Childhood Intussusception: A Literature Review

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**Abstract**

**Background:** Postlicensure data has identified a causal link between rotavirus vaccines and intussusception in some settings. As rotavirus vaccines are introduced globally, monitoring intussusception will be crucial for ensuring safety of the vaccine programs.

**Methods:** To obtain updated information on background rates and clinical management of intussusception, we reviewed studies of intussusception in children <18 years of age published since 2002. We assessed the incidence of intussusception by month of life among children <1 year of age, seasonality, method of diagnosis, treatment, and case-fatality.

**Findings:** We identified 82 studies from North America, Asia, Europe, Oceania, Africa, Eastern Mediterranean, and Central & South America that reported a total of 44,454 intussusception events. The mean incidence of intussusception was 74 per 100,000 (range: 9–328) among children <1 year of age, with peak incidence among infants 5–7 months of age. No seasonal patterns were observed. A radiographic modality was used to diagnose intussusception in over 95% of the cases in all regions except Africa where clinical findings or surgery were used in 65% of the cases. Surgical rates were substantially higher in Africa (77%) and Central and South America (86%) compared to other regions (13–29%). Case-fatality also was higher in Africa (9%) compared to other regions (<1%). The primary limitation of this review relates to the heterogeneity in intussusception surveillance across different regions.

**Conclusion:** This review of the intussusception literature from the past decade provides pertinent information that should facilitate implementation of intussusception surveillance for monitoring the postlicensure safety of rotavirus vaccines.

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**Background**

Intussusception is the invagination of one segment of the intestine within a more distal segment [1,2]. It is the most common cause of bowel obstruction in infants, occurring usually between 4 and 10 months of age [3]. In most infants, the intussusception involves the ileum invaginating through the ileocecal valve into the cecum. As the bowel intusscepts, it pulls along its blood supply. If the intussusception is not relieved, the vascular supply of the bowel may be compromised, resulting in intestinal ischemia and possibly perforation. Untreated intussusception may be fatal.

In 1999, an association was found between a tetravalent rhesus reassortant rotavirus vaccine (RotaShield) and intussusception in US infants prompting the manufacturer to withdraw the vaccine from the market [4,5]. Because of this association, the two rotavirus vaccines that are currently recommended by the World Health Organization [RotaTeq (RV5), Merck & Co.; Rotarix (RV1), GSK Biologicals] were evaluated in large safety trials which excluded a risk of intussusception similar to that found with RotaShield (1 excess case per 10,000 vaccinated infants) [5,6]. However, postlicensure studies in some high and middle income settings have identified a low level risk of 1–2 excess cases of intussusception per 100,000 infants after both RV1 and RV5 [7,8]. These vaccines have now been introduced in some 45 countries worldwide, primarily in middle and high income countries, but broader introductions in low income countries of Africa and Asia are expected in next 3–5 years [9].

The past experience with RotaShield and the identification of a lower level risk of intussusception after RV1 and RV5 highlights the importance of ongoing intussusception monitoring as these new vaccines are broadly adopted in other regions of the world. In 2002, the WHO published a comprehensive literature review of childhood intussusception globally between the years 1960–2002 [3]. In anticipation of the global introduction of rotavirus vaccines, the objective of this literature review was to describe the epidemiology, diagnosis, and clinical manifestations of intussusception between the years 2002–2012. This review of the epidemiology of intussusception based on contemporary studies published in the last decade should serve as a valuable resource for implementing surveillance for intussusception to monitor the safety of these vaccines as they are broadly rolled out across the world.
Methods

Search strategy and selection criteria
We followed the PRISMA guidelines to identify all intussusception studies published between January 2002 (when the last review was conducted) and June 2012. We included all peer-reviewed articles and selected meeting abstracts. We searched PubMed MEDLINE and Google Scholar using the following keywords: "intussusception" or "intestinal invagination." We included all human studies of intussusception among children 18 years of age published in English. Because we were interested in understanding the epidemiology of all intussusception events among children, full-text articles were not reviewed if they were case reports, animal studies, follow-up evaluation of chronic or recurrent intussusception, reports of intussusception events secondary to other conditions (e.g., vascular or congenital malformations, tumors), or reports of surgical or radiological management of intussusception. We also excluded those studies which did not include children <1 year of age. We reviewed the reference lists of all included articles to identify additional sources of data, missing articles, or meeting abstracts. Where there were multiple sources of data from the same study population, we relied on the data from the most complete peer-reviewed publication.

Data Extraction and Management
Data from included studies were extracted onto a standardized table by JJ and MP. Reviewers were not blinded to study authors, affiliations, or journal name. Variables recorded from each article included, study locations (city & country), sample size, study period, age at diagnosis, month of presentation, diagnostic modality, treatment, death, and incidence.
| Country   | Study dates | National or Hospital based | No. of cases | Age, yrs | Ref.                  |
|-----------|-------------|-----------------------------|--------------|---------|-----------------------|
| Africa    |             |                             |              |         |                       |
| Multiple  | 1993–2003   | International               | 2895         |         | (Steele, 2012 #92)    |
| Kenya     | 2000–2003   | Hospital                    | 1069         | <1      | (Kuremu, 2004 #55)    |
| Kenya     | 1992–1999   | Hospital                    | 29           | NR      | (Muyembe, 2000 #65)   |
| Ghana     | 2004–2007   | Hospital                    | 44           | <13     | (Abantanga, 2008 #1)  |
| Ghana     | 2008–2009   | Hospital                    | 77           | <5      | (Emveronu-Laryea, 2012 #35) |
| Nigeria   | 1980–1998   | Hospital                    | 80           | <12     | (Ameh, 2002 #3)       |
| Nigeria   | 1988–1998   | Hospital                    | 33           | <1      | (Ameh, 2002 #4)       |
| Nigeria   | 1989–1998   | Hospital                    | 89           | <1      | (Archibong, 2001 #5)  |
| Nigeria   | 1995–2001   | Hospital                    | 174          | <7      | (Bode, 2008 #12)      |
| Nigeria   | 1996–2005   | Hospital                    | 38           | <15     | (Ogunsuyin, 2009 #69) |
| Nigeria   | 1998–2003   | Hospital                    | 29           | <8      | (Edino, 2003 #30)     |
| Nigeria   | 1998–2007   | Hospital                    | 87           | <8      | (Ekenze, 2010 #31)    |
| Nigeria   | 2008–2009   | Hospital                    | 20           | <2      | (Ekenze, 2011 #32)    |
| So. Africa| 1998–2003   | 9 Hospitals                 | 423          | <14     | (Moore, 2010 #63)     |
| So. Africa| 1996–2001   | Hospital                    | 106          | NR      | (Wiersma, 2004 #112)  |
| Tanzania  | 2000–2004   | Hospital                    | 28           | <10     | (Cameiro, 2004 #21)   |
| Tunisia   | 1984–2003   | National                    | 533          | <5      | (Chouikha, 2009 #27)  |
| Asia-high u5MR |  |                             | 356          |         |                       |
| Bangladesh| 2001–2006   | Regional                    | 4            | <2      | (Zaman, 2009 #109)    |
| India     | 2000–2003   | Hospital                    | 5            | <1      | (Bahl, 2009 #7)       |
| India     | 2001–2004   | Hospital                    | 31           | <5      | (Bhowmick, 2009 #8)   |
| India     | 1991–2000   | Hospital                    | 137          | <5      | (Raman, 2003 #75)     |
| India     | ---         | Hospital                    | 179          | NR      | (Ramachandran, 2008 #74) |
| Asia-low & very low u5MR |  |                             | 14382        |         |                       |
| China     | 2004–2009   | Hospital                    | 56           | <14     | (Zhang, 2011 #110)    |
| Hong Kong | 1997–2003   | National                    | 531          | <5      | (Hong Kong Intussusception Study, 2007 #44) |
| Japan     | 2007–2008   | National                    | 2427         | <18     | (Takeuchi, 2012 #93)  |
| Japan     | 1978 – 2002 | Hospital                    | 91           | <5      | (Nakagomi, 2006 #66)  |
| So. Korea | 2000–2002   | Regional                    | 408          | <5      | (Jo, 2009 #47)        |
| Malaysia  | 2000–2003   | Regional                    | 62           | <5      | (Gia, 2008 #40)       |
| Singapore | 1997–2007   | National                    | 217          | <2      | (Tan, 2009 #96)       |
| Taiwan    | 1998–2007   | National                    | 8217         | <15     | (Chen, 2010 #24)      |
| Thailand  | 1992–2009   | Hospital                    | 737          | NR      | (Kruatrachue, 2011 #54) |
| Thailand  | 2001–2006   | 5 hospitals                 | 112          | <5      | (Khumjul, 2009 #51)   |
| Thailand  | 2000–2005   | Hospital                    | 94           | <14     | (Pruskananonda, 2007 #73) |
| Uzbekistan| 2004–2008   | Regional                    | 67           | <2      | (Latipov, 2011 #58)   |
| Vietnam   | 2002–2003   | Hospital                    | 640          | <2      | (Justice, 2007 #50)   |
| Vietnam   | 2002–2004   | Hospital                    | 533          | <2      | (Bines, 2006 #9)      |
| Central & South Americas |  |                             | 538          |         |                       |
| Latin America | n/a     | International               | 222          | <2      | (Abate, #111)         |
| Chile     | 2000–2001   | Regional                    | 95           | <2      | (O’Ryan, 2003 #71)    |
| Panama    | 1998–2002   | National                    | 103          | <1      | (Saez-Lorens, 2004 #80) |
| Trinidad  | 2000–2007   | Hospital                    | 65           | <3      | (Tota-Maharaj, 2010 #98) |
| Venezuela | 1998–2001   | Regional                    | 53           | <1      | (Perez-Schael, 2003 #72) |
| Eastern Mediterranean |  |                             | 644          |         |                       |
| Saudi Arabia | 1993 – 2000 | Hospital                    | 34           | <8      | (Al-Malki, 2005 #2)   |
| Saudi Arabia | 1984–2000   | Hospital                    | 37           | <3      | (Crankson, 2003 #29)  |
| Country   | Study dates | National or Hospital based | No. of cases | Age, yrs | Ref.                  |
|-----------|-------------|----------------------------|--------------|----------|-----------------------|
| Israel    | 1990–2004   | Hospital                   | 316          | <5       | {Greenberg, 2008 #41} |
| Israel    | 1990–2002   | Hospital                   | 148          | <5       | {Eshed, 2003 #36}     |
| Jordan    | 1979–2003   | Hospital                   | 109          | <14      | {Saleem, 2008 #81}    |
| Europe    |             |                            | 6280         |          |                       |
|           | Austria     | Hospital                   | 111          | <10      | {Saxena, 2007 #85}    |
|           | Denmark     | National                   | 1814         | <5       | {Fischer, 2004 #39}   |
|           | Finland     | National                   | 53           | <13      | {Lappalainen, 2012 #57} |
|           | Germany     | Regional                   | 169          | <1       | {Wei, 2011 #102}      |
|           | Germany     | Regional                   | 1200         | <15      | {Jenke, 2011 #46}     |
|           | Germany     | Regional                   | 518          | <17      | {Kohl, 2010 #53}      |
|           | Ireland     | Hospital                   | 256          | <12      | {Tareen, 2011 #96}    |
|           | Ireland     | Hospital                   | 24           | <2.5     | {Hilal, 2002 #42}     |
|           | Russia      | Hospital                   | 280          | <14      | {Shapkina, 2006 #86}  |
|           | Spain       | unspecified                | 151          | <12      | {Rubí, 2002 #78}      |
|           | Switzerland | National                   | 294          | <18      | {Buettcher, 2007 #17} |
|           | Turkey      | Hospital                   | 105          | <15      | {Sommes, 2012 #91}    |
|           | Turkey      | Hospital                   | 179          | <1       | {Yalcin, 2009 #107}   |
|           | UK/Ireland  | National                   | 261          | <1       | {Samad, 2012 #83}     |
|           | UK/Ireland  | Hospital                   | 32           | <1.5     | {Willetts, 2001 #104} |
|           | England     | National                   | 833          | <1       | {Gay, 1999 #113}      |
| North America |          |                            | 16425        |          |                       |
|           | Canada      | Regional                   | 961          | <6       | {Somme, 2006 #90}     |
|           | US          | National                   | 10,836       | <1       | {Yen, 2012 #108}      |
|           | US          | National                   | 22           | <1       | {Eng, 2012 #34}       |
|           | US          | Hospital                   | 405          | <7       | {Fike, 2012 #38}      |
|           | US          | Regional                   | 188          | <17      | {Shekherdimian, 2011 #87} |
|           | US          | Military hospitals         | 293          | <5       | {Nylund, 2010 #68}    |
|           | US          | 3 Hospitals                | 183          | <1       | {Cortese, 2009 #28}   |
|           | US          | National                   | 3463         | <1       | {Tate, 2008 #97}      |
|           | US          | Hospital                   | 26           | <14      | {Burjonrappa, 2007 #18} |
|           | Mexico      | Regional                   | 48           | <1       | {Velazquez, 2004 #100}|
| Oceania   |            |                            | 2761         |          |                       |
|           | Australia   | Regional                   | 197          | <2       | {Lloyd-Johnsen, 2012 #59} |
|           | Australia   | Hospital                   | 51           | <2       | {Bines, 2006 #9}      |
|           | Australia   | Regional                   | 147          | <12      | {Blanch, 2007 #11}    |
|           | Australia   | Regional                   | 23           | <18      | {Webby, 2006 #101}    |
|           | Australia   | National                   | 1794         | <1       | {Justice, 2006 #49}   |
|           | New Zealand | Hospital                   | 189          | <14      | {Kodikara, 2010 #52}  |
|           | New Zealand | National                   | 277          | <3       | {Chen, 2005 #25}      |
|           | New Zealand | Regional                   | 83           | NR       | {Reid, 2001 #76}      |
| Intercontinental/Global |          |                            | 173          |          |                       |
|           | India, Brazil, Egypt Kenya | International | 173         | <10      | {Awasthi, 2009 #6}    |

- a: Botswana, Cote D'Ivoire, Ghana, Kenya, Nigeria, South Africa, Tanzania, Zambia, Zimbabwe.
- b: these 2 studies had overlapping study years in same location but were included because data on age and clinical treatment were split.
- c: authors randomly sampled a cohort of 100,000 infants from a national insurance claims database.

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Data Analysis

We grouped data according to seven geographic regions of the world: Africa, Asia, Central & South America, Eastern Mediterranean, Europe, North America, and Oceania. Because of heterogeneity in under 5 mortality rates (u5MR) in Asia, we grouped Asian countries into high u5MR and low/very low u5MR according to WHO classification [10]. We present data on incidence of intussusception among children <1 year of age. We averaged the annual rate when rates for multiple years were presented individually. Among countries reporting incidence of intussusception, we were also interested in determining incidence by month during the first year of life. To determine a pooled estimate of intussusception incidence by month of age globally, we extrapolated the proportion of intussusception events by month of age from studies that either presented monthly incidence or number of cases to the remaining studies that only presented aggregate intussusception incidence among children <1 year of age. While only 5 studies reported intussusception incidence by month of age, 17 studies reported number of cases by month of age and the incidence among children <1 year of age, and 13 only reported aggregate intussusception incidence among children <1 year of age. Among studies (n = 35) reporting incidence of intussusception among children <1 year of age, the mean incidence was 74 per 100,000 infant years (range: 9–328) (Table 2). While incidence in a majority (83%) of the studies was <100 per 100,000, higher incidence was observed in some populations including: Australia (101), Hong Kong (108), Japan (185), Israel (219), Vietnam (302), and South Korea (328) (Table 2). Incidence of intussusception was <20 per 100,000 in some populations from Finland (20), India (18), Malaysia (18), and Bangladesh (9). Five studies reported incidence of intussusception by month of age and 15 reported number of cases by month of age among children <1 year of age. We extrapolated the proportion of intussusception incidence by month of age relative to the mean incidence among children <1 year from the 5 studies to the 30 studies that only reported incidence among children <1 year (Figure 3). The age distribution of intussusception incidence and prevalence of death by geographic region. For diagnosis and treatment, we excluded cases where this information was missing or unspecified.

All analyses were done with Microsoft EXCEL (Microsoft Corp, 2007).

Results

We reviewed 2757 abstracts to identify a total of 113 potential full-text articles and 1 meeting abstract, from which 82 studies met the inclusion criteria for our analysis (Figure 1; Table 1) [11–91]. We excluded 31 articles due to non-English language (n = 8), duplicate data (n = 14), non-epidemiology study or review (6), included in previous review (2), or age <1 excluded (1). Included studies reported a total of 44,454 intussusception events from North America (n = 16,425), Asia: low or very low mortality (n = 14,382), Europe (n = 6,280), Oceania (2,761), Africa (2,895), Eastern Mediterranean (n = 644), and Central & South America (n = 538). Among 82 studies, 44 (60%) were hospital-based studies, whereas 38 (40%) represented national or regional data on intussusception hospitalizations. Five reports presented incidence data by month of age, 17 studies presented data on number of cases by month of age and the incidence among children <1 year of age, and 13 only reported aggregate intussusception incidence among children <1 year of age. Among studies (n = 35) reporting incidence of intussusception among children <1 year of age, the mean incidence was 74 per 100,000 infant years (range: 9–328). While incidence in a majority (83%) of the studies was <100 per 100,000, higher incidence was observed in some populations including: Australia (101), Hong Kong (108), Japan (185), Israel (219), Vietnam (302), and South Korea (328). Incidence of intussusception was <20 per 100,000 in some populations from Finland (20), India (18), Malaysia (18), and Bangladesh (9). Five studies reported incidence of intussusception by month of age and 15 reported number of cases by month of age among children <1 year of age. We extrapolated the proportion of intussusception incidence by month of age relative to the mean incidence among children <1 year from the 5 studies to the 30 studies that only reported incidence among children <1 year (Figure 3). The age distribution of intussusception incidence and prevalence of death by geographic region. For diagnosis and treatment, we excluded cases where this information was missing or unspecified.

All analyses were done with Microsoft EXCEL (Microsoft Corp, 2007).
number of cases were similar, with lowest incidence among children 0–2 months of age (13–37 per 100,000) and peak incidence among those 4–7 months of age (97–126 per 100,000).

Distribution of intussusception cases by calendar month of year was reported in 21 studies (Figure 4). No particular seasonal pattern in intussusception was seen globally or in any of the regions except North America (Figure 5); however, only 1 small study of 36 cases provided data on seasonality of intussusception in North America [82].

Diagnosis of intussusception varied substantially by region. Diagnosis of intussusception was made by a radiographic modality (e.g., air-contrast enema, ultrasound, or computed tomography) in 95%–100% of the cases from all regions of the world except Africa where intussusception was diagnosed by clinical findings or surgery in 65% of the case; however, data on method of diagnosing intussusception were limited in countries from Eastern Mediterranean, Americas, and Oceania (Figure 6). Treatment of intussusception also differed by region (Figure 7).

| Continent                  | Country           | National/Regional/Hospital | Incidence per 100,000 <1 Yr. | Rates stratified by month of age |
|----------------------------|-------------------|---------------------------|------------------------------|---------------------------------|
| Africa                     | South Africa      | National                  | 56*                          | No                              |
| Asia (high u5MR)           | Bangladesh        | Regional                  | 9                            | No                              |
|                            | India             | Regional – Delhi          | 18                           | No                              |
|                            | Tunisia           | National                  | 62                           | No                              |
| Asia-low/very low u5MR     | Hong Kong         | National                  | 108                          | No                              |
|                            | Japan             | National                  | 185*                         | No                              |
|                            | South Korea       | Regional (Jeonbuk Province)| 328*                         | No                              |
|                            | Malaysia          | National                  | 18                           | No                              |
|                            | Singapore         | National                  | 51                           | No                              |
|                            | Taiwan            | National                  | 77                           | No                              |
|                            | Thailand          | National                  | 36                           | No                              |
|                            | Uzbekistan        | Regional – Bukhara        | 23                           | No                              |
|                            | Vietnam           | Regional                  | 302                          | No                              |
| Central & South America    | 11 countries      | 11 countries              | 51                           | No                              |
|                            | Chile             | Regional – Santiago       | 51                           | No                              |
|                            | Panama            | National                  | 30                           | No                              |
|                            | Venezuela         | Regional – Carabobo       | 35                           | No                              |
| Eastern Mediterranean      | Israel (Jewish)   | Hospital                  | 219                          | No                              |
|                            | Israel (Bedouin)  | Hospital                  | 75                           | No                              |
| Europe                     | Denmark           | National                  | 66                           | Yes                             |
|                            | Finland           | National                  | 20                           | No                              |
|                            | Germany           | Regional – Bavaria & NRW  | 62                           | Yes                             |
|                            | Germany           | National                  | 60                           | No                              |
|                            | Germany           | Regional – Bavaria        | 72                           | No                              |
|                            | Switzerland       | National                  | 38                           | No                              |
|                            | England           | National                  | 66                           | Yes                             |
| North America              | US*               | National                  | 33                           | Yes                             |
|                            | US                | National                  | 33                           | No                              |
|                            | US 3 hospitals    | National                  | 49                           | No                              |
|                            | US*               | National                  | 34                           | Yes                             |
| Oceania                    | Australia         | Regional – Melbourne      | 27                           | No                              |
|                            | Hospital          |                          | 71                           | No                              |
|                            | Regional – Northern Territory | 65 | No |
|                            | National          |                          | 101                          | No                              |
|                            | New Zealand       | National                  | 65                           | No                              |
| ALL REGIONS (Average)      |                   |                           | 74                           | No                              |

- a: rate for <2 year olds in the paper; we recalculated rate for <1 year of age based on presented data.
- b: midpoint of the range presented in the study.
- c: rates presented for <6 and 6–11 months in the paper; we recalculated rates for <1 based on these data.
- d: rates by age in months for the most recent surveillance years 1995–1999 were obtained from figure using Digitize-It; mean incidence for <1 presented [Fischer, 2004 #39].
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prevalence of surgery in Central/South America (86%) and Africa (77%) compared to Eastern Mediterranean (29%), Oceania (29%), North America (28%), Europe (20%), and Asia (13%).

The proportion of children with intussusception who died after presenting to the hospital was substantially higher in Africa (9.4%; range = 2–25) compared to Asia (0.2%; range = 0–6), Central and South America (0.6%; range = 0–1), Eastern Mediterranean (0.8%; range = 0–5), Europe (0.1%; range = 0–1), North America (0.4%; range = 0–1); and Oceania (0%; range 0–0.1%) (Table 3).

**Discussion**

A key issue for rotavirus immunization programs in the postlicensure era is the need for safety monitoring with regard to intussusception [2,5,92]. Our review of the intussusception literature from the past decade provides pertinent information that should facilitate implementation of intussusception surveillance for monitoring the postlicensure safety of rotavirus vaccines.

First, we demonstrate that natural intussusception is a very rare condition in most regions of the world, particularly among infants <3–4 months of age when the first dose of rotavirus vaccine is typically administered. Because any potential risk with rotavirus vaccines is greatest after the first dose of vaccine which is typically recommended to be administered at 6–15 weeks of age, [5] the lower rates of intussusception in this age group suggests that timely administration of vaccine would minimize the attributable risk of vaccine [93]. That is, the higher rates of intussusception among infants in Central/South America and Africa compared to other regions may be due to differences in age of vaccination.
infants older than 3–4 months indicates that any vaccine associated risk of intussusception could lead to more cases of intussusception associated with vaccine in settings where delays in vaccination are common. If vaccine is linked to a potential risk of intussusception, age-stratified data on intussusception are necessary for interpreting these estimates of vaccine-associated risk and calculating the number of cases that are potentially attributable to vaccine after the implementation of a vaccine program [93]. The age-stratified data in this review will be a valuable resource for conducting benefit risk analyses, should a rotavirus vaccine program be linked to any potential risk of intussusception.

Second, the incidence of intussusception varies substantially by region, thus highlighting the importance of the need for regional baseline data when evaluating postlicensure trends of intussusception for assessing any potential vaccine-associated risk. Risk of intussusception after the current rotavirus vaccines has also varied by region. In Mexico and Australia, postlicensure studies have identified an increased low-level risk of intussusception after the first dose of both rotavirus vaccines, ranging from 1 to 2 cases of intussusception per 100,000 vaccinated infants [7,8]. While an early study in the United States did not identify a risk of intussusception after RV5 [94], a recent study has shown that a low level risk of intussusception is likely to exist with both vaccines [95]. However, a similar level of risk was not observed in Brazil after RV1 [7]. While these differences in risk might be related to a chance finding, effect modification of risk related to an environmental or genetic factor that differs between the populations cannot be excluded. In our review, we observed a wide range in the incidence of intussusception globally. The cause of natural intussusception in a majority of infants is not known and has been previously reviewed. Differences in infant diet, breastfeeding, maternal antibody levels, prevalence of enteropathogens (e.g., respiratory adenovirus, rotavirus) might all contribute to the differences in background rates of intussusception [3,96]. It remains unclear whether populations with higher background risk of intussusception also would carry a higher risk of vaccine-associated risk. However, any potential risk of intussusception associated with vaccine in populations with higher background risk would lead to higher number of excess cases that would be attributable to vaccine.

Third, the clinical management of intussusception in Africa differs markedly from other regions of the world where data exist, predominantly relying on clinical manifestations for diagnosis and surgery for treatment. The paucity of data on method of diagnosing intussusception from Eastern Mediterranean, Americas, and Oceania region limits the generalizability of this information in countries from these regions. In addition, limited published data are available on clinical management and outcome of intussusception in high mortality Asian countries but it would seem that surgical rates are likely to be higher than the lower mortality Asian countries. The differences in clinical management of intussusception in high mortality settings compared to low mortality settings emphasizes the need for augmenting surveillance practices depending on the location. For example, strengthening collaborations with surgeons to improve case-capture should be prioritized when monitoring the postlicensure safety of rotavirus vaccines in Africa. As rotavirus vaccines are more broadly introduced into immunization programs in Africa and Asia, these current data on the epidemiology and clinical management of intussusception should facilitate the future implementation of intussusception surveillance and inform benefit risk calculations for defining policy and decision making.

Figure 5. Seasonality of intussusception, by WHO region.
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Studies assess the role of wild-type rotavirus infection as a cause of intussusception have led to conflicting findings with several studies suggesting that a significant association is unlikely [3]. The absence of any marked seasonal patterns in intussusception, particularly in settings of Europe, Oceania, and Central and South America where rotavirus disease is quite seasonal supports the

Figure 6. Diagnosis of intussusception by WHO region. Studies where diagnosis was unspecified were not included. Data from Central and South America were from one prospective research study that might not reflect clinical practice under routine conditions. doi:10.1371/journal.pone.0068482.g006
contention that rotavirus is unlikely to be a prominent etiologic cause of natural intussusception. This has some implications for postlicensure monitoring because attempts have previously been made to assess whether rotavirus vaccination would have a protective effect against intussusception vis-à-vis protecting against wild-type rotavirus infection. Establishing whether vaccine confers protection against intussusception might be challenging if only a
Table 3. Case-fatality among children hospitalized with intussusception.

| Country | No. of IS cases | Deaths |
|---------|-----------------|--------|
|         | No.  | %     |
| Total (Africa) | 1961 | 185  | 9.4% |
| Multi-country: Botswana, Cote D'Ivoire, Ghana, Kenya, Malawi, Nigeria, South Africa, Tanzania, Zambia, Zimbabwe | 863  | 108  | 12.5% |
| Kenya | 36   | 5    | 13.9% |
| Ghana | 29   | 5    | 17.2% |
| Nigeria | 44   | 1    | 2.3% |
|         | 33   | 6    | 18.2% |
|         | 89   | 2    | 2.2% |
|         | 174  | 21   | 12.1% |
|         | 29   | 4    | 13.8% |
|         | 87   | 7    | 8.0% |
|         | 20   | 0    | 0.0% |
| South Africa | 423  | 9    | 2.1% |
|         | 106  | 10   | 9.4% |
| Tanzania | 28   | 7    | 25.0% |
| Total (Asia) | 4323 | 8    | 0.19% |
| China | 56   | 0    | 0.0% |
| India | 31   | 0    | 0.0% |
|         | 137  | 1    | 0.7% |
|         | 179  | 0    | 0.0% |
| Japan | 2427 | 2    | 0.1% |
| Korea | 406  | 1    | 0.2% |
| Malaysia | 62  | 0    | 0.0% |
| Singapore | 217 | 0    | 0.0% |
| Thailand | 112 | 0    | 0.0% |
|         | 94   | 0    | 0.0% |
| Uzbekistan | 67  | 4    | 6.0% |
| Vietnam | 533  | 0    | 0.0% |
| Total (Central and South America) | 538  | 3    | 0.6% |
| Latin America | 222 | 2    | 0.9% |
| Chile | 95   | 0    | 0.0% |
| Panama | 103  | 1    | 1.0% |
| Trinidad & Tobago | 65  | 0    | 0.0% |
| Venezuela | 53  | 0    | 0.0% |
| Total (Eastern Mediterranean) | 644  | 5    | 0.8% |
| Saudi Arabia | 34  | 0    | 0.0% |
| Israel | 316  | 0    | 0.0% |
| Jordan | 148  | 0    | 0.0% |
|         | 109  | 5    | 4.6% |
| Total (Europe) | 2588 | 3    | 0.1% |
| Austria | 111  | 0    | 0.0% |
| Germany | 1189 | 0    | 0.0% |
| Ireland | 256  | 0    | 0.0% |
|         | 24   | 0    | 0.0% |
| Russia | 280  | 0    | 0.0% |
| Spain | 151  | 1    | 0.7% |
| Turkey | 105  | 1    | 1.0% |
small etiologic fraction of naturally occurring intussusception is related to wild-type rotavirus infection [5,97].

Our review provides background rates of intussusception against which rates of intussusception after the introduction of vaccine could be compared for assessing potential vaccine-associated risk. However, the paucity of background rates from most settings supports the need for relying on other analytic methods of safety monitoring after the introduction of rotavirus vaccine [2]. The self-controlled case-series method has now been successfully applied in several settings for assessing a potential link between vaccine and intussusception [7]. This method relies on active, hospital based surveillance of intussusception and does not require information on background rates of intussusception in the population under surveillance [98]. Our review provides important considerations when establishing surveillance for intussusception. First, in resource poor settings of Africa, specific attention should be placed on hospitals with surgery suites which are likely to manage most intussusception events. While background rates are not specifically needed for the case-series method, in settings where no background rates are available, some efforts could be made to establish population-based studies which would be necessary for determining the attributable risk of vaccine, should any increased risk be identified. Lastly, the varying incidence of intussusception during the first six months of life when rotavirus vaccines are administered strongly indicates the need for addressing confounding effects of age when determining whether a causal link exists between rotavirus vaccine and intussusception cases identified through surveillance.

Intussusception case-fatality was <1% in all developed countries of the world. However, the marked difference in case-fatality between Asia (<1%) and Africa (9%) was intriguing. This finding might reflect differences in healthcare infrastructure or delays in care, or perhaps might be related to a publication bias with a paucity of surveillance data in the poorest populations of Asia. Previous analyses of benefits versus risk of rotavirus vaccine have conservatively assumed intussusception case-fatality rate of 25% in Asia, which in light of this review is high and could be reconsidered for future benefit risk deliberations [93]. Even if case-fatality rates were to be higher than those identified in this review, some adjustment would be prudent for obtaining valid estimates of any potential risk associated with rotavirus vaccine in Asia.

Our review must be considered with some limitations. Because intussusception is a very rare condition, a fair amount of heterogeneity in surveillance practice is likely to exist across regions. In particular, establishing incidence of intussusception is rather challenging in many settings without established national or regional electronic records and thus published rates of intussusception might be prone to over or underestimation. The availability of a standardized case definition by the Brighton Collaboration reduces case misclassification but sensitivity of the case-definition might be reduced in resource poor settings where diagnostic modalities are not available and relying on clinical judgment and surgery is required for diagnosis [1]. The case-fatality from these hospital based surveillance studies in resource poor settings also certainly underestimates the true case-fatality because deaths are likely to occur out of hospital. While some 30 countries had introduced a rotavirus between 2006 and 2011, all but one of the studies included in this review [83] captured data before the introduction of a rotavirus vaccine.

In summary, this review of current epidemiology and clinical management of intussusception should prove to be a valuable resource for establishing intussusception surveillance and interpreting these surveillance data from various regions of the world where rotavirus vaccines are likely to be introduced in the next several years.

**Ethics statement**

Because these are publicly available non-identifiable data, an ethics statement was not required for this work.

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**Table 3.** Cont.

| Country          | No. of IS cases | Deaths |
|------------------|-----------------|--------|
|                  | No. | %       | No. | %     |
| UK/Ireland       | 179 | 0       | 0   | 0.0%  |
|                  | 261 | 1       | 4   | 0.4%  |
|                  | 32  | 0       | 0   | 0.0%  |
| **Total (No. America)** | **3860** | **16** | **0.4%** |
| US               | 188 | 0       | 0   | 0.0%  |
|                  | 183 | 2       | 1.1%|
|                  | 3463| 14      | 0.4%|
|                  | 26  | 0       | 0   | 0.0%  |
| **Total (Oceania)** | **2738** | **1** | **0.0%** |
| Australia        | 51  | 0       | 0   | 0.0%  |
|                  | 197 | 0       | 0   | 0.0%  |
|                  | 147 | 0       | 0   | 0.0%  |
|                  | 1794| 1       | 0.1%|
| New Zealand      | 189 | 0       | 0   | 0.0%  |
|                  | 277 | 0       | 0   | 0.0%  |
|                  | 83  | 0       | 0   | 0.0%  |

**Table 3.** Cont.
Supporting Information

Checklist S1 PRISMA Checklist for the preferred reporting list for the intussusception literature review.

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Author Contributions

Conceived and designed the experiments: BJ UP TN JB MP. Performed the experiments: JJ MP. Analyzed the data: JJ MP. Wrote the paper: MP. Design, data review, data interpretation and manuscript review: BJ UP TN JB.

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