GSK Vaccines Controlled Document

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Additional Analysis Request Form

Study alias & e-track number(s): EPI-IS-104435

Analysis ID / Description: ANALYSIS_E1_16 / Meta-analysis of IS

Detailed Title:	**Post-Authorization Safety Study (PASS) of** Post-Marketing Surveillance for Intussusception Following Rotarix Introduction into the Instituto Mexicano del Seguro Social (IMSS) in Mexico
Date of request	24-JAN-2014
Requestor with function	[redacted], Head VVHS
Target Date for distribution of results	31-JAN-2014
Request Leading to	☐ Statistical Analysis Report Amendment (give Reference) ☐ New Study Report (i.e New Statistical Analysis report) ☒ Publication ☐ Regulatory questions ☐ Safety Pooling ☒ Other, Specify: VSMB request

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Distribution list	[redacted] (Head Global Epidemiology), [redacted] (Lead Epidemiologist), [redacted] (Head VVHS), [redacted] (Therapeutic Area Head VCSP), and [redacted] (Director BDS)
Post Analysis meeting required	**No**
Approved by:	
Epidemiologist	[redacted]
Project Statistician	[redacted]
Lead Statistician	[redacted]

1. RATIONALE

A meta-analysis of the risk of intussusception after after vaccination with Rotarix or Rotateq was performed (EPI-IS-104435 SAR E01_15). At the time of the analysis, three studies were not published yet but the results were publically available. During the preparation of the manuscript, these three studies were published and were re-assessed for inclusion in the meta-analysis (see section 3.1). Based on this re-evaluation, the meta-analysis will be updated.

2. OBJECTIVES

As per Additional Analysis Request (AAR) EPI-IS-104435, ANALYSIS_E1_15:

- To provide a single estimate of the relative risk of IS after the 1st and the 2d dose of Rotarix
- To provide a single estimate of the relative risk of IS after the 1st and the 2d dose of Rotateq

3. DESCRIPTION OF ANALYSIS

3.1 Selection of studies

Three studies have been published since the meta-analysis completion:

- Carlin et al. 2013
- Weinstraub et al. 2014
- Yih at al. 2014

Carlin et al. 2013 and Yih et al. 2014 data have been already included in the meta-analysis and the review of the full publication confirmed their inclusion (see AAR ANALYSIS_E1_15 for description of the inclusion criteria). However in the discussion of the Carlin et al. paper, the authors mentioned "*For RV1, these findings are similar to those from a smaller Australian study, which included some of the same cases but used different methods,[Buttery et al. 2011]*".

The first author confirmed (personal communication by email) that the two publications include similar cases : '*The two studies were performed independently using different methods (both for case ascertainment – apart from some minor overlap with respect to the role of the "PAEDS" surveillance system in both studies – and analysis). Therefore we have no way of directly linking the identity of cases between the two studies. However, given the overlap in geography and in time between the ascertainment periods, many of the cases in the 2011 paper would also have been used in the more comprehensive later study. The latter study included many more cases of course, while some of the Buttery 2011 cases would have been omitted from it because of failure to reach the case verification criteri*a.'

For this reason, we decided to include the more recent and more comprehensive study (Carlin et al. 2014) in the meta-analysis and to remove Buttery et al. 2011

Weinstraub et al. 2014 is the full publication of the results presented at the ACIP 20 June 2013 meeting. At the time of analysis, only the slides presented at ACIP were available. The publication mentioned case ascertainement "*We reviewed medical records using the Brighton Collaboration definition for all suspected intussusception events that occurred within 7 days after any vaccination, excluding day 0 (the day of vaccination).*" However the discussion suggested inclusion of non-confirmed cases in the observed vs. expected analysis which is the analysis included in the meta-analysis "*A potential limitation of the study is the use of unconfirmed cases of intussusception in the sequential analyses.*

However, both the background rates used to calculate the expected number of cases and the observed cases were restricted to inpatient and emergency department settings". The first author confirmed (personal communication by email) the inclusion of non-confirmed cases.

Moreover this publication included a risk estimate for RV5 which is an update of a previous analysis (Shui et al. 2012). Shui et al. 2012 used the same approach as Wreinstaub et al.2014 and included non-confirmed case in the O/E analysis. However, they also presented results of a cohort comparison of he risk after RV5 vs. the risk after other vaccines using only confirmed cases (see table 1 of Shui et al. 2012).

In conclusion, Weinstraub et al. 2014 will not be included in the meta-analysis. Shui et al. 2012 will be included but using the cohort analysis instead of the O/E analysis.

In summary the following studies will be included in the main analysis:

Author & year	**Country**	**Results included in the meta-analysis** [¥]	**Risk periods**	**Vaccine**
Patel et al 2011	Mexico[$] Brazil[$]	SCCS	7 days	Rotarix
Velazquez et al. 2012	Mexico	SCCS	7 days	Rotarix
Shui et al. 2012	US	Cohort	7 days	Rotateq
Carlin et al. 2013	Australia	SCCS	7 days	Rotarix Rotateq
Haber et al. 2013	US	SCRI	3-6 days	Rotateq
Yih et al. 2014	US	SCRI	7 days	Rotarix Rotateq

[¥]: SCCS: self-control case-series ; O/E: oberserved versus Expect, SCRI: self-control risk interval
[$]: analysis per country

Because Weinstraub 2014 is one of the rare studies which provided estimate of the risk for both RV1 &nd RV5using the same method and setting, a sensitivity analysis including this study will be done.

Of Note: During the preparation of the manuscript, we did also a systematic literature review to identify other possible studies. This literature search was done in Medline, Embase, and Central databases, using the following key-words (Intussusception OR Intestinal Obstruction) AND (Rotavirus) AND (Vaccine OR Rotarix OR Rotateq). Titles and abstracts of 914 retrieved references were independently assessed against the

inclusion criteria for this meta-analysis by two reviewers (a statistician and an epidemiologist). Forty references were selected for full review (21 by both reviewers and 19 by one reviewer only). This systematic literature review did not identify any additional publications which meet the meta-analysis inclusion criteria

3.2 Analyses

Two analyses will be done

1. Main analysis including the 6 above-listed studies;
2. A sensitivity analysis including in addition, Weinstrub et al. 2014.

3.3 Statistical Methods

See AAR – ANALYSIS_E1_15

Undefined risk estimates (i.a. risk estimate ≅ 0 or ∞) will not be included in the statistical calculations

4 REFERENCES

Buttery J.P. et al. 2011. Intussusception following rotavirus vaccine administration: Post-marketing surveillance in the National Immunization Program in Australia, Vaccine; 29 (16); 3061-3066.

Carlin JB, Macartney KK, Lee KJ, Quinn HE, Buttery J, Lopert R, et al. 2013. Intussusception risk and disease prevention associated with rotavirus vaccines in Australia's national immunization program. Clin Infect Dis;57:1427-34..

Haber P. et al. 2013. Intussusception After Rotavirus Vaccines Reported to US VAERS, 2006-2012. Pediatrics 131; 1042–1049.

Patel M et al 2011. Intussusception Risk and Health Benefits of Rotavirus Vaccination in Mexico and Brazil. N Engl J Med 364; 2283-2292.

Shui I.M. et al. 2012. Risk of intussusception following administration of a pentavalent rotavirus vaccine in US infants. JAMA 307; 598-604.

Velázquez et al. (2012) Postmarketing Surveillance of Intussusception Following Mass Introduction of the Attenuated Human Rotavirus Vaccine in Mexico. PIDJ 31; 736-744.

Weintraub E. et al. 2014. Risk of Intussusception after monovalent rotavirus vaccination. NEJM DOI: 10.1056/NEJMoa1311738

Yih W.K. et al. 2014 Intussusception Risk after Rotavirus Vaccination in U.S. Infants. NEJM DOI: 10.1056/NEJMoa1303164.