Safety of a heat-stable rotavirus vaccine among children in Niger: Data from a phase 3, randomized, double-blind, placebo-controlled trial

Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Safety of a heat-stable rotavirus vaccine among children in Niger: Data from a phase 3, randomized, double-blind, placebo-controlled trial

Matthew E. Coldiron [a,*], Ousmane Guindo [b], Rockyath Makarimi [b], Issaka Soumana [b], Amadou Matar Seck [b], Souna Garba [b], Emilie Macher [c], Sheila Isanaka [a], Rebecca F. Grais [a]

[a] Epicentre, 8 rue Saint-Sabin, Paris, France
[b] Epicentre, Maradi, Niger
[c] Médecins Sans Frontières, 78 rue de Lausanne, Geneva, Switzerland

ARTICLE INFO

Article history:
Received 21 March 2018
Received in revised form 2 May 2018
Accepted 3 May 2018
Available online xxxx

Keywords:
Rotavirus vaccines
Rotavirus infection
Niger
Intussusception
Diarrhea
Gastroenteritis
Adverse event
Safety

ABSTRACT

Background: Rotavirus remains a major cause of diarrhea among children under 5 years of age. The efficacy of RotaSIIL, a pentavalent rotavirus vaccine, was shown in an event-driven trial in Niger. We describe the two-year safety follow-up of this trial.

Methods: Follow-up of safety outcomes began upon administration of the first dose of RotaSIIL or placebo. Adverse events were followed until 28 days after the third dose, and serious adverse events were followed until 2 years of age. Suspected cases of intussusception were evaluated at first point of contact and then referred to hospital for surgical evaluation. Causes of death were obtained by chart review and verbal autopsy. Passive surveillance was carried out in health centers. Community health workers carried out active surveillance in villages. Between-group differences were evaluated using the chi-squared test and Fisher's exact test.

Results: A total of 4092 children were randomized, and 4086 received at least one dose of RotaSIIL or placebo, constituting the intention-to-treat population, who accrued a total of 7385 child-years of follow-up time. At two years of follow-up, 58 (2.8%) participants who received RotaSIIL and 49 (2.4%) participants who received placebo had died (p = 0.38). Most deaths were due to infectious causes common to the study area. One participant had confirmed intussusception, 542 days after receiving the third dose of RotaSIIL. A total of 395 (19.3%) participants receiving RotaSIIL and 419 (20.5%) participants receiving placebo experienced any serious adverse event (p = 0.36). Most serious adverse events were hospitalizations due to infection (malaria, lower respiratory tract infection and gastroenteritis) or marasmus. Overall, 1474 (72.1%) participants receiving RotaSIIL and 1456 (71.1%) participants receiving placebo had at least one adverse event (p = 0.49) in the follow-up period.

Conclusions: At two years of follow-up, RotaSIIL was found to be safe.

Trial registration: ClinicalTrials.gov: NCT02145000.

1. Introduction

Rotavirus is the leading cause of severe gastroenteritis in children and is responsible for an estimated 450,000 deaths per year in children <5 years of age, most of which occur in low-income countries [1]. In Niger, health facility-based surveillance showed that rotavirus was found in 30% of children aged <5 years with diarrhea, and that 96% of those who were positive were aged <18 months [2].

There are several rotavirus vaccines, of which three are currently pre-qualified by the World Health Organization (WHO) (RotaTeq®, Rotarix®, and Rotavac®). The impact on childhood

Abbreviations: AE, adverse event; CI, confidence interval; DSMB, Data and Safety Monitoring Board; LRTI, Lower Respiratory Tract Infection; SAE, Serious Adverse Event; SRVGE, severe rotavirus gastroenteritis ; WHO, World Health Organization.

* Corresponding author.
E-mail addresses: matthew.coldiron@epicentre.msf.org (M.E. Coldiron), ousmane.guindo@epicentre.msf.org (O. Guindo), rockyiath.makarimi@epicentre.msf.org (R. Makarimi), issaka.soumana@epicentre.msf.org (I. Soumana), amadou.matar@epicentre.msf.org (A. Matar Seck), souna.garba@epicentre.msf.org (S. Garba), emilie.macher@geneva.msf.org (E. Macher), sheila.isanaka@epicentre.msf.org (S. Isanaka), rebecca.grais@epicentre.msf.org (R.F. Grais).

https://doi.org/10.1016/j.vaccine.2018.05.023
0264-410X/

gastroenteritis following vaccine roll-out is substantial. In Europe, routine rotavirus vaccination was shown to be highly effective on an individual level, and reduced rotavirus-related hospitalizations by 65–84% [3]. Studies from low-income countries have shown reductions in all-cause gastroenteritis hospitalizations and rotavirus-related hospitalizations after vaccine introduction [4,5], as well as favorable cost-effectiveness, with costs per case averted ranging between US$27-38 [6]. However, there are several challenges in the introduction of rotavirus vaccination in low-income countries including cost, availability, cold chain requirements and concerns about safety, primarily the risk of intussusception. In high-income countries, post-licensure monitoring of RotaTeq® and Rotarix® has shown an increased risk of intussusception in the 10 days following the first dose vaccine, although the absolute risks are low [7,8]. The WHO Global Advisory Committee on Vaccine Safety has stated that the benefits of rotavirus vaccination far outweigh the risks, while noting that epidemiological differences warrant continued follow-up as the vaccines are rolled-out in other parts of the world [9].

New rotavirus vaccines have recently been tested and licensed by national regulatory authorities, including RotaSIIL, a live attenuated bovine-human [UK] reassortant oral vaccine against rotavirus serotypes G1, G2 G3, G4 and G9, that is stored in a lyophilized form that is thermostable at 40 °C for 18 months [10]. In a randomized, double-blind, placebo-controlled trial of RotaSIIL in Niger, efficacy against severe rotavirus gastroenteritis (SRVGE) was 66.7% (95% confidence interval [CI], 49.9–77.9) and 69.1% (95% CI 55.0–78.7) in the per-protocol and intention-to-treat analyses, respectively [11]. The trial was event-driven and the primary analysis was triggered after 117 cases of SRVGE were confirmed. When this number of cases had been met, the intention-to-treat population of the trial had not fully accrued the two-year follow-up time. On October 17, 2017, the last study participant of the intention-to-treat population was two years old, marking the end of the two-year safety follow-up of this group. Here, we report the safety of RotaSIIL as part of the efficacy trial in Niger.

2. Materials and methods

2.1. Study site

Madarounfa District is a predominantly rural area located in south-central Niger along the border with Nigeria. The population relies primarily on subsistence agriculture. The under-5 mortality rate in 2016 in Niger was 91 per 1000 live births, the infant mortality rate was 51 per 1000 live births, and the fertility rate was 7.3 births per woman [12]. As with many Sahelian countries, after the neonatal period, the major causes of morbidity and mortality are largely infectious (principally malaria, diarrhea, lower respiratory tract infections, and meningitis) or related to severe acute malnutrition [13].

2.2. Enrolment procedures and outcome definitions

Full trial methods have been published previously [11]. In brief, children were randomized to receive RotaSIIL or placebo at 6, 10 and 14 weeks of age, and were actively and passively followed for gastroenteritis and all other health problems for two years, both in the community and also in health facilities including 5 health centers, their associated health posts, and the district hospital. Stool samples taken within seven days of a reported gastroenteritis episode were tested for rotavirus antigen, in duplicate, using an EIA kit (PremierTM Rotaclone®, Meridian Bioscience, Inc., Cincinnati OH, USA) at the Epicentre Maradi laboratory. The primary outcome of the trial was efficacy against SRVGE.

The trial was conducted in accordance with Good Clinical Practice guidelines, and the protocol was approved by the ethics committee of the World Health Organization (WHO), the Western Institutional Review Board in Olympia, Washington, the Comité Consultatif National d'Ethique of Niger; the Comité de Protection des Personnes of Saint-Germain-en-Laye, France; and the Hôpitaux Universitaires de Genève in Switzerland. An independent data and safety monitoring board (DSMB) reviewed outcomes and safety data. The first review occurred after 1000 children had completed 28 days of follow-up after their third dose of RotaSIIL or placebo, and then at 6-month intervals thereafter. An independent adjudication committee reviewed clinical data and imaging of suspected cases of intussusception.

An adverse event (AE) was defined as any untoward medical occurrence in a participant that did not necessarily have a causal relationship with the vaccine or placebo. All adverse events were monitored in home-based and facility-based surveillance, as described below, and judged for severity.

Serious adverse events (SAE), including intussusception, were defined as any untoward medical occurrence that at any dose of study product resulted in death, was life threatening, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability or incapacity [14], or any medically important event or reaction that may have jeopardized the subject and may have required medical or surgical intervention to prevent one of the outcomes listed above [15,16].

The clinical case definition of intussusception was based on level of diagnostic certainty (definite, probable, or possible) [17], and all suspected cases were followed by the site principal investigator and medical monitor following WHO guidance [18]. Suspected cases were graded as Level 1, 2 or 3 according to the certainty of the diagnosis and the Brighton Collaboration clinical case definition. A case was considered a potential rotavirus vaccine-related intussusception case if RotaSIIL was received prior to the episode of intussusception. Cases for which there was insufficient information to establish the diagnosis according to the Brighton Collaboration clinical case definition would have been classified as unconfirmed and analyzed accordingly with other SAEs, but there were no cases to which this scenario applied.

2.3. Surveillance

Monitoring of safety endpoints began at the time of administration of RotaSIIL or placebo, when all participants were observed for 30 min after each dose, at which point vital signs were measured and a targeted physical exam was performed if indicated. AEs were assessed from the time of the administration of the first dose until 28 days after the third dose. SAEs were assessed from the time of the administration of the first dose until 2 years of age. Immediate adverse events were defined as any adverse event occurring within 30 min of receiving a dose of RotaSIIL or placebo. Surveillance was both active and passive, and occurred in health facilities and at participants' homes.

At enrolment, caregivers of study participants were informed of the signs and symptoms of AEs and SAEs, including intussusception (including bloody stools, continuous vomiting, abdominal distention and/or abdominal "lumps"), and were advised to present to their community health worker or the nearest health facility for any health concern.

Scheduled study visits occurred in health centers with each dose of study product, and then at 6, 9, 12, 18 and 24 months of age. During these visits, staff conducted a detailed history and physical exam, and appropriate medical care was provided free of charge. For any episode of gastroenteritis or AE that necessitated outpatient care, a nursing assistant performed daily home-based follow-up visits until the resolution of the episode. For any event

Please cite this article in press as: Coldiron ME et al. Safety of a heat-stable rotavirus vaccine among children in Niger: Data from a phase 3, randomized, double-blind, placebo-controlled trial. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.05.023

necessitating hospitalization, the participant was immediately transferred to the district hospital and home-based follow-up was arranged post-discharge until full resolution.

Community health workers also carried out weekly scheduled study visits at the homes of participants. During these visits, caregivers were asked to detail all medical signs and symptoms that were a concern at that time, and any symptoms since the previous week's home visit. If the symptoms met the definition of AE or SAE, appropriate documentation occurred during these home visits, and children needing further medical evaluation were referred to health centers.

For children who died in a health facility, study staff transcribed events before and at the time of death from hospital records to establish the cause of death. Standard verbal autopsy forms [19] were then completed during interviews with the deceased participant's caregiver to further describe the clinical state and treatment received prior to death. For children who died outside of a health facility, only the verbal autopsy form was used to establish the cause of death.

2.4. Intussusception

Children in whom intussusception was suspected during scheduled or unscheduled home or facility-based visits were immediately referred to the Maradi Regional Reference Hospital. The on-call surgeon carried out a clinical assessment, including a physical and ultrasound examination, and surgical intervention when necessary. Complicated cases were referred to the Zinder National Hospital. Study staff followed all suspected cases throughout hospitalization, and at home after discharge from hospital until complete resolution of all symptoms. All participants with suspected intussusception had ultrasound images and intraoperative photographs taken for adjudication by an independent intussusception evaluation committee.

2.5. Treatment, causality and classification

Throughout the study, at all scheduled and unscheduled visits, study staff provided evaluation and treatment free of charge.

All AEs and SAEs were assessed for a causal relationship with the study product by the Site Principal Investigator and the Medical Monitor using appropriate medical judgment and considering all relevant factors including the pattern of reaction, temporal relationship, re-challenge, biological plausibility, and confounding factors such as concomitant medication, concomitant disease and relevant history. The event was judged related when there was a reasonable possibility that the study product contributed to the event and unrelated when administration of the study product was not suspected to have contributed to the event [20]. All immediate adverse events were considered related to vaccination.

All AEs and SAEs were coded using the Medical Dictionary for Regulatory Authorities (MedDRA), version 20.0.

2.6. Statistical analysis

Safety analyses were performed in the intention-to-treat population and included follow-up from the time of enrolment until 28 days after the third dose (for adverse events) or until two years of age or the end of follow-up (for serious adverse events). We used chi-squared and Fisher's exact (when fewer than five events occurred per diagnosis) tests to analyze the between-group difference in the number of participants experiencing at least one adverse event and at least one serious adverse event. Each participant was considered once per System Organ Class and once per Preferred Term.

3. Results

A total of 4092 children were randomized, and 4086 received at least one dose of RotaSIIL or placebo, constituting the intention-to-treat population, who accrued a total of 7385 child-years of follow-up time, including 3680 in the RotaSIIL group and 3705 in the placebo group (Fig. 1).

3.1. Deaths

A total of 107 deaths occurred during the two-year follow-up period, 58 among participants who received RotaSIIL, and 49 among participants who received placebo ($p = 0.38$). The majority of deaths among all participants were due to infectious causes, with malaria, gastroenteritis and lower respiratory tract infections as the most frequent causes of death. There were no between-group differences for any cause of death (Table 1).

3.2. Intussusception

Over two years of follow-up, a total of six participants presented with signs and symptoms consistent with intussusception and warranting a transfer to the Maradi Regional Reference Hospital for further evaluation. Only one participant had definite intussusception, a 21-month old boy who received his third dose of RotaSIIL 542 prior days to the onset of symptoms. Surgical resection and anastomosis was performed and the child fully recovered. Of the 5 suspected cases that were eventually ruled out (2 had received placebo, 3 RotaSIIL), all had complete recovery, and their final diagnoses were gastroenteritis with lower respiratory tract infection (LRTI), malaria with LRTI (two participants), marasmus with gastroenteritis, and gastroenteritis.

3.3. Serious adverse events

A total of 1445 SAEs were notified during the full length of follow-up (Table 2), including the 107 deaths and the confirmed case of intussusception described above. The remaining 1337 SAEs were related to hospitalization. Overall, the SAEs occurred in 814 participants, 395 (19.3%) who had received RotaSIIL and 419 (20.5%) who had received placebo ($p = 0.36$). The most common causes of SAEs were malaria, lower respiratory tract infections, gastroenteritis, and marasmus. More participants who received placebo had at least one SAE due to lower respiratory tract infection compared to participants who received RotaSIIL (8.8% vs 6.9%, $p = 0.02$), but there were no other significant between-group differences. No SAE were judged related to RotaSIIL or placebo.

3.4. Adverse events

A total of 8515 AEs were reported between the first dose of RotaSIIL or placebo and 28 days following the third dose, 4267 (50.1%) in participants who received RotaSIIL and 4248 (49.9%) in participants who received placebo. Overall, 1474 (72.1%) participants receiving RotaSIIL and 1456 (71.1%) participants receiving placebo had at least one AE ($p = 0.49$) in the follow-up period. The most commonly-reported AEs included cough, pyrexia, conjunctivitis and rhinorrhea. No between-group differences were seen (Table 3).

3.5. Immediate adverse events

Four immediate adverse events were reported among children within 30 min of receiving a dose of study product, including three

Please cite this article in press as: Coldiron ME et al. Safety of a heat-stable rotavirus vaccine among children in Niger: Data from a phase 3, randomized, double-blind, placebo-controlled trial. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.05.023

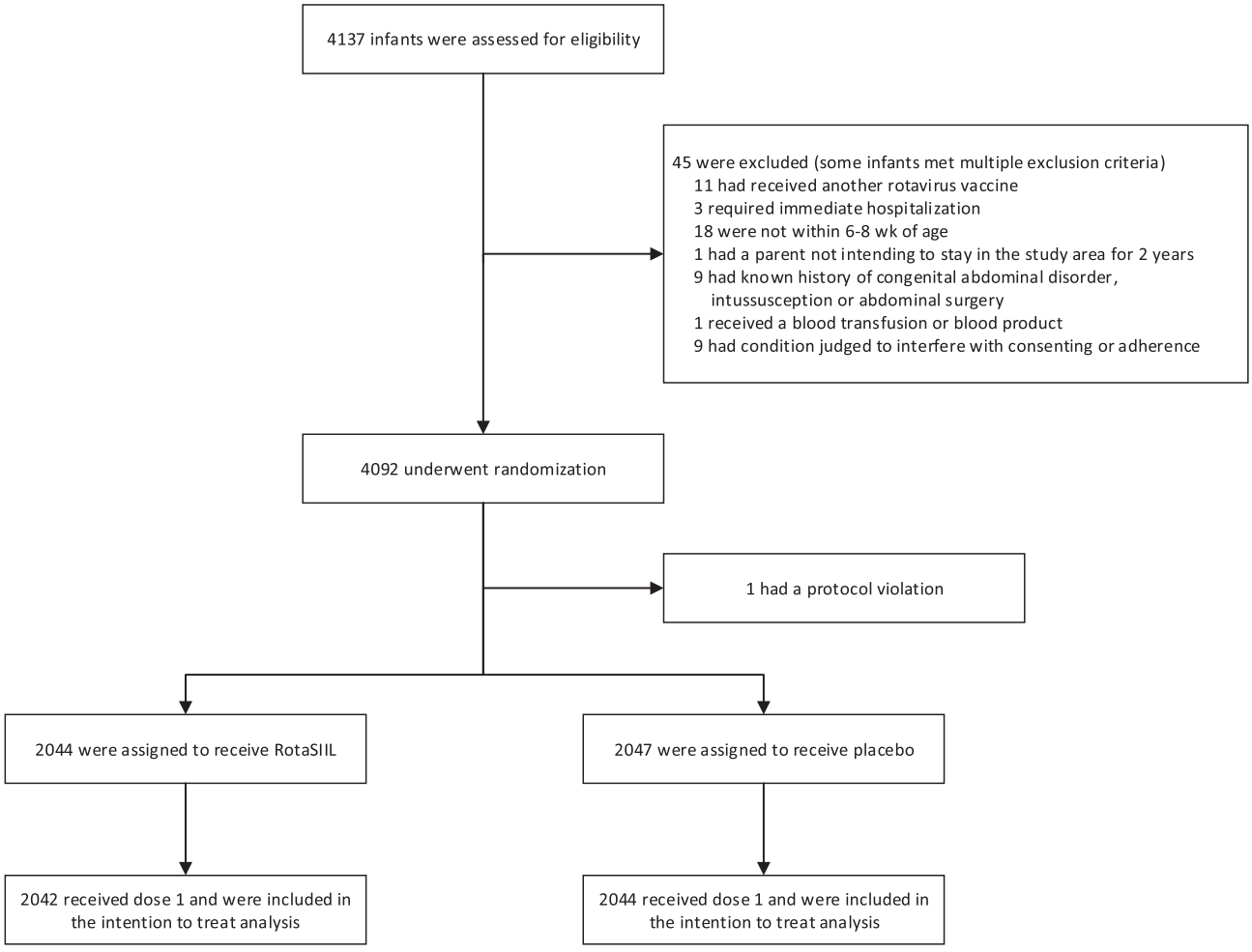

Fig. 1. Screening and enrolment of participants.

Table 1
Causes of death.

System Organ Class *Preferred term*	RotaSIIL N = 2042 n (%)	Placebo N = 2044 n (%)	p
All causes	**58 (2.8)**	**49 (2.4)**	**0.38**
Infections and infestations	**47 (2.3)**	**43 (2.1)**	**0.67**
Malaria	19 (0.9)	13 (0.6)	0.29
Cerebral malaria	4 (0.2)	4 (0.2)	1
Gastroenteritis	14 (0.7)	9 (0.4)	0.30
Lower respiratory tract infection	6 (0.3)	12 (0.6)	0.16
Sepsis	3 (0.1)	1 (0.05)	0.38
Wound sepsis	0	1 (0.05)	1
Bronchiolitis	0	1 (0.05)	1
Measles	0	1 (0.05)	1
Meningitis	1 (0.05)	1 (0.05)	1
Metabolism and nutritional disorders	**4 (0.2)**	**4 (0.2)**	**1**
Marasmus	4 (0.2)	4 (0.2)	1
General disorders and administration site conditions	**5 (0.2)**	**1 (0.05)**	**0.13**
Sudden death	4 (0.2)	1 (0.05)	0.22
Pyrexia	1 (0.05)	0	1
Gastrointestinal disorders	**1 (0.05)**	**0**	**1**
Gastrointestinal disorder	1 (0.05)	0	1
Congenital, familial and genetic disorders	**1 (0.05)**	**0**	**1**
Sickle cell anemia	1 (0.05)	0	1
Injury, poisoning and procedural complications	**0**	**1 (0.05)**	**1**
Toxicity to various agents	0	1 (0.05)	1

Please cite this article in press as: Coldiron ME et al. Safety of a heat-stable rotavirus vaccine among children in Niger: Data from a phase 3, randomized, double-blind, placebo-controlled trial. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.05.023

Table 2
Proportion of participants with at least one SAE in a given System Organ Class and Preferred Term.

System Organ Class *Preferred term*	RotaSIIL N = 2042 n (%)	Placebo N = 2044 n (%)	P
Any SAE	**395 (19.3)**	**419 (20.5)**	**0.35**
Blood and lymphatic system disorders	**9 (0.4)**	**12 (0.6)**	**0.51**
Anemia	9 (0.4)	11 (0.5)	0.66
Hemolytic anemia	0	1 (0.05)	1
Congenital, familial and genetic disorders	**10 (0.5)**	**9 (0.4)**	**0.82**
Sickle cell anemia	9 (0.4)	7 (0.3)	0.62
Congenital genital malformation female	1 (0.05)	0	1
Congenital megacolon	0	1 (0.05)	1
Heart disease congenital	0	1 (0.05)	1
Gastrointestinal disorders	**4 (0.2)**	**3 (0.1)**	**0.73**
Gastrointestinal disorder	1 (0.05)	0	1
Intussusception	1 (0.05)	0	1
Umbilical hernia	0	2 (0.1)	0.25
Vomiting	2 (0.1)	1 (0.05)	0.63
General disorders and administration site conditions	**5 (0.2)**	**1 (0.05)**	**0.13**
Sudden death	4 (0.2)	1 (0.05)	0.22
Pyrexia	1 (0.05)	0	1
Hepatobiliary disorders	**1 (0.05)**	**0**	**1**
Hepatomegaly	1 (0.05)	0	1
Infections and infestations	**365 (17.9)**	**393 (19.2)**	**0.27**
Bronchiolitis	7 (0.3)	9 (0.4)	0.62
Cerebral malaria	26 (1.3)	27 (1.3)	0.89
Conjunctivitis	2 (0.1)	1 (0.05)	0.63
Croup infectious	1 (0.05)	0	1
Dysentery	5 (0.2)	9 (0.4)	0.29
Gastroenteritis	108 (5.3)	124 (6.1)	0.28
Gastrointestinal candidiasis	1 (0.05)	0	1
Infection	4 (0.2)	1 (0.05)	0.22
Lower respiratory tract infection	141 (6.9)	181 (8.9)	0.02
Lymph node abscess	1 (0.05)	1 (0.05)	1
Lymph node tuberculosis	0	1 (0.05)	1
Malaria	142 (7.0)	162 (7.9)	0.24
Mastoiditis	0	1 (0.05)	1
Measles	15 (0.7)	14 (0.7)	0.85
Meningitis	4 (0.2)	4 (0.2)	1
Meningitis aseptic	2 (0.1)	1 (0.05)	0.63
Orchitis	1 (0.05)	0	1
Osteomyelitis	1 (0.05)	0	1
Otitis media	1 (0.05)	2 (0.1)	0.63
Parotitis	1 (0.05)	1 (0.05)	1
Pulmonary tuberculosis	2 (0.1)	0	0.25
Sepsis	9 (0.4)	10 (0.5)	1
Skin infection	2 (0.1)	0	0.25
Staphylococcal skin infection	2 (0.1)	1 (0.05)	0.63
Subcutaneous abscess	4 (0.2)	2 (0.1)	0.45
Typhoid fever	1 (0.05)	1 (0.05)	1
Upper respiratory tract infection	2 (0.1)	3 (0.2)	1
Urinary tract infection	2 (0.1)	4 (0.2)	0.69
Varicella	2 (0.1)	1 (0.05)	0.63
Wound sepsis	0	3 (0.2)	0.25
Injury, poisoning and procedural complications	**12 (0.6)**	**21 (1.0)**	**0.12**
Accidental overdose	1 (0.05)	1 (0.05)	1
Burns second degree	2 (0.1)	8 (0.4)	0.11
Chemical poisoning	1 (0.05)	2 (0.1)	1
Femur fracture	1 (0.05)	0	1
Foreign body	1 (0.05)	0	1
Injury	2 (0.1)	2 (0.1)	1
Toxicity to various agents	4 (0.2)	8 (0.4)	0.39
Metabolism and nutrition disorders	**64 (3.1)**	**68 (3.3)**	**0.73**
Dehydration	2 (0.1)	0	0.25
Kwashiorkor	3 (0.2)	4 (0.2)	1
Marasmus	60 (2.9)	63 (3.1)	0.79
Poor weight gain	0	1 (0.05)	1
Renal and urinary disorders	**2 (0.1)**	**0**	**0.25**
Nephrotic syndrome	2 (0.1)	0	0.25
Skin and subcutaneous tissue disorders	**1 (0.05)**	**0**	**1**
Eczema	1 (0.05)	0	1

cases of fever (two in RotaSIIL group, one in placebo) and one of vomiting (RotaSIIL group). Further vaccinations were withheld for the three children whose immediate adverse events occurred after receiving the first or second dose of study product. All four immediate adverse events were judged to be of mild or moderate severity, and all resolved within 5 days.

Please cite this article in press as: Coldiron ME et al. Safety of a heat-stable rotavirus vaccine among children in Niger: Data from a phase 3, randomized, double-blind, placebo-controlled trial. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.05.023

Table 3
Proportion of participants with at least one AE in a given System Organ Class and Preferred Term.

System Organ Class *Preferred term*	RotaSIIL N = 2044 n (%)	Placebo N = 2047 n (%)	P
Any AE	**1474 (72.1)**	**1456 (71.1)**	**0.49**
Blood and lymphatic system disorders	**2 (0.1)**	**3 (0.1)**	**1**
Ear and labyrinth disorders	**42 (2.1)**	**26 (1.3)**	**0.05**
Ear pain	42 (2.1)	26 (1.3)	0.05
Gastrointestinal disorders	**79 (3.9)**	**96 (4.7)**	**0.19**
Abdominal pain	17 (0.8)	14 (0.7)	0.59
Diarrhea	7 (0.3)	15 (0.7)	0.09
Vomiting	49 (2.4)	64 (3.1)	0.15
Others	9 (0.4)	7 (0.3)	0.62
General disorders and administration site conditions	**637 (31.2)**	**636 (31.1)**	**0.96**
Pyrexia	636 (31.2)	635 (31.1)	0.96
Others	4 (0.2)	3 (0.2)	0.73
Hepatobiliary disorders	**0**	**1 (0.05)**	**1**
Infections and infestations	**535 (26.2)**	**515 (25.2)**	**0.46**
Abscess	6 (0.3)	2 (0.1)	0.18
Candida infection	33 (1.6)	36 (1.8)	0.72
Conjunctivitis	487 (23.6)	469 (23.0)	0.61
Furuncle	5 (0.2)	4 (0.2)	0.75
Otitis media acute	3 (0.2)	2 (0.1)	0.69
Tinea capitis	10 (0.5)	16 (0.8)	0.24
Urinary tract infection	3 (0.2)	5 (0.2)	0.73
Others	6 (0.3)	8 (0.4)	0.59
Injury, poisoning and procedural complications	**35 (1.7)**	**31 (1.5)**	**0.62**
Accident	24 (1.2)	23 (1.1)	0.88
Injury	10 (0.5)	7 (0.3)	0.46
Thermal burn	1 (0.05)	1 (0.05)	1
Metabolism and nutrition disorders	**2 (0.1)**	**1 (0.05)**	**0.63**
Nervous system disorders	**1 (0.05)**	**0**	**1**
Renal and urinary disorders	**6 (0.3)**	**3 (0.2)**	**0.34**
Respiratory, thoracic and mediastinal disorders	**1267 (62.1)**	**1253 (61.3)**	**0.62**
Cough	1165 (56.6)	1178 (57.6)	0.49
Dyspnea	79 (3.9)	71 (3.5)	0.50
Rhinorrhea	354 (17.3)	317 (15.5)	0.12
Others	2 (0.1)	4 (0.2)	0.69
Skin and subcutaneous tissue disorders	**177 (8.7)**	**147 (7.2)**	**0.08**
Skin irritation	176 (8.6)	146 (7.1)	0.08
Umbilical discharge	1 (0.05)	1 (0.05)	1

4. Discussion

After two years of follow-up among the primary analysis population, we found that children who received RotaSIIL had similar safety outcomes to children who received placebo. One of the striking results of this trial is the low rate of early childhood mortality among the study participants. Despite improvements in recent years, infant and child mortality remain high in Niger, with highest risk among infants, and a majority of deaths occurring due to infectious diseases [21]. In 2016, the under-5 mortality rate in Niger was estimated at 91 per 1000 live births and the infant mortality at 51 per 1000 live births [12], while in this trial, the overall mortality rate was 2.6%, and did not differ between groups. Even though participants in this trial were followed until only two years of age, this period corresponds to the highest mortality rates, and the mortality seen in this study was much lower than would be expected in rural Niger. Weekly home-based follow-up of participants means that this low rate is not likely to be due to underreporting or loss to follow-up, but is more likely to be due to the provision of comprehensive and free health care, particularly following any AE or SAE.

The rarity of intussusception makes it difficult to evaluate its potential association with rotavirus vaccination, even in large trials [22]. In this study, there is no indication of an increased risk of intussusception following vaccination with RotaSIIL. In comparison to the one confirmed case of intussusception in this trial, another trial of the same vaccine in India detected 13 cases of intussusception (6/3749 or 0.2% of children who had received RotaSIIL and 7/3751 or 0.2% of children who had received placebo) [23]. Other rotavirus vaccine trials in Africa have also detected few, if any, cases of intussusception [24,25]. The reason for this difference is not known but may be due to an environmental or other factor. Reliable estimates on the incidence of intussusception in Niger are not available, but over a two-year period beginning in January 2016, the Maradi Regional Hospital recorded 22 cases of intussusception among children under 5 years of age. It is the main hospital for a city of 300,000 persons and the reference hospital for a region with a total population of 3.1 million. The diagnosis of only one case of intussusception among the 4091 trial participants is therefore in line with the overall rarity of the condition in this region.

The majority of SAEs were hospitalizations, and the indications for admission were consistent with the main pathologies affecting young children in the rural Sahel: malaria, gastroenteritis, malnutrition and lower respiratory tract infections [13]. We note that hospitalization for lower respiratory tract infection was more common among children in the placebo group, but this finding has no obvious explanation, neither in terms of a biological mechanism nor in terms of any reporting bias, and is therefore most likely due to chance alone. The vulnerability of the children participating in this trial is underscored by the fact that nearly 20% of study participants needed hospitalization for any cause over the two-year follow-up period, which is higher than reported in other rotavirus vaccine trials in Africa. This gives further evidence of the need of affordable and accessible vaccines against rotavirus, and also of other vaccine-preventable conditions like invasive pneumococcal disease.

Please cite this article in press as: Coldiron ME et al. Safety of a heat-stable rotavirus vaccine among children in Niger: Data from a phase 3, randomized, double-blind, placebo-controlled trial. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.05.023

Similarly, AEs were extremely prevalent, with over two-thirds of study participants experiencing at least one AE up to 28 days post Dose 3. Most AEs were mild, consistent with minor complaints common in the early infant period in this area, including cough, rhinorrhea and conjunctivitis, and were largely self-limited.

Our analysis has certain limitations, one of which is the complexity of accurate diagnosis in a low-resource environment where overlapping clinical features and concurrent pathologies can make definitive classification of safety endpoints challenging. For example, a commonly-encountered case is a child hospitalized with severe acute malnutrition, fever with a positive malaria rapid diagnostic test, and focal consolidation on pulmonary auscultation with productive cough and tachypnea. All three might be considered as the cause of hospitalization and hence as individual SAEs, but if the child died, judgment was made on the most likely primary cause of death; we acknowledge uncertainty in such cases.

5. Conclusion

RotaSIIL was previously shown to be effective against SRVGE. Data regarding safety after two years of follow-up are now available and confirm that the vaccine is safe when compared to placebo. All-cause mortality in children participating in the trial, both in the RotaSIIL and placebo groups, was much lower than the overall mortality rate in the region and no between-group difference was found. A single case of confirmed intussusception occurred nearly two years after vaccination with RotaSIIL, and was judged to be unrelated to the vaccine. SAEs and AEs reported in the trial population reflected the main pathologies affecting this overall population of rural Niger, and there were no differences between study groups. Immediate adverse events were rare and of mild severity. RotaSIIL is therefore safe and effective.

Acknowledgements

We thank the trial participants and their families; local, regional and national authorities; and the staff of the 5 health centers, the Madarounfa District Hospital and the Maradi Regional Hospital. We thank the members of the trial Data Safety and Monitoring Board: Jacqueline Deen (Chair), Milagritos Tapia, Nathanael Lapidus, Irène Adehossi, and Hamadou Ousseini Adamou. We also thank the members of the Intussusception Adjudication Committee.

Funding source

This work was supported by Médecins Sans Frontières – Operational Center Geneva and the Kavlionet Foundation, Norway.

Declarations of interest

None.

References

[1] Tate JE, Burton AH, Boschi-Pinto C, Steele AD, Duque J, Parashar UD. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis 2012;12:136–41. https://doi.org/10.1016/S1473-3099(11)70253-5.

[2] Page AL, Jusot V, Mamaty AA, Adamou L, Kaplon J, Pothier P, et al. Rotavirus surveillance in urban and rural areas of Niger, April 2010-March 2012. Emerg Infect Dis 2014;20:573–80. https://doi.org/10.3201/eid2004.131328.

[3] Karafillakis E, Hassounah S, Atchison C. Effectiveness and impact of rotavirus vaccines in Europe, 2006–2014. Vaccine 2015;33:2097–107. https://doi.org/10.1016/J.VACCINE.2015.03.016.

[4] de Deus N, Chilaúle JJ, Cassocera M, Bambo M, Langa JS, Sitoe E, et al. Early impact of rotavirus vaccination in children less than five years of age in Mozambique. Vaccine 2017. https://doi.org/10.1016/J.VACCINE.2017.10.060.

[5] Bonkoungou IJO, Aliabadi N, Leshem E, Kam M, Nezien D, Drabo MK, et al. Impact and effectiveness of pentavalent rotavirus vaccine in children. Vaccine 2017. https://doi.org/10.1016/J.VACCINE.2017.12.056.

[6] Nonvignon J, Atherly D, Pecenka C, Aikins M, Gazley L, Groman D, et al. Cost-effectiveness of rotavirus vaccination in Ghana: examining impacts from 2012 to 2031. Vaccine 2012;2017. https://doi.org/10.1016/J.VACCINE.2017.11.080.

[7] Patel MM, Haber P, Baggs J, Zuber P, Bines JE, Parashar UD. Intussusception and rotavirus vaccination: a review of the available evidence. Expert Rev Vaccines 2009;8:1555–64. https://doi.org/10.1586/erv.09.106.

[8] World Health Organization. Global Advisory committee on vaccine safety, December 2011. Wkly Epidemiol Rec 2012;87:53–60.

[9] Weekly epidemiological record Relevé épidémiologique hebdomadaire 2014;89:53–60.

[10] Naik SP, Zade JK, Sabale RN, Pisal SS, Menon R, Bankar SG, et al. Stability of heat stable, live attenuated Rotavirus vaccine (ROTASIIL®). Vaccine 2017;35:2962–9. https://doi.org/10.1016/J.VACCINE.2017.04.025.

[11] Isanaka S, Guindo O, Langendorf C, Matar Seck A, Plikaytis BD, Sayinzoga-Makombe N, et al. Efficacy of a low-cost, heat-stable oral rotavirus vaccine in niger. N Engl J Med 2017;376:1121–30. https://doi.org/10.1056/NEJMoa1609462.

[12] Niger | Data n.d. <https://data.worldbank.org/country/niger> [accessed December 14, 2017].

[13] GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1151–210. 10.1016/S0140-6736(17)32152-9.

[14] Council for International Organizations of Medical Sciences. Guidelines for preparing core clinical safety information on drug from CIOMS Working Group III; 1995.

[15] Bonhoeffer J, Kohl K, Chen R, Duclos P, Heijbel H, Heininger U, et al. The Brighton Collaboration: addressing the need for standardized case definitions of adverse events following immunization (AEFI). Vaccine 2002;21:298–302. https://doi.org/10.1016/S0264-410X(02)00449-8.

[16] Bonhoeffer J, Heininger U, Kohl K, Chen RT, Duclos P, Heijbel H, et al. Standardized case definitions of adverse events following immunization (AEFI). Vaccine 2004;22:547–50. https://doi.org/10.1016/S0264-410X(03)00511-5.

[17] Bines JE, Ivanoff B, Justice F, Mulholland K. Clinical case definition for the diagnosis of acute intussusception. J Pediatr Gastroenterol Nutr 2004;39:511–8.

[18] World Health Organization. Post-marketing surveillance of rotavirus vaccine safety. Geneva: n.d.

[19] World Health Organization. Manual for the training of interviewers on the use of the 2016 WHO VA instrument. Geneva;2017.

[20] CIOMS. Management of safety information from clinical trials. Geneva: Council for International Organizations of Medical Sciences; 2005.

[21] Amouzou A, Habi DESS-ASAD O, Bensaïd MPH K. Niger Countdown Case Study Working Group the. Reduction in child mortality in Niger: a Countdown to 2015 country case study. Lancet 2012;380:1169–78. 10.1016/S0140-6736(12)61376-2.

[22] Bines JE, Patel M, Parashar U. Assessment of postlicensure safety of rotavirus vaccines, with emphasis on intussusception. J Infect Dis 2009;200(Suppl):S282–90. https://doi.org/10.1086/605051.

[23] Kulkarni PS, Desai S, Tewari T, Kawade A, Goyal N, Garg BS, et al. A randomized Phase III clinical trial to assess the efficacy of a bovine-human reassortant pentavalent rotavirus vaccine in Indian infants. Vaccine 2017;35:6228–37. https://doi.org/10.1016/j.vaccine.2017.09.014.

[24] Madhi SA, Cunliffe NA, Steele D, Witte D, Kirsten M, Louw C, et al. Effect of human rotavirus vaccine on severe diarrhea in African infants. N Engl J Med 2010;362:289–98. https://doi.org/10.1056/NEJMoa0904797.

[25] Armah GE, Kapikian AZ, Vesikari T, Cunliffe N, Jacobson RM, Burlington DB, et al. Efficacy, immunogenicity, and safety of two doses of a tetravalent rotavirus vaccine RRV-TV in Ghana with the first dose administered during the neonatal period. J Infect Dis 2013;208:423–31. https://doi.org/10.1093/infdis/jit174.

Please cite this article in press as: Coldiron ME et al. Safety of a heat-stable rotavirus vaccine among children in Niger: Data from a phase 3, randomized, double-blind, placebo-controlled trial. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.05.023