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Associations of intussusception with adenovirus, rotavirus, and other pathogens: a review of the literature

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Abstract

Background: Intussusception is the leading cause of acute intestinal obstruction in infants. Intussusception is mostly idiopathic, but infectious pathogens are sometimes implicated. In addition, live oral rotavirus vaccines have been associated with intussusception.

Methods: We searched the literature published between January 1, 1990- March 16, 2020, to describe the association between intussusception among infants and young children and various pathogens, particularly adenovirus and wild rotavirus. We tallied the number of evaluations reporting a statistically significant positive association, no association, and a protective association by pathogen, using any statistical method. We also calculated the median reported odds ratios (OR) of intussusception with adenovirus and rotavirus.

Results: We identified 3,793 records; 17 evaluations from 15 countries that evaluated 52 pathogens were included in the analysis. All 14 evaluations of adenovirus reported a statistically significant positive association with intussusception; the median OR from 9 evaluations was 3.7 (IQR: 3.3, 8.2). Nine of 12 evaluations assessing rotavirus found no statistically significant association, 1 found a positive association, and 2 reported a protective effect; the median OR from 12 evaluations was 0.9 (IQR: 0.2, 1.8). No consistent relationship was observed between any other pathogens and intussusception.

Conclusions: We documented a consistent association of intussusception with adenovirus, but no relationship between wild-type rotavirus and intussusception. Future research should focus on better understanding the mechanisms of intussusception with infectious pathogens, including following rotavirus vaccination.

Keywords

Intussusception; adenovirus; rotavirus; literature review

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Introduction

Intussusception is the leading cause of acute intestinal blockage in infants and can lead to death if untreated (1, 2). Though rare, rates of naturally occurring intussusception vary by region from >300 per 100,000 infants in Vietnam and Korea to <10 in Bangladesh (3). Anatomical leadpoints cause some cases of intussusception; however, for most intussusception cases the cause is unknown. In some articles, a seasonal pattern of intussusception has been reported, suggesting an infectious pathogen may cause some cases of intussusception (3). Many case reports or case series noted the presence of various pathogens in intussusception cases, but firm conclusions could not be derived as they did not formally assess association using case-control approach (4-10).

In addition to naturally occurring intussusception, a slightly increased risk of intussusception has been shown following vaccination against rotavirus (11-16). About 1 to 5 excess cases are estimated per 100,000 infants vaccinated in high- and middle-income countries (13); though no risk was detected in 7 African countries, South Africa, or India (17-19). As the biological mechanisms are unknown, researchers have considered if wild-type rotavirus could be similarly associated with intussusception. Additionally, understanding any association between wild-type rotavirus and intussusception may be useful to rotavirus vaccines in the pipeline, as some vaccines currently under development aim to minimize or eliminate the vaccine-related risk of intussusception (20).

In this review, we describe the available literature assessing the relationship between intussusception and pathogens. We also quantify the magnitude of any associations between intussusception and adenovirus or rotavirus as a secondary objective.

Methodxs

Literature search

We (EB) searched PubMed for English language articles with the key word “intussusception” published January 1, 1990 through March 16, 2020. We limited the time period of interest to ensure laboratory detection methods would be similar. We excluded descriptive analyses, evaluations of only children ≥1 year old or adults, and studies that did not have a case-control design. Articles that assessed the relationship between any pathogen detected in stool by laboratory methods and intussusception using any statistical method were considered for inclusion. We excluded articles evaluating the relationship between rotavirus vaccines and intussusception; literature reviews, modeling studies, and other non-original research; descriptive analyses; and evaluations of other etiologies of intussusception, such as nutritional status.

Data abstraction and analysis

For studies meeting inclusion criteria, we (EB) abstracted information about study design, enrollment criteria, numbers of cases and controls, statistical methods, pathogens tested, and findings into a Microsoft Excel spreadsheet. When articles reported individual estimates from more than one country or group of countries, each population was included as a separate evaluation in this analysis. For the primary objective, we included statistically significant associations as reported by the authors, by any statistical test. In the secondary analysis of the magnitude of associations, we limited the analysis to evaluations that reported odds ratios (OR). If the OR was not reported and the study design was not matched, we used the published data to calculate the crude OR and confidence limits when available and included this in summary analyses. A priori, we decided to summarize the magnitude of the association between a pathogen and intussusception where there were 8 or more evaluations with ORs for that pathogen.

To describe characteristics of the included evaluations, we reported the number and percent of evaluations with select characteristics as well as the median and interquartile range (IQR) of continuous variables. For the primary objective of this literature review, we tallied the number of evaluations reporting a statistically significant positive association, no association, and a protective association by pathogen. For the secondary objective, we calculated the median and IQR of the OR of intussusception with adenovirus and rotavirus. All analyses were performed using SAS v.9.4 and R v.3.6.1.

Results

The literature search identified 3,793 records, of which the abstracts were reviewed for 312 (Figure 1). More than half (n=1480) of those excluded were descriptive reports of individual or small groups of intussusception cases. From PubMed, 14 full length articles and 1 abstract are included in this review; 2 articles stratified their analyses and each country or group of countries is included as a separate evaluation. Overall, 17 evaluations from 15 countries were included (Table 1). All of the evaluations enrolled cases over >12-month period.

The 17 included evaluations were published from 1992-2019 (median: 2010; IQR: 2006, 2014) (Table 1). There were a median 53 (IQR: 37, 106) cases and 106 (IQR: 60, 136) controls in each evaluation. A range of intussusception case definitions were used: 4 evaluations used the Brighton Collaboration case definition criteria for diagnostic certainty, 5 included cases diagnosed by ultrasound or other imaging, enema, or surgery, 1 included cases confirmed by enema only and 3 included cases confirmed by ultrasound or other diagnostic imaging only, and 1 evaluation identified cases with intussusception-specific ICD codes. Three evaluations did not specify how intussusception cases were identified and confirmed. Eleven evaluations (65%) identified viral pathogens by PCR and 10 (59%) by ELISA (Table 2). The oldest age of cases was 1 year in 2 evaluations, 2 years in 4 evaluations, and 3-5 years in 5 evaluations. In 3 additional evaluations, the oldest children were >5 years old. Two evaluations did not specify the cases' ages but otherwise indicated they were infants and young children.

Control groups were similarly diverse across evaluations. Including community and hospitalized control groups, 8 evaluations (47%) explicitly excluded controls with diarrhea and 8 evaluations (47%) included controls with diarrhea (Table 2). One evaluation (6%) with hospitalized controls did not specify whether controls with diarrhea were excluded. Fourteen (82%) of the evaluations used matched controls. Of those, 14 (100%) matched cases and controls by age, 9 (64%) matched by sex; and 3 (21%) matched by geography.

The relationships between intussusception and 52 pathogens were assessed in these 17 evaluations (Table 3). The most commonly included pathogen was adenovirus (n=14 evaluations) and of which, all showed a statistically significant positive association with intussusception. Of the 9 evaluations reporting an OR, the median OR was 3.7 (IQR: 3.3, 8.2) (Figure 2). Additionally, 12 adenovirus types have been evaluated, mostly with mixed results. Adenovirus type C was included in 6 evaluations, of which 4 showed a positive association with intussusception. Adenovirus types F and B were assessed in 5 and 4 evaluations, respectively, and did not consistently show any statistically significant association.

There were 12 evaluations that assessed the relationship between rotavirus and intussusception; 9 found no statistically significant association, 1 found a positive association, and 2 reported a protective effect (Table 3). The study that reported a positive association was noteworthy in that cases were enrolled after rotavirus vaccine had been introduced and researchers were not able distinguish between wild-type and vaccine-type rotavirus strains in a subset of sample. Eleven of these evaluations reported ORs, with a median OR of 0.9 (IQR: 0.2, 1.8) (Figure 2).

Four evaluations have assessed the association between norovirus and intussusception, of which 2 reported a protective effect and 2 reported no statistically significant effect (Table 3). One evaluation showed norovirus GII had a protective effect and 1 showed no statistically significant association; 1 evaluation showed norovirus GI had no association with intussusception. Two evaluations found no statistically significant association of intussusception with human herpes virus 6 (HHV6) and one that found a positive association. One of the evaluations showing no association with HHV6 alone did find a statistically significant association between intussusception and co-infection with adenovirus and HHV6.

Other commonly included pathogens were astrovirus, enterovirus, and cytomegalovirus (CMV). There was no statistically significant relationship found between astrovirus, enterovirus, and CMV in 6, 5, and 3 evaluations, respectively (Table 3). No consistent association was found between any other pathogen and intussusception.

Discussion

Our findings clearly and consistently demonstrate that adenovirus is associated with intussusception, with 3-4 times the odds of intussusception among children infected with adenovirus than those not infected. In particular, adenovirus type C, which often has respiratory symptoms, appears to be associated with intussusception, while enteric adenovirus type F was not. Study size may not have been large enough to detect small effect sizes from other adenovirus types or from adenovirus types that were rare in the study populations. While this relationship was clear and consistent, not all adenovirus infections resulted in an intussusception in these study populations and adenovirus infection does not account for all the enrolled intussusception cases.

The summary findings from this literature review suggest there is no statistically significant causative relationship between wild-type rotavirus and intussusception. Twelve evaluations exploring this association were conducted on 4 continents and in countries with a wide range of natural rates of intussusception in infants. Given three rotavirus vaccines (Rotashield, Rotarix, and RotaTeq) have been associated with intussusception (11-16), these findings are a bit surprising. One possible explanation is that oral administration of the vaccine or the high titer of virus from vaccination compared to natural infection. Alternatively, these case-control studies were not adequately powered to exclude an association between wild type rotavirus and intussusception of the same magnitude as with rotavirus vaccine. Further research to understand the mechanism of intussusception after rotavirus vaccination is needed.

This literature review has several limitations. First, many of the studies had very small sample sizes, possibly too small to detect the modest effect of some pathogens. For example, evidence from descriptive studies and 2 of 3 evaluation in this review suggest HHV6 as a cause of intussusception, but it was only found to be statistically significantly associated in 1 evaluation (5, 21-23). However, since the magnitude of the relationship and number of cases are very small, HHV6 is unlikely to be causing a large number of cases. Second, variation in study design, analytic methods, and case definition makes combining and comparing these findings challenging. We had more stringent criteria for the secondary analysis than the primary analysis however we did not limit the inclusion criteria by age group due to the small number of evaluations. The causes of intussusception may vary substantially between infants and 13-year-olds, the oldest child enrolled. We were also concerned that differences in control group enrollment criteria may have biased the results. However, in summarizing magnitude of association of intussusception with adenovirus and rotavirus, we did not find a substantial difference in the median OR based on control group. Though the small number of evaluations and other differences in study design may mask a true difference in OR between diarrhea and non-diarrhea controls. Third, we were limited in our analysis by the pathogens included in at least one evaluation. The current literature did not allow for the exploration of the role of co-infections or the gut microbiome in intussusception.

In conclusion, the available literature consistently showed an association between adenovirus and intussusception and suggests that there is no relationship between wild-type rotavirus and intussusception, though we did not have the power to detect a level of risk as low as that found with rotavirus vaccines. Future research should focus on other natural causes of intussusception in infants and better understanding the mechanisms leading to intussusception including following rotavirus vaccination.

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References

1. Acute intussusception in infants and children: Incidence, clinical presentation and management: a global perspective. Geneva: World Health Organization Vaccines and Biologicals; 2002.

2. Bines JE, Kohl KS, Forster J, et al. Acute intussusception in infants and children as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine. 2004;22:569–574. [PubMed: 14741146]
3. Jiang J, Jiang B, Parashar U, Nguyen T, Bines J, Patel MM. Childhood intussusception: a literature review. PLoS One. 2013;8:e68482. [PubMed: 23894308]
4. Gardner PS, Knox EG, Court SD, Green CA. Virus infection and intussusception in childhood. Br Med J. 1962;2:697–700. [PubMed: 13896906]
5. Asano Y, Yoshikawa T, Suga S, Hata T, Yamazaki T, Yazaki T. Simultaneous occurrence of human herpesvirus 6 infection and intussusception in three infants. Pediatr Infect Dis J. 1991;10:335–337. [PubMed: 1648199]
6. Gardner PS. Adenovirus and intussusception. Br Med J. 1961;2:495–496. [PubMed: 13703619]
7. Ross JG, Potter CW, Zachary RB. Adenovirus infection in association with intussusception in infancy. Lancet. 1962;2:221–223. [PubMed: 14494185]
8. Konno T, Suzuki H, Kutsuzawa T, et al. Human rotavirus and intussusception. N Engl J Med. 1977;297:945.
9. Konno T, Suzuki H, Kutsuzawa T, et al. Human rotavirus infection in infants and young children with intussusception. J Med Virol. 1978;2:265–269. [PubMed: 212529]
10. Mulcahy DL, Kamath KR, de Silva LM, Hodges S, Carter IW, Cloonan MJ. A two-part study of the aetiological role of rotavirus in intussusception. J Med Virol. 1982;9:51–55. [PubMed: 6278072]
11. Buttery JP, Danchin MH, Lee KJ, et al. Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. Vaccine. 2011;29:3061–3066. [PubMed: 21316503]
12. Yih WK, Lieu TA, Kulldorff M, et al. Intussusception risk after rotavirus vaccination in U.S. infants. N Engl J Med. 2014;370:503–512. [PubMed: 24422676]
13. Patel MM, Lopez-Collada VR, Bulhoes MM, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. N Engl J Med. 2011;364:2283–2292. [PubMed: 21675888]
14. Weintraub ES, Baggs J, Duffy J, et al. Risk of intussusception after monovalent rotavirus vaccination. N Engl J Med. 2014;370:513–519. [PubMed: 24422678]
15. Kramarz P, France EK, Destefano F, et al. Population-based study of rotavirus vaccination and intussusception. Pediatr Infect Dis J. 2001;20:410–416. [PubMed: 11332666]
16. Murphy TV, Gargiullo PM, Massoudi MS, et al. Intussusception among infants given an oral rotavirus vaccine. N Engl J Med. 2001;344:564–572. [PubMed: 11207352]
17. Tate JE, Mwenda JM, Armah G, et al. Evaluation of Intussusception after Monovalent Rotavirus Vaccination in Africa. N Engl J Med. 2018;378:1521–1528. [PubMed: 29669224]
18. Groome MJ, Tate JE, Arnold M, et al. Evaluation of Intussusception After Oral Monovalent Rotavirus Vaccination in South Africa. Clin Infect Dis. 2020;70:1606–1612. [PubMed: 31125061]
19. Bhandari N, Antony K, Balraj V, et al. Assessment of risk of intussusception after pilot rollout of rotavirus vaccine in the Indian public health system. 2020.
20. Burke RM, Tate JE, Kirkwood CD, Steele AD, Parashar UD. Current and new rotavirus vaccines. Curr Opin Infect Dis. 2019;32:435–444. [PubMed: 31305493]
21. Burnett E, Kabir F, Van Trang N, et al. Infectious etiologies of intussusception among children <2 years old in 4 Asian countries. J Infect Dis. 2019.
22. Lappalainen S, Ylitalo S, Arola A, Halkosalo A, Rasanen S, Vesikari T. Simultaneous presence of human herpesvirus 6 and adenovirus infections in intestinal intussusception of young children. Acta Paediatr. 2012;101:663–670. [PubMed: 22296119]
23. Hsu HY, Kao CL, Huang LM, et al. Viral etiology of intussusception in Taiwanese childhood. Pediatr Infect Dis J. 1998;17:893–898. [PubMed: 9802631]
24. Bines JE, Liem NT, Justice FA, et al. Risk factors for intussusception in infants in Vietnam and Australia: adenovirus implicated, but not rotavirus. J Pediatr. 2006;149:452–460. [PubMed: 17011313]

25. Minney-Smith CA, Levy A, Hodge M, et al. Intussusception is associated with the detection of adenovirus C, enterovirus B and rotavirus in a rotavirus vaccinated population. J Clin Virol. 2014;61:579–584. [PubMed: 25464971]
26. El-Hodhod MA, Nassar MF, Ezz El-Arab S, Ahmed EF. Rotavirus fecal antigen retrieval in infantile intussusception. Eur J Clin Microbiol Infect Dis. 2008;27:879–881. [PubMed: 18443833]
27. Mansour AM, El Koutby M, El Barbary MM, et al. Enteric viral infections as potential risk factors for intussusception. J Infect Dev Ctries. 2013;7:28–35. [PubMed: 23324817]
28. Bahl R, Saxena M, Bhandari N, et al. Population-based incidence of intussusception and a case-control study to examine the association of intussusception with natural rotavirus infection among indian children. J Infect Dis. 2009;200 Suppl 1:S277–281. [PubMed: 19817609]
29. Okimoto S, Hyodo S, Yamamoto M, Nakamura K, Kobayashi M. Association of viral isolates from stool samples with intussusception in children. Int J Infect Dis. 2011;15:e641–645. [PubMed: 21757385]
30. Jang J, Lee YJ, Kim JS, et al. Epidemiological Correlation between Fecal Adenovirus Subgroups and Pediatric Intussusception in Korea. J Korean Med Sci. 2017;32:1647–1656. [PubMed: 28875609]
31. Velazquez FR, Luna G, Cedillo R, Torres J, Munoz O. Natural rotavirus infection is not associated to intussusception in Mexican children. Pediatr Infect Dis J. 2004;23:S173–178. [PubMed: 15502698]
32. Bode CO, Omilabu SA. Viral isolates of intussusception in Nigerian infants. S Afr J Surg. 2002;40:57–58. [PubMed: 12162233]
33. Ukarapol N, Khamrin P, Khorana J, Singhavejsakul J, Damrongmanee A, Maneekarn N. Adenovirus infection: A potential risk for developing intussusception in pediatric patients. J Med Virol. 2016;88:1930–1935. [PubMed: 27097123]
34. Bhisitkul DM, Todd KM, Listernick R. Adenovirus infection and childhood intussusception. Am J Dis Child. 1992;146:1331–1333. [PubMed: 1415074]
35. Nylund CM, Denson LA, Noel JM. Bacterial enteritis as a risk factor for childhood intussusception: a retrospective cohort study. J Pediatr. 2010;156:761–765. [PubMed: 20138300]

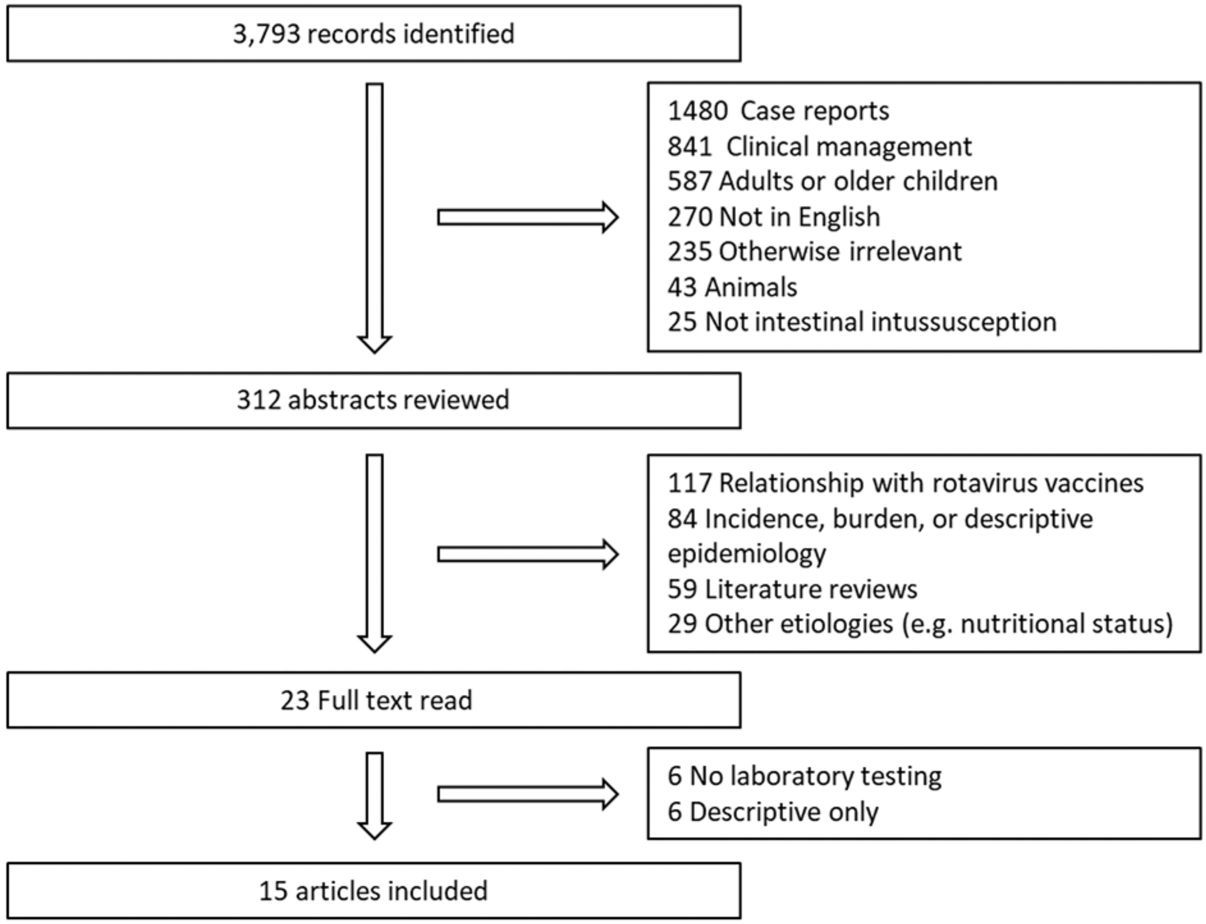

Figure 1.
Flowchart of literature search and exclusion criteria.

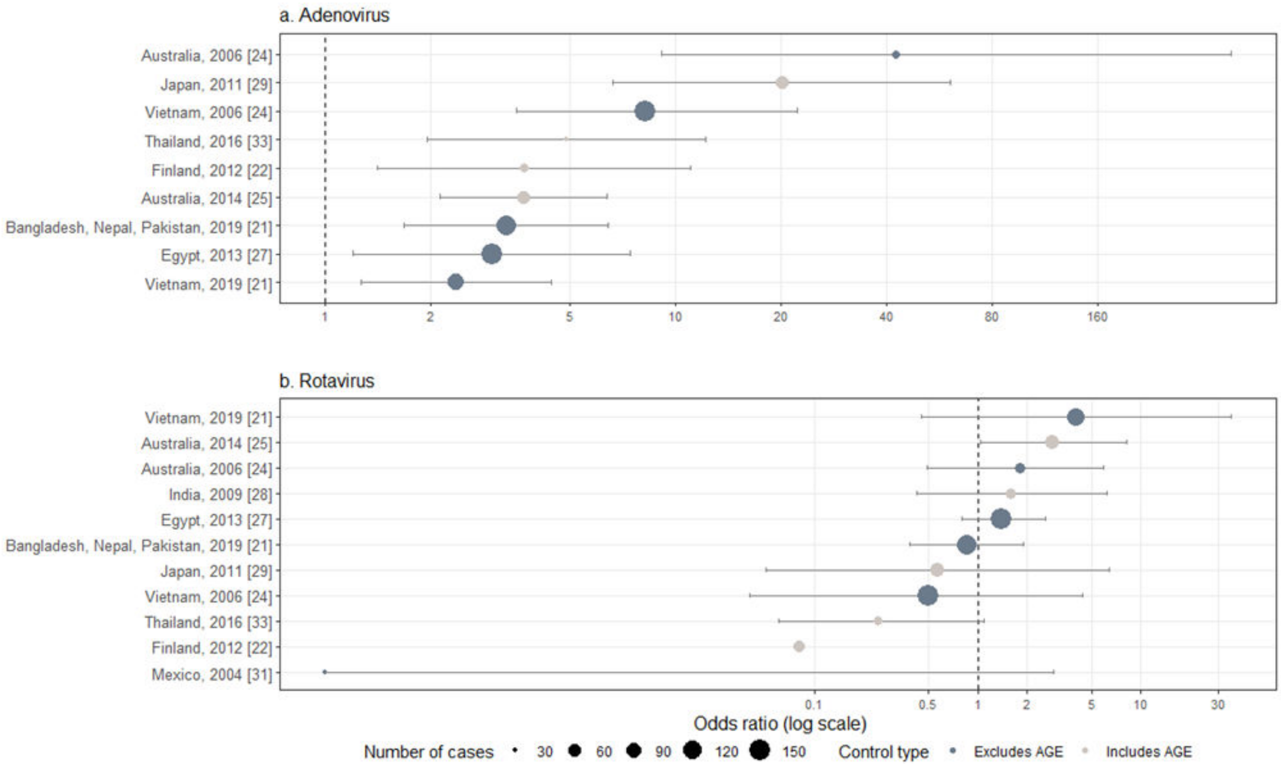

Figure 2.
Published estimates of the odds ratio of adenovirus and rotavirus with intussusception.

Table 1.

List of studies included in literature review and key characteristics

Country of enrollment	Year of publication	First author	Intussusception case definition	Number of cases	Number of controls	Reference number
Australia	2006	Bines	Primary idiopathic intussusception confirmed by air enema or surgery	48	128	(24)
Australia	2014	Minney-Smith	Confirmed by diagnostic imaging and notified to the Western Australian Notifiable Infectious Diseases Database	74	289	(25)
Bangladesh, Nepal, Pakistan	2019	Burnett	Level 1 of the Brighton Criteria	143	143	(21)
Egypt	2008	El-Hodhod	Acute GE complicated by intussusception	21	40	(26)
Egypt	2013	Mansour	Level 1 of the Brighton Criteria	156	370	(27)
Finland	2012	Lappalainen	Not reported	53	61	(22)
India	2009	Bahl	Confirmed by ultrasound or surgery	47	110	(28)
Japan	2011	Okimoto	Brighton Criteria (level not specified)	71	82	(29)
Korea	2017	Jang	Enema or ultrasound; excluded with surgical or anatomical anomaly associated with intussusception	126	106	(30)
Mexico	2004	Velazquez	Confirmed by enema, ultrasound, or surgery	30	60	(31)
Nigeria	2002	Bode	Not reported	28	20	(32)
Taiwan	1998	Hsu	Confirmed by barium enema or surgery	64	52	(23)
Thailand	2016	Ukarapol	Confirmed by ultrasound	40	136	(33)
United States	1992	Bhisitkul	Confirmed by barium enema	25	24	(34)
United States	2010	Nylund	ICD code for intussusception	37	1412	(35)
Vietnam	2006	Bines	Primary idiopathic intussusception confirmed by air enema or surgery	159	118	(24)
Vietnam	2019	Burnett	Level 1 of the Brighton Criteria	106	106	(21)

Table 2.

Characteristics of evaluations examining the relationship between intussusception and selected pathogens

	n=17	%
Oldest age of cases included in analysis		
1 year	2	12
2 years	5	29
3 years- 5 years	5	29
>5 years	3	17
Not specified	2	12
Controls		
Excludes acute gastroenteritis	8	47
Includes acute gastroenteritis	8	47
Not specified	1	6
Matched controls	14	82
Matching characteristics		
Age	14	100
Sex	9	64
Geography	3	21
Viral laboratory testing		
PCR	11	65
ELISA	10	59
Other	2	12

Table 3.

Number of studies finding statistically significant associations with intussusception by pathogen (any statistical method)

	Number of evaluations			
Pathogen	**Total reporting pathogen**	**Positive association**	**Not significant**	**Protective association**
Bacterial				
Campylobacter (pan)	3	1	1	1
jejuni/coli	2	0	1	1
C. difficile	2	0	1	1
E. coli	1	1	0	0
Atypical enteropathogenic	2	0	2	0
Enteroaggregative	2	0	2	0
Enteroinvasive	1	0	1	0
Enterotoxigenic	2	0	2	0
Typical enteropathogenic	2	0	2	0
Salmonella	3	1	2	0
Shigella	1	1	0	0
Y. enterocolitica	1	0	1	0
Parasitic				
Cryptosporidium	2	0	2	0
Giardia	1	0	1	0
Viral				
Adenovirus (pan)	15	15	0	0
A	3	0	3	0
A31	1	0	1	0
B	4	1	3	0
B3	1	1	0	0
C	6	4	2	0
C1	2	2	0	0
C2	1	1	0	0
C5/6	1	0	1	0
D	2	0	2	0
E4	1	1	0	0
F	5	0	5	0
F41	1	0	0	1
Non-type C	2	1	1	0
Astrovirus	6	0	6	0
Bocavirus	1	0	1	0
Calicivirus	1	0	1	0
Cytomegalovirus	3	0	3	0
Echovirus	2	0	2	0
Enterovirus (pan)	5	0	5	0

Pathogen	Number of evaluations: Total reporting pathogen	Positive association	Not significant	Protective association
A	1	0	1	0
B	1	1	0	0
C	1	0	1	0
Herpes simplex virus	1	0	1	0
Human herpes virus 6	3	1	2	0
Human herpes virus 7	1	0	1	0
Influenza	1	0	1	0
Norovirus (pan)	4	0	2	2
GI	1	0	1	0
GII	2	0	1	1
Parechovirus	1	0	1	0
Poliovirus	1	0	1	0
Rhinovirus (pan)	1	0	1	0
A	1	0	1	0
B	1	0	1	0
C	1	0	1	0
Rotavirus	12	1	9	2
Sapovirus	3	0	3	0