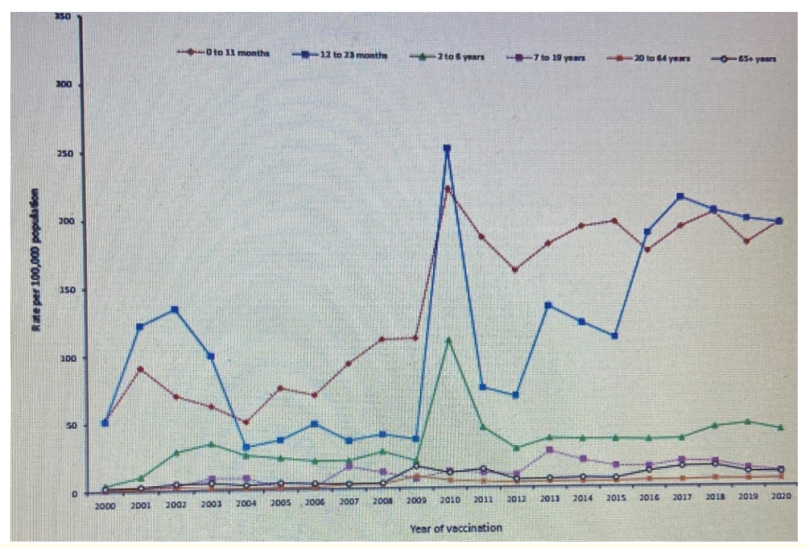

Figure 3: *Reporting rate of AEFI per 100,000 population, AEMS database year 2000-2020 by age group and year of vaccination.*

Based on the AEMS database the number of AEFI for rotavirus were n = 358; 9.4% per 100,000 children.

The vaccines against rotavirus introduce in Australia on July 1, 2007 were Rotateq and Rotarix and reporting AEFI for these vaccines are in table 4 [27]. The IS cases are reported in different countries for rotavirus vaccines as show in table 5.

Vaccine	AEFI records	Vaccine doses 2020	Reporting rate/100,000 95% CI year 2020
Rotarix [27]	351	532,175	660,573

Table 4: *AEFI reporting for Rotavirus on year 2020.*

Country	Doses	IS AEFI report after vaccination	References
Spain-Valencia Rotarix vaccine Rotateq vaccine	 1 2 3 1 2 0	 3 cases/1-7 days after 1 case/1-7 days after 0 case 1 cases/8-21 day after 3 cases/8-21 day after	[28]
Finland		1.04/100,000	[29]
Vietnam: Ho Chi Minh Hanoi		 287 302	
Korea		328	
India clinical trial phase 3 Surveillance was 375 days after the vaccination, longer than time for significantly event happen around 214 days		254/ year children till 2 yrs. according to the Brighton criteria level 1 406/year in second half of the first year of life	[22]
Italy the first study conducted for IS which resulted higher for male than female		1-5 weeks- 15 6-14 weeks- 19 15-24 weeks- 47 25-32 weeks- 60 33-52 weeks- 41 1-3 years- 15 4-6 years- 15	[30]

Table 5: *Summarize for IS cases from rotavirus vaccine in different countries.*

Conclusion

1. The vaccines against rotavirus infection has decrease significantly the number of infection of infants.
2. All data showed that the benefit from the rotavirus vaccines are high and this vaccines is necessary to implemented not only in countries with low or middle income but and in developed countries.
3. The reporting AEFI is very important for increasing the risk for any adverse events.
4. The education of health care staff also is important to have all information for quick and necessary intervention to eliminate fatal cases for children's lives.
5. Parents also should inform exactly for every situation can happen with the child after vaccination for to increase their vigilance for any AEFI and to address it in right time in healthcare providers or hospital.

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