

RESEARCH PAPER

 OPEN ACCESS



Lack of impact of rotavirus vaccines on seizure-related hospitalizations in children under 5 years old in Spain

Alejandro Orrico-Sánchez ^{a,†}, Mónica López-Lacort^{a,b,†}, Cintia Muñoz-Quiles ^{a,b}, and Javier Díez-Domingo ^{a,b}

^aVaccine Research, Fundación para el Fomento de la Investigación Sanitaria y, Biomédica de la Comunitat Valenciana, FISABIO-Public Health, Valencia, Spain; ^bUniversidad Católica de Valencia ‘San Vicente Martir’, Valencia, Spain

ABSTRACT

Introduction: Up to date the impact of rotavirus (RV) vaccines on seizures has been poorly evaluated, with some studies but not all, showing different degrees of protection.

Objectives: To assess the impact of RV vaccines on convulsions-related hospitalizations among children under 5 years of age residing in the Region of Valencia, Spain.

Methods: A population-based, ecological study using the hospital discharge record (MBDS), the population-based administrative database (SIP) and the vaccine register (SIV), among Valencia Region’s children <5 years old, during 2003 – 2015. Impact of vaccination on seizures-related hospitalization rates (780.3* ICD-9-MC code) was estimated by a multivariate Bayesian mixed Poisson regression model.

Results: Since RV vaccines licensure in 2007, its coverage rate increased up to around 42%. When the impact of vaccination against seizures was controlled for potential confounders in the multivariate analysis, there was a non-statistically significant protective effect.

Conclusions: We could not find any impact of RV vaccine coverage on seizure-related hospitalizations in children <5 years.

ARTICLE HISTORY

Received 5 September 2017

Revised 16 January 2018

Accepted 27 January 2018

KEYWORDS

Child; hospitalization; Impact; Rotavirus; Seizures; Spain; vaccines

Introduction

Rotavirus (RV) was the commonest cause of acute gastroenteritis (AGE) in young children before vaccination, and had a major impact on health care systems and the quality of life of children and their families.^{1–5} Less recognized are the effects of rotavirus infections on the central nervous system, which have been associated with seizures and other systemic manifestations.^{6–11}

Some authors have shown that approximately 2%–7% of pediatric patients with rotavirus gastroenteritis had also seizures, either febrile or non-febrile.^{11–14} The pathogenesis of the seizures is still unknown, although several hypotheses have been postulated.^{8,15} Recently, the rotavirus non-structural protein 4 (NSP4) has been implicated in the neurological manifestations of rotavirus and serum anti-NSP4 IgGs could play a possible role in seizure protection in patients with rotavirus gastroenteritis.^{10,12,15} Rotavirus-related higher levels of nitric oxide in cerebrospinal fluid,¹⁶ and/or calcium channel fluctuations have also been described.^{12,17}

Up to date the impact of RV vaccines on seizures has been poorly evaluated, with some studies but not all, showing different degrees of protection.^{12,18–21}

Rotavirus vaccines are available in Spain since 2007. Their inclusion in national immunization programmes is strongly recommended by institutions such as the World Health Organization, the Centers for Disease Control and Prevention, and the Pediatric Spanish Society.^{1,22,23} However, rotavirus vaccines

are not funded by the Spanish National Health System (NHS), therefore, RV vaccines coverage rates are relatively low (around 40%).^{24,25}



It is, therefore, necessary to continue the search for scientific evidence in this field. Continuation of the surveillance and further population-based studies are needed to clarify the above-mentioned findings. These studies should be designed in such a way that the results could be directly attributed to the vaccine, minimizing thus potential bias.

The present study aims to assess the specific impact of rotavirus vaccines on convulsion-related hospitalizations among children under 5 years of age residing in the Region of Valencia by using a very restricted analytical model, to control for potential confounders and avoid external bias.

Results

Characteristics of the study population

Among the total 295,364 hospitalizations of children < 5 years of age in our study cohort, 9170 (3%) had a convulsion diagnosis code (780.3X ICD-9-CM). Age was related to the frequency of admissions and also to the length of stay (LOS), Almost 45% of the admissions were consisted by patients in the age group of 12 – 24 months. Younger children had longer hospitalizations. Boys were admitted more frequently for convulsions (54%) than girls (Table 1).

CONTACT Alejandro Orrico-Sánchez  orrico_ale@gva.es  Director of the Vaccine Research Department, FISABIO-Public Health, Valencia, Spain.

[†]These authors contributed equally to the work.

© 2018 Alejandro Orrico-Sanchez, Monica Lopez-Lacort, Cintia Muñoz-Quiles, and Javier Díez-Domingo. Published with license by Taylor & Francis
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

Table 1. Descriptive analysis of cumulative hospitalizations for convulsions in children <5 years old of The Region of Valencia between 2002 and 2015.

	Hospitalizations (780.3 ICD-9_CM)		
	Number	Days	LOS
Age (years)			
0	1644	10110	615
1	4101	13713	3.34
2	2019	6490	3.21
3	919	2955	3.22
4	487	1517	3.11
Gender			
Boys	5020	18716	3.73
Girls	4150	16069	3.87

Number of hospitalizations (Number). Total days of stay (Days). Average length of stay in days (LOS).

Rotavirus vaccine impact

Hospitalizations with a seizure diagnostic code (780.3X ICD-9-CM code) showed a decreasing trend over the study period, while the mean RV vaccine coverage increased to include up to 42.1% of the cohort. In fact, the annual hospitalization rate for convulsions in children < 3 years was negatively correlated with RV vaccine coverage ($p < 0.05$) (Table 2). However, all-cause hospitalizations (for any cause except RVAGE and convulsions) rate decreased over the study period and was negatively correlated with the vaccination coverage ($p < 0.05$) (Table 2).

The adjusted Bayesian mixed Poisson regression model was performed to assess the impact of vaccination on convulsion-related hospitalizations and to control potential bias (e.g. all-cause hospitalizations rate) (Table 3). The model showed that the seizure-associated hospitalizations risk was 11% (7-15%) higher in boys than in girls (Table 3). There was an age-related association of convulsion-hospitalizations, so that the highest incidence of hospitalizations was in children 1-2 years, and when the impact of vaccination against seizures was controlled for potential bias, there was a non-statistically significant protective effect (Table 3). The risk of seizure-hospitalizations decreased slightly (about 5%) but not significantly in children <5 years old and it was unrelated to vaccine coverage (Table 3).

Discussion

In the present study we did not find the introduction of the rotavirus vaccines to have an impact on seizure-related hospitalizations in Spain, although vaccination coverage has increased up to around 40%.

Table 2. Spearman's correlation coefficient between rotavirus vaccine coverage, convulsions and Other hospitalizations (for any cause except RVAGE and Seizures) rates for the different age groups.

Age	Convulsions	Other hosp.
0	-0.7395*	-0.7465*
1	-0.9248*	-0.8109*
2	-0.6383*	-0.6322*
3	-0.5333	-0.6167
4	-0.5000	-0.0953

*p-value < 0.05

RV vaccines were licensed in Spain around 2007, when the economic crisis started. This had a major impact on funding and provisioning for the healthcare system.²⁶ It has been described that changes in admission policies can be the result of economic constraints.²⁷ Accordingly, we have shown that the use of rotavirus vaccines was significantly correlated with reductions not only in convulsion-related hospitalizations, but also in all-cause hospitalizations. Therefore, when these data were analyzed, controlling for potential bias, as it is needed in observational studies and especially in ecological studies,²⁸ we did not find any impact of the vaccine on the prevention of seizures. The model showed a non-significant reduction in the risk of hospitalization for convulsions by around 5%, which was unrelated to vaccine coverage. Therefore, other non-controlled variables may explain these findings.

These results are in disagreement with some recent studies which showed a risk reduction in seizures in RV vaccinated populations^{18,20} and in the impact on seizure-related hospitalizations.¹⁹ The authors of these recent studies suggested that rotavirus vaccination directly prevents systemic rotavirus infection reducing thus both non-febrile¹⁸ and febrile seizures.^{19,20}

Only one other methodologically comparable ecological study¹⁹ showed that the hospitalization rate for convulsions was negatively correlated with the rotavirus vaccination coverage in the same range with our study analysis (Table 2). When they compared convulsion-related hospitalizations mean rates in the pre- and post-vaccination period, they noted a decrease between 18.7% and 42.5%.¹⁹ Authors did not control for potential bias variables, as for the number of hospitalizations for other causes, seasonality, etc. Interestingly, we found that the impact of RV vaccines coverage on seizures disappeared in the multivariate analysis.

A retrospective analysis of a cohort of US children using the vaccine safety datalink (VSD) found that a full course of rotavirus vaccination significantly reduced the risk of seizures in children attending emergency rooms or in the hospitalized ones, by 18-21%, at least during the year following the last rotavirus vaccination. This study is not comparable with ours due to methodological differences. First, they collected data by using a larger number of ICD-9 related codes (780.3 + 779.0 + 333.2 + 345) including thus epilepsy and neonatal seizures, which may not add relevant information.²⁹ Second, their vaccine coverage reached 75%. Despite the differences found, the expected decrease of cases in our study should be proportional to the percentage of children vaccinated, and should reach 8 to 16% with a vaccination coverage of around 40%. Finally, it is important to highlight that these results may have some potential bias, as they had a moderate (64%) positive predictive value (PPV) in children attended in emergency room,^{18,30,31} which accounted for the 68% of the study.

Sheridan et al. showed using linked databases that rotavirus vaccine was 38% effective at preventing hospitalization for febrile seizures in Australia.²⁰ Both groups, vaccinated and unvaccinated, as stated by the authors,²⁰ could differ in influenza vaccination rates, as it was more likely that children vaccinated with rotavirus vaccine would have also been vaccinated against influenza, another common cause of febrile seizures, which could lead to a possible bias. This possible bias is also presented in the USA study,¹⁸ where, as they mentioned, they

Table 3. Adjusted Relative Risk (RR) of convulsions-associated hospitalizations depending on the gender, age group and vaccination coverage.

	Convulsions (780,3 ICD-9-CM code)
Age (years)	<5
Gender	
Male	1
Female	0.89 (0.85 – 0.93)
Age group	
4	1
0	2.22 (1.89 – 2.58)
1	6.23 (5.60 – 6.84)
2	3.39 (3.07 – 3.75)
3	1.70 (1.53 – 1.87)
RV vaccine coverage	
0%	1
1-19%	0.95 (0.88-1.03)
20-39%	0.96 (0.86-1.05)
≥40%	0.95 (0.84-1.08)

(95% CrI)

*Poisson regression adjusted for gender, time, time in post-vaccination period, month of the year, health department and total hospitalization rate except convulsions (780.3 ICD-9).

were unable to control for some other seizure-causing pathogen with similar seasonality as RV. Indeed, the influenza vaccination coverage in the USA during the study period was between 43–52%³² and it could, therefore, have influenced seizures variations. Other authors, when estimated the RV vaccine effectiveness, controlled the variable of “other vaccines received” in order to make both groups comparable.³³

Other studies made in Asia have also described the lack of impact of rotavirus vaccination in seizure-related hospitalizations.^{12,21} They even showed a higher incidence of seizures in the post-vaccination period, potentially related to specific neurotransmitter interferences at calcium/sodium channels level or the increasing rate of rotavirus immunization and norovirus infection.^{17,21,34-37} Supporting this hypothesis, norovirus has been increasingly reported as one of the most prevalent causes of AGE since the introduction of rotavirus vaccines,^{18,37} and one of the most important causative viral agents for convulsions.³⁵⁻³⁸

Although, we have been able, with this methodology, to assess a coverage-dependent response impact of non routine vaccination on AGE,²⁴ our study may have some limitations. The fact that rotavirus vaccines are not funded by the Spanish health system may lead to socio-economic differences between rotavirus vaccinated and non-vaccinated populations.⁴ In addition, we could have missed some data of vaccines administered in private vaccination centres not using SIV. Nonetheless, this percentage should be minimal, as a recent study showed that approximately 83% of the rotavirus vaccines distributed in Valencia were registered in SIV.³⁹ Data about seizures in Emergency Departments (ED) were not considered for the analysis, due to the moderate PPV of seizure codes in ED published¹⁸ and the fact that the ethics committee did not allow to review clinical charts. Finally, our design cannot distinguish between non-febrile and febrile seizures.

In conclusion, after controlling for potential bias variables we could not find any impact of RV vaccines coverage on seizure-related hospitalizations in children < 5 years of age.

Based on the limited number of studies and the lack of quality in some of them, there is not enough scientific evidence to

ensure a direct association between RV vaccination and the prevention of seizures.

Materials and methods

Study settings and population

This is a retrospective population-based ecological study performed with routinely collected health data in the Valencia Region of Spain. The study included all children residing in the Region born between January 1st 2003 and December 31st 2014, aged less than 5 years. The study period lasted from the 1st of January 2003 until the 30th of September 2015.

The total population of The Region is approximately 5,000,000 people, with an annual birth cohort of 48,000 infants. Approximately 98.3% of the population is covered by the public health system.⁴⁰ The current regional health system consists of 24 Departments. Each of them includes at least one hospital and a number of ambulatory centres. However, this distribution has varied over the years, so we have considered for analysis the structure of 2002 consisting of 19 departments. All primary care visits and hospitalizations are recorded in clinical databases.

Data sources

The population data was obtained from the regional population-based administrative database (SIP) that collects and updates demographic data, health services assignment and usage of the health system.⁴¹ For hospitalization, we used the hospital discharge database, MBDS (minimum basic data set)³³ that collects diagnosis and procedures as an assessment of medical activity. The coding system used is ICD-9-CM.

Case definition

Seizure-associated hospitalizations were codified in MBDS with the ICD-9-CM code 780.3X (corresponding to convulsions).

Our outcome was: convulsion-related hospitalization, defined as hospitalization with a discharge diagnosis convulsion (ICD-9-CM code 780.3X) in any diagnosis position.

Vaccine coverage

Vaccination coverage was defined as the proportion of the study population vaccinated with at least one dose of RV vaccines, without distinction between vaccines brands. It was obtained from the regional vaccine information system (SIV), where administered doses are registered.³³

Statistical analysis

Database administrators provided the information regarding population, vaccination and hospitalizations aggregated by gender, age, year, month and health department. There was no sample size calculation as we analyzed the whole population.

In a preliminary analysis the correlation between vaccine coverage and annual admission rates for convulsions was studied. As analysis of secular trends in ecological studies may be

biased for a number of reasons,²⁸ we also analyzed the correlation between vaccination coverage and the total hospitalizations for any cause (except for convulsions and RVAGE), by age groups, using the Spearman correlation coefficient.

As there was also a correlation between vaccination coverage and all-cause hospitalizations, a multivariate model was used to assess the impact of vaccination on monthly seizure-related hospitalization rates. This Bayesian mixed Poisson regression model controlled by age, gender, vaccine coverage (stratified in 4 groups: 0%, 1–19%, 20–39% and $\geq 40\%$), health department (as a random variable), time in months from the start of the observation period, time from vaccines licensure, and seasonality as the month of the year. The id. variable (corresponding with records from the database) was also controlled as a random effect to avoid over-dispersion.^{1,24} In addition, the model was adjusted by the total hospitalization rate for all causes except convulsions (in quintiles) to decrease external bias.

The confounder variables adjustment in the multivariate model allows mitigating potential bias such as: clinical variations in medical practice among health departments, seasonality (important in seasonal illnesses as RVAGE), gender, age and population.

Results are presented with 95% credible intervals (CrI) that are comparable to 95% confidence intervals in frequentist statistics.

Analyses were carried out using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria) and WinBUGS.

Conclusions

We could not find any impact of RV vaccine coverage on seizure-related hospitalizations in children <5 years.

Ethical considerations

The Ethics Research Committee of the Dirección General de Salud Pública/Centro Superior de Investigación en Salud Pública approved the study.

Disclosure of potential conflicts of interest

JDD has been principal investigator in clinical trials sponsored by SPMSD, MSD, GSK, Pfizer. JDD acted as Advisor for GSK and SPMSD and received travel grants to attend meetings sponsored by SPMSD, MSD and GSK. AOS also received travel grants to attend meeting sponsored by MSD and Pfizer.

Funding

This study was funded by SPMSD. The company had no role in the analysis or discussion of the results.

Authors' contributions

AOS, JDD, MLL and CMQ contributed to the study design. MLL managed the data.

All authors participated in the analysis and interpretation of the data. AOS drafted the manuscript.

All authors were involved in the critical revision of drafts and approved the final manuscript version.

ORCID

Alejandro Orrico-Sánchez  <http://orcid.org/0000-0002-3780-3187>

Cintia Muñoz-Quiles  <http://orcid.org/0000-0002-6519-4905>

Javier Díez-Domingo  <http://orcid.org/0000-0003-1008-3922>

References

- Parashar UD, Gibson CJ, Bresee JS, Glass RI. Rotavirus and severe childhood diarrhea. *Emerg Infect Dis*. 2006;12(2):304–6. doi:10.3201/eid1202.050006. PMID:16494759
- Patel M WM, Cortese M, Gentsch J, Glass R, Parashar U. Generic protocol for monitoring impact of rotavirus vaccination on gastroenteritis disease burden and viral strains. *Immunization, Vaccines and Biologicals* [Internet]. 2008; (Immunization, Vaccines and Biologicals). Available from: www.who.int/vaccines-documents/.
- Giaquinto C, van Damme P. Age distribution of paediatric rotavirus gastroenteritis cases in Europe: the REVEAL study. *Scand J Infect Dis*. 2010;42(2):142–7. doi:10.3109/00365540903380495. PMID:19916900
- Alvarez Aldean J, Aristegui J, Lopez-Belmonte JL, Pedros M, Sicilia JG. Economic and psychosocial impact of rotavirus infection in Spain: a literature review. *Vaccine*. 2014;32(30):3740–51. doi:10.1016/j.vaccine.2014.04.058. PMID:24837768
- Diez Domingo J, Patrzalek M, Cantarutti L, Arnould B, Meunier J, Soriano-Gabarro M, Meyer N, Pirçon JY, Holl K. The impact of childhood acute rotavirus gastroenteritis on the parents' quality of life: prospective observational study in European primary care medical practices. *BMC Pediatr*. 2012;12:58. PMID:22650611
- Wong V. Acute gastroenteritis-related encephalopathy. *J Child Neurol*. 2001;16(12):906–10. doi:10.1177/088307380101601208. PMID:11785505
- Candy DC. Rotavirus infection: a systemic illness? *PLoS Med*. 2007;4(4):e117. doi:10.1371/journal.pmed.0040117. PMID:17439293
- Rivero-Calle I, Gomez-Rial J, Martinon-Torres F. Systemic features of rotavirus infection. *J Infect*. 2016;72 Suppl:S98–s105. doi:10.1016/j.jinf.2016.04.029. PMID:27181101
- Blutt SE, Conner ME. Rotavirus: to the gut and beyond! *Curr Opin Gastroenterol*. 2007;23(1):39–43. doi:10.1097/MOG.0b13e328011829d. PMID:17133083
- DiFazio MP, Braun L, Freedman S, Hickey P. Rotavirus-induced seizures in childhood. *J Child Neurol*. 2007;22(12):1367–70. doi:10.1177/0883073807307083. PMID:18174553
- Lloyd MB, Lloyd JC, Gesteland PH, Bale JF, Jr. Rotavirus gastroenteritis and seizures in young children. *Pediatr Neurol*. 2010;42(6):404–8. doi:10.1016/j.pediatrneurol.2010.03.002. PMID:20472191
- Yeom JS, Kim YS, Kim RB, Park JS, Seo JH, Park E, Lim JY, Park CH, Woo HO, Youn HS. Impact of rotavirus vaccine introduction on rotavirus-associated seizures and a related possible mechanism. *J Child Neurol*. 2015;30(6):729–34. doi:10.1177/0883073814542944. PMID:25117417
- Kang B, Kim DH, Hong YJ, Son BK, Kim DW, Kwon YS. Comparison between febrile and afebrile seizures associated with mild rotavirus gastroenteritis. *Seizure*. 2013;22(7):560–4. doi:10.1016/j.seizure.2013.04.007. PMID:23642407
- Le Saux N, Bettinger JA, Halperin SA, Vaudry W, Scheifele DW. Substantial morbidity for hospitalized children with community-acquired rotavirus infections: 2005–2007 IMPACT surveillance in Canadian hospitals. *Pediatr Infect Dis J*. 2010;29(9):879–82. doi:10.1097/INF.0b013e3181e20c94. PMID:20467353
- Yeom JS, Kim YS, Jun JS, Do HJ, Park JS, Seo JH, Park ES, Lim JY, Woo HO, Park CH, et al. NSP4 antibody levels in rotavirus gastroenteritis patients with seizures. *Eur J Paediatr Neurol*. 2017;21(2):367–73. doi:10.1016/j.ejpn.2016.10.006. PMID:27847298
- Kawashima H, Inage Y, Ogihara M, Kashiwagi Y, Takekuma K, Hoshika A, Mori T, Watanabe Y. Serum and cerebrospinal fluid nitrite/nitrate levels in patients with rotavirus gastroenteritis induced convulsion. *Life Sci*. 2004;74(11):1397–405. doi:10.1016/j.lfs.2003.08.014. PMID:14706570
- Yeom JS, Kim YS, Park JS, Seo JH, Park ES, Lim JY, Park CH, Woo HO, Youn HS. Role of Ca²⁺ homeostasis disruption in rotavirus-associated seizures. *J Child Neurol*. 2014;29(3):331–5. doi:10.1177/0883073812469052. PMID:23271755

18. Payne DC, Baggs J, Zerr DM, Klein NP, Yih K, Glanz J, Curns AT, Weintraub E, Parashar UD. Protective association between rotavirus vaccination and childhood seizures in the year following vaccination in US children. *Clin Infect Dis*. 2014;58(2):173–7. doi:10.1093/cid/cit671. PMID:24265355
19. Pardo-Seco J, Cebey-Lopez M, Martinon-Torres N, Salas A, Gomez-Rial J, Rodriguez-Tenreiro C, Martínón-Sánchez JM, Martínón-Torres F. Impact of Rotavirus Vaccination on Childhood Hospitalization for Seizures. *Pediatr Infect Dis J*. 2015;34(7):769–73. doi:10.1097/INF.0000000000000723. PMID:25923425
20. Sheridan SL, Ware RS, Grimwood K, Lambert SB. Febrile Seizures in the Era of Rotavirus Vaccine. *J Pediatric Infect Dis Soc*. 2016;5(2):206–9. doi:10.1093/jpids/piu097. PMID:27199471
21. Park SH, Kim YO, Kim HK, Kim HS, Kim BY, Cheon KR, Kim MJ, Kim SH, Chung JK, Woo YJ. Incidence of benign convulsions with mild gastroenteritis after introduction of rotavirus vaccine. *Brain Dev*. 2015;37(6):625–30. doi:10.1016/j.braindev.2014.09.002. PMID:25266417
22. Rotavirus vaccines WHO position paper: January 2013 – Recommendations. *Vaccine*. 2013;31(52):6170–1.
23. Cortese MM, Parashar UD. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2009;58(Rr-2):1–25. PMID:19194371
24. Orrico-Sanchez A, Lopez-Lacort M, Perez-Vilar S, Diez-Domingo J. Long-term impact of self-financed rotavirus vaccines on rotavirus-associated hospitalizations and costs in the Valencia Region, Spain. *BMC Infect Dis*. 2017;17(1):267. doi:10.1186/s12879-017-2380-2. PMID:28399824
25. Gil-Prieto R, Gonzalez-Escalada A, Alvaro-Meca A, Garcia-Garcia L, San-Martin M, Gonzalez-Lopez A, Gil-de-Miguel A. Impact of non-routine rotavirus vaccination on hospitalizations for diarrhoea and rotavirus infections in Spain. *Vaccine*. 2013;31(43):5000–4. doi:10.1016/j.vaccine.2013.05.109. PMID:23911782
26. Colombo F, Garcia-Goni M, Schwierz C. Addressing multimorbidity to improve healthcare and economic sustainability. *J Comorb*. 2016;6(1):21–7. doi:10.15256/joc.2016.6.74. PMID:29090168
27. Economou K, kentikelenis, Sisouras, Maresso. The impact of the final crisis on the health system and health in Greece. *World Health Organization*; 2014.
28. (BMJ) TBMJ. Chapter 6: ecological studies [Available from: <http://www.bmj.com/about-bmj/resources-readers/publications/epidemiology-uninitiated/6-ecological-studies>.
29. Uemura N, Okumura A, Negoro T, Watanabe K. Clinical features of benign convulsions with mild gastroenteritis. *Brain Dev*. 2002;24(8):745–9. doi:10.1016/S0387-7604(02)00097-9. PMID:12453597
30. Fein JA, Lavelle JM, Clancy RR. Using age-appropriate prolactin levels to diagnose children with seizures in the emergency department. *Acad Emerg Med*. 1997;4(3):202–5. doi:10.1111/j.1553-2712.1997.tb03741.x. PMID:9063547
31. Vukmir RB. Does serum prolactin indicate the presence of seizure in the emergency department patient? *J Neurol*. 2004;251(6):736–9. doi:10.1007/s00415-004-0418-z. PMID:15311351
32. (CDC) CfDCaP. Flu vaccination coverage, United States, 2009–2016 2017 [Available from: <https://www.cdc.gov/flu/fluview/coverage-1516estimates.htm>].
33. Perez-Vilar S, Diez-Domingo J, Lopez-Lacort M, Martinez-Ubeda S, Martinez-Beneito MA. Effectiveness of rotavirus vaccines, licensed but not funded, against rotavirus hospitalizations in the Valencia Region, Spain. *BMC Infect Dis*. 2015;15:92. doi:10.1186/s12879-015-0811-5. PMID:25872565
34. van Beek J, Ambert-Balay K, Botteldoorn N, Eden JS, Fonager J, Hewitt J, Iritani N, Kroneman A, Vennema H, Vinjé J, et al. Indications for worldwide increased norovirus activity associated with emergence of a new variant of genotype II.4, late 2012. *Euro Surveill*. 2013;18(1):8–9. PMID:23305715
35. Chen SY, Tsai CN, Lai MW, Chen CY, Lin KL, Lin TY, Chiu CH. Norovirus infection as a cause of diarrhea-associated benign infantile seizures. *Clin Infect Dis*. 2009;48(7):849–55. doi:10.1086/597256. PMID:19239351
36. Higuchi Y, Kubo T, Mitsuhashi T, Nakamura N, Yokota I, Komiyama O, et al. Clinical Epidemiology and Treatment of Febrile and Afebrile Convulsions With Mild Gastroenteritis: A Multicenter Study. *Pediatr Neurol*. 2017;67:78–84. doi:10.1016/j.pediatrneurol.2016.05.011. PMID:28094168
37. Kim GH, Byeon JH, Lee DY, Jeong HJ, Eun BL. Norovirus in benign convulsions with mild gastroenteritis. *Ital J Pediatr*. 2016;42(1):94. doi:10.1186/s13052-016-0303-2. PMID:27809881
38. Chan CM, Chan CW, Ma CK, Chan HB. Norovirus as cause of benign convulsion associated with gastro-enteritis. *J Paediatr Child Health*. 2011;47(6):373–7. doi:10.1111/j.1440-1754.2010.01986.x. PMID:21309881
39. Perez-Vilar S, Diez-Domingo J, Gomar-Fayos J, Pastor-Villalba E, Sastre-Canton M, Puig-Barbera J. [Post-licensure passive safety surveillance of rotavirus vaccines: reporting sensitivity for intussusception]. *An Pediatr (Barc)*. 2014;81(2):77–85. PMID:24252603
40. Ministerio de Sanidad PSeI. Informe Anual del Sistema Nacional de Salud 2011. Available from: http://www.mssi.gob.es/organizacion/sns/planCalidadSNS/pdf/equidad/informeAnualSNS2011/05_INFOME_SNS_2011_ESPANYOL.pdf.
41. Morant-Talamante N, Diez-Domingo J, Martinez-Ubeda S, Puig-Barbera J, Aleman-Sanchez S, Perez-Breva L. Herpes zoster surveillance using electronic databases in the Valencian Community (Spain). *BMC Infect Dis*. 2013;13:463. doi:10.1186/1471-2334-13-463. PMID:24094135