Comments received during public consultation and ECDC responses

Expert opinion on rotavirus vaccination in infancy

Comments provided by	Section of document	Page and line number	Comment and rationale	Proposed change	Assessment by ECDC and, where appropriate, change implemented
Ministry of Health, Department for Vaccines, Austria *M. Paulke-Korinek*	Rotavirus immunisation programmes in EU/EEA countries	P17, line 801-804	Clarification of the Austrian RV mass vaccination programme and reporting of RV infections	Rotavirus vaccination was recommended in Austria even before vaccines were available. RV1 and RV5 both have been available since 2006. In August 2007, rotavirus vaccines were included in the free national immunisation programme for all children at the respective age. Since then, either of the vaccine has been used in the national immunisation programme, depending on the annual contracts: RV5 was used in 2007 and 2009; RV1 was used in 2008 and 2010-2012. Sind 2013, RV5 has been used. Reporting of RV infections only is mandatory in Austria if associated to food contamination. Optional, genotyping of RV strains from children with breakthrough infections is available.	Expert Opinion updated in line with proposal
	Table 4	P18, line 842	Correction of data	Year of introduction in NIP in 2007, vaccine coverage reported: approx. 77% (based on distributed number of doses)	Expert Opinion updated in line with proposal
Public Health Institute, Sweden *Ann Lindstrand*	P2 executive summary	303	Not clear if these cited studies do include societal costs or not.	Clarify?	Please see chapter on cost-effectiveness
	P4 Background	364	Update reference on number of deaths due to rotavirus infection	Add Global Burden of Disease 2015?	The Child Health Epidemiology Reference Group (CHERG)/2015 GBD has estimated the major causes of child deaths since 2001 - pathogen-specific diarrhoea mortality among children under five years of age. They estimated the global burden of diarrhoea mortality by pathogen for children under five years for 2011, when a number of countries had introduced rotavirus vaccination. The Global Burden of Disease 2015 data is based on a larger number of countries that have introduced vaccination. The Expert Opinion has therefore not been updated since ECDC wished to provide a mortality estimate for the pre-vaccine era.

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	P5 figure 1	392	Very busy x-axis with many decimals.	Delete decimals after 10 years?	Expert Opinion updated in line with proposal.
	P6	432-433	Please give a reference for the statement that neonates are protected through maternal antibodies.		Expert opinion updated in line with proposal, two new references added.
	P6 nosocomial infection	419-420	Add any estimation of risk of nosocomial infection?		Estimates already available in Results section under subtitle 'Nosocomial infections'.
	P7	466	Add any other reference than personal communication?		Expert Opinion updated in line with proposal, a new reference has been added.
	P7	476-477	It is stated that no other therapy than fluid replacement is required. Racecadotril (Hidrasec) is available in addition to fluid replacement as symptomatic treatment		Expert Opinion updated in line with proposal.
	P7	500	It is said that after primary infection with group A that the immune response is homotypic. This is in contradiction to the immune response induced by the vaccines that provides broad cross-protection/-immunity against other sero-/genotypes. It is also stated in Figure 2 p14 that there is cross-immunity. Please, explain the distinction of cross-immunity between immune responses to the wild virus vs vaccine viruses.		Expert Opinion updated in line with proposal, one new reference has been added.
	P8	532	Instead of specifying the ages that were less prone to develop IS it should be specified at what ages the increased risk of IS was observed.		Expert Opinion updated in line with proposal, adding a sentence with this information. A new reference has been added.
	P9	Table 1	p9 Table 1, Excipients: in the SPC for RV1 it is stated that it contains 1073 mg sackaros (English: sucrose)	Also make line more prominent between rows – difficult to see the row lines.	Expert Opinion updated in line with proposal.
	P15		Rotavirus samples from Sweden are not representative of all age groups because age groups <5 years are selected for genotyping. The samples sent to the reference lab are voluntarily sent samples and more samples are taken and sent in from younger age groups.		No country-specific data protocol presented but EuroRotanet website provided for reference.
	P10	606	Infants exposed to biological therapy in utero: I do not know that the EMA has declared such a warning statement in the SPC as the congress of gastroenterology. Please provide a reference with a publication or other evidence to support the recommendation to avoid rotavirus vaccine in these infants.		Expert Opinion already contains a reference to the decision by the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization.
	P19-p20	Table 4	The table should use a harmonised terminology for the time point of doses either expressed as weeks or months.		Unfortunately this is not possible since the countries have varying recommendations and those in the table follow the country recommendations.

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	P20	Table 4	Correction: For Sweden RV1 are fully reimbursed (since beginning of year) in all counties.		Expert Opinion updated in line with proposal.
	P31	1259	Please modify statement about protection against mild-to-moderate RV disease which was clearly shown in the RCT trials.		Expert Opinion updated in line with proposal. Meta-analysis results on efficacy against RVGE any severity from conducted RCTs is presented on page 30.
	P31	1282	The statement about catch-up campaigns difficult to interpret . Could be deleted.		It is common when new vaccines are introduced that catch-up campaigns are conducted but this is not possible in the case of rotavirus vaccines and ECDC finds it important to mention that this is not possible.
	P31		Herd immunity. Reference to herd immunity in adults should be included: Indirect Protection of Adults From Rotavirus by Pediatric Rotavirus Vaccination. Evan J. Anderson, Deanna B. Shippee,1 Melissa H. Weinrobe,Melissa D. Davila, Ben Z. Katz, Susheel Reddy, Mary Gene Karen P. Cuyugan, Samuel Y. Lee, Yael M. Simons,1Ram Yogev, and Gary A. Noskin. Clin Infect Dis 2013		Expert Opinion updated in line with proposal.
	P36	1414	The number of doses sold of the two vaccines should be mentioned to be able to interpret the number of IS cases given for the Us and EU (e.g. much higher for RV5 than for RV1 in the US than in the EU).		The number of doses sold in the time period are specified on page 24 in the section on vaccine safety. Although the number of doses sold is known it is difficult to interpret the data with no knowledge of whether the doses sold were administered at all or as dose no. 1, 2 or 3, depending upon which vaccine was used.
	P41	1567	In Stockholm rotavirus vaccine is offered at 8 weeks. In Jönköping at 6 weeks		Expert Opinion updated in line with proposal.
	P44	1733	True that Sweden has made a cost-effectiveness analysis – however RV vaccine is not introduced into the programme. The two regions Stockholm and Jönköping introduced it regionally without any cost-effectiveness study.		Expert Opinion updated in line with proposal.
	P47	1754	A study on parental attitudes towards RV vaccination was submitted to Vaccine from Stockholm, Sweden about 2 months ago. We will send the reference to Dr Johansen as soon as is it is accepted.		Thank you, will include if arrives before publication of this Expert Opinion.
	P49	1840-1844	A question: Is this a relevant age group division? Actually the herd immunity does give a more broad effect on disease incidence early on. I mean that monitoring should be done in all age groups <1 year, <2 years and <5 years – as most other published studies or?		Expert Opinion updated in line with proposal.

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RIVM, Netherlands *Hester de Melker*	Page 19	Table 4	For the Netherlands it is stated that a negative decision was made. This is incorrect. A decision has not yet been made.	Change to 'No decision by national health authorities (yet)'. At present the Health Council is preparing advice on rotavirus vaccination in the Netherlands.	Expert Opinion updated in line with proposal.
	Summary	p. 3, line 307	Veldwijk J et al. Vaccine 2014 reported a DCE on rotavirus vaccination. It was mentioned that there are no studies on attitude. This is a study were attitude is included and impact on willingness to vaccinate is studied	Include results from this study; also in the main text.	Expert Opinion updated in line with proposal.
	Results	p. 24	Ref 264 (P. Bruijning) is applicable here. Deaths occur among risk group.	Add information of this paper showing in the study period 7 deaths in NL that all had congenital pathology and two had a history of LBW. We think more attention should be given to the possibility of vaccinating risk groups.	Expert Opinion updated in line with proposal.
	Safety	Table 6, p. 34	NL has estimated background incidence of intussusception	Data are presented in RIVM report 'The National Immunisation Programme in the Netherlands. Surveillance and developments in 2015-2016.' p.70	Expert Opinion updated in line with proposal.
	Herd Immunity	p. 32, Lines 1293-1296	Info is missing	Please add the underlined text: These reductions are additional effects, on top the direct effect. If that is not added, it seems as if a higher coverage is less effective.	Expert Opinion updated in line with proposal.
	Herd Immunity	P 32	Lines 1306-1308: it says 'possibly older age groups', but we would argue that herd immunity is definitely observed in older age groups (if vaccine coverage is high), e.g. in: Mast TC, Wang FT, Su S, Seeger JD. Evidence of herd immunity and sustained impact of rotavirus vaccination on the reduction of rotavirus-related medical encounters among infants from 2006 through 2011 in the United States. Pediatr Infect Dis J. 2015;34(6):615-20. Gastanaduy PA, Curns AT, Parashar UD, Lopman BA. Gastroenteritis hospitalisations in older children and adults in the United States before and after implementation of infant rotavirus vaccination. JAMA. 2013;310(8):851-3. Lopman BA, Curns AT, Yen C, Parashar UD. Infant rotavirus vaccination may provide indirect protection to older children and adults in the United States. J Infect Dis. 2011;204(7):980-6. Sabbe M, Berger N, Blommaert A, Ogunjimi B, Grammens T, Callens M, et al. Sustained low		Expert Opinion updated in line with proposal.

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			rotavirus activity and hospitalisation rates in the post-vaccination era in Belgium, 2007 to 2014. Euro Surveill. 2016;21(27).		
	Overview rotavirus	p. 14-16	Page 14 - The text refers to VP4 in the picture as being red, while it is orange. - Page 14 - It seems that the end of the sentence of the last bullet point is missing. - Page 16 - The X-axis of figure 4 is difficult to read due to the low resolution. - Page 16, sentence 763 to 765 - In order to improve readability, we recommend rephrasing the sentence to *[...] in most seasons in the majority of participating EU/EEA countries [...]*	Please adapt.	Expert Opinion updated in line with proposal.
	Methods	p. 21	The term 'burden' is used for hospitalisation. We think this term not preferred for this, i.e. Dalys is the measure for burden.	Please rephrase - i.e. severe rotavirus was defined as rotavirus disease leading to hospitalization (also further on in the document.)	Literature reviews were conducted using search terms addressing burden of disease and outbreaks of rotavirus in Europe (see Annex 5), while in the cost-effectiveness chapter the term QALY is used in most studies presented (see Ref 49).
	Monitoring of circulating rotavirus	p. 16, Fig4	In the text is it is relevant to add the variation in seasonality, in particular that was observed recently in the Netherlands with both in 2014 and 2016 low endemic years, while no vaccination is implied in the Netherlands.	Please add information regarding the publication by Hahné S et al. Eurosurveillance 2014. Exceptionally low rotavirus incidence. See for update on 2016 annual report RIVM 'The National Immunisation in the Netherlands. Surveillance and developments in 2015-2016. Chapter on rotavirus. It would be good that there is awareness for this (largely unexplained) phenomenon when considering rotavirus vaccination.	Expert Opinion updated in line with proposal.
Children´s hospital, University of Leipzig, Germany *Volker Schuster*	RV vaccination is contraindicated in infants with inherited immunodeficiency	Line 572 Line 1328	'Live attenuated rotavirus vaccines should always be administered <u>with caution</u> in individuals with congenital or acquired immunodeficiency' 'Subsequently, EMA and other global regulatory agencies approved a labelling change in the SPC for the two (RV1 1328 and RV5) vaccines <u>contraindicating</u> administration to individuals with a history of SCID.'		Expert Opinion uses SPC wording.
	Contraindications	557	A prior intussusception is a <u>definite</u> contraindication against RV vaccination		Expert Opinion uses SPC wording.
	Breastfeeding and RV vaccination		'Vaccine efficacy was equally high in breast-fed and exclusively formula-fed children	'Breastfeeding should be continued adlib around the time of rotavirus vaccination and withholding breastfeeding at that time is unlikely	Expert Opinion updated in line with proposal.

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			in the first season. Breast-feeding seemed to reduce slightly the efficacy in the second season.' *Vesikari T, et al. Efficacy and immunogenicity of live-attenuated human rotavirus vaccine in breast-fed and formula-fed European infants. Pediatr Infect Dis J. 2012 May;31(5):509-13*	to improve the vaccine immunogenicity.'	
		538	Additionally: MenB;		Expert Opinion updated in line with proposal.
	Clinical management	Line 473	Probiotics (Lactobacillus GG) may reduce length of RV gastroenteritis in infants by approx. one day		Expert Opinion updated in line with proposal.
Head of Pediatrics, Hospital Clínico Universitario de Santiago, Spain *Federico Martinon-Torres*	Conclusions and practical recommendation .		I don't understand very well the scope of the revision according to the title vs document contents. There is no positioning, no practical recommendation. The conclusions are mainly focused on intussusception and gaps, despite all the findings in the literature that support general recommendation of the vaccination considering the burden in EU and the known effectiveness in EU . It is expected that ECDC has a more useful approach to inform public health authorities. On the top of this, it is already outdated as several papers are missing from 2015 and 2016	ECDC should state a position regarding rotavirus vaccination considering the amount of information that exists. This artificially neutral or nihilistic approach does not help to support RV vaccination in the EUD, while it is by recommended by most of scientific societies in EU and even included in the NIP of many EU countries. If it is only a review-update of the evidence, it should be updated and include more recent references.	Recommendation of vaccines is the responsibility and mandate of each EU Member State. Hence, ECDC can only collect and summarise scientific evidence. Following recommendations from the Scientific Panel, ECDC's Advisory Forum and public consultations, references from 2015, 2016 and 2017 have been included where relevant.
	Design		To pretend to inform public health and neglect all the published papers on unexpected benefits through an average 40% reduction in hospitalisations due to seizures related to RV vaccination seems illogical. You should review this literature, include in the text and comment. This is an important support to RV inclusion into the NIP of European countries	Check these references below for example and include other newly discovered effects of RV vaccines beyond acute gastroenteritis. American CDC, Australian and Spanish data on this regard are congruent and encouraging. This is one of the potential added values of RV inclusion in the NIP. 1. Febrile Seizures in the Era of Rotavirus Vaccine. Sheridan SL, Ware RS, Grimwood K, Lambert SB. J Pediatric Infect Dis Soc. 2016 Jun;5(2):206-9. doi: 10.1093/jpids/piu097. Epub 2014 Oct 13. PMID: 27199471 Similar articles Select item 25923425 2.	Topic already addressed on p. 32. Additional references added as per proposal.

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				Impact of Rotavirus Vaccination on Childhood Hospitalization for Seizures. Pardo-Seco J, Cebey-López M, Martinón-Torres N, Salas A, Gómez-Rial J, Rodriguez-Tenreiro C, Martinón-Sánchez JM, Martinón-Torres F. Pediatr Infect Dis J. 2015 Jul;34(7):769-73. doi: 10.1097/INF.0000000000000723. PMID: 25923425 Similar articles Select item 25117417 3. Impact of rotavirus vaccine introduction on rotavirus-associated seizures and a related possible mechanism. Yeom JS, Kim YS, Kim RB, Park JS, Seo JH, Park E, Lim JY, Park CH, Woo HO, Youn HS. J Child Neurol. 2015 May;30(6):729-34. doi: 10.1177/0883073814542944. Epub 2014 Aug 12. PMID: 25117417 Similar articles Select item 24265355 4. Protective association between rotavirus vaccination and childhood seizures in the year following vaccination in US children. Payne DC, Baggs J, Zerr DM, Klein NP, Yih K, Glanz J, Curns AT, Weintraub E, Parashar UD. Clin Infect Dis. 2014 Jan;58(2):173-7. doi: 10.1093/cid/cit671. Epub 2013 Nov 20. PMID: 24265355 Free PMC Article Similar articles Select item 24265354 5. Editorial commentary: unexpected benefits of immunisation: rotavirus vaccines reduce childhood seizures. Weinberg GA. Clin Infect Dis. 2014 Jan;58(2):178-80. doi: 10.1093/cid/cit681. Epub 2013 Nov 20. No abstract available.	

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				PMID: 24265354 Free Article Similar articles	
Servicio de Microbiología. Hospital University Donostia, San Sebastián, Spain *Gustavo Cilla*	1. Background	Page 16, lines 759-761	I think this sentence has a discrepancy. It explains that six genotypes are responsible for > 90% of all human rotavirus disease, but only five have been specified at the end of the sentence. Perhaps genotype G12P[8] is lacking.	Add genotype G12P[8] to the five genotypes specified at the end of sentence in lines 759-761 or consider rewrite the paragraph	Expert Opinion updated in line with proposal. On page 17 results are presented from the Eurorotanet surveillance network on the six genotypes.
	1. Background	Page 17, line 796 and Table 4 (pages 19 and 20)	A comment about countries that have taken a negative decision regarding the introduction of rotavirus vaccination into routine paediatric immunisation programmes. Denmark and Netherlands appear in a different category in line 796 and in Table 4.	Please check Denmark and Netherlands in Page 17-line 796, and Table 4.	Expert Opinion updated in line with proposal.
	3. Results	Page 24, line 1037	In my opinion reference 119 should be deleted from Table 5 (see the following point), and then reconsider the end of the sentence in line 1037 in relation to Spain.	See in the box on the left	Expert Opinion updated in line with proposal.
	3. Results	Page 26, reference 119 (Cilla et al)	The focus of this study was not on incidence/burden of disease, so I think this reference should be deleted of table 5 (the study described the epidemiological and virological characteristics of the first rotavirus epidemic due to the G12P[8] genotype of rotavirus in Europe). In addition, the figures written in relation to this reference in Table 5 are incorrect. This study was carried out between 2009 and 2011, not in 2002-2005 as it has been referred in Table 5. It obtained data of incidence of hospitalisation in children less than 2 years-old and not in children less than 5 years-old as table 5 assures. Median duration of hospitalisation (days) was 4.3 and not 6.3 as it has been referred in Table 5.	Table 5: Delete the line corresponding to ref 119	Expert Opinion updated in line with proposal.
	3. Results	Page 26, Table 5	Study of Koch et al (ref 105). I think that the number of children hospitalised <5 years per 100 000/year should be 510 instead of 1000.	Please check these numbers.	Expert Opinion updated in line with proposal.
	3. Results	Page 26, Table 5	Study of Cilla et al (ref 153). The results of this study, spanning 1996-2008, were divided into four triennia. In this document, table 5, column 5 (number of children hospitalised <5 years per 100000/year), the figure '136' corresponds to the third triennium of the referred study-153	Table 5, line for reference 153, column 5: Instead of number '136', write the number '215'.	Expert Opinion updated in line with proposal.

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			(2002-2005). We think that the better solution to refer properly the results of this long study would be to change this figure ('136') by the mean annual incidence of hospitalisation obtained during the complete period of study (1996-2008) which was 215/100,000. This figure can be easily inferred from the table 1 of the study ref 153.		
Institute of Public Health, Catholic University Rome, Italy *Flavia Kheiraoui*	Cost effectiveness studies performed in EU. Table 10	P 42 L 1627 P 45 L743	Publication of Capri S in 2014 http://www.ijph.it/pdf/2014-v3-n7.pdf	Evaluate the Cost-Effective Analysis of Capri S. in the HTA Report on Rotavirus vaccination in Italy	Unfortunately this report is in Italian and cannot therefore be included.
	Table 11	P 46 L 1747	Publication of Capri S in 2014 http://www.ijph.it/pdf/2014-v3-n7.pdf	Evaluate the Cost-Effective Analysis of Capri S. in the HTA Report on Rotavirus vaccination in Italy	Unfortunately this report is in Italian and cannot therefore be included.
Sanofi Pasteur MSD *Susanne Hartwig*	Executive summary	1, 206-208	'…main objective of RV vaccination… protection against moderate to severe disease' is not accurate for RotaTeq. In the large scale Phase III pivotal efficacy and safety study the endpoint was against any severity of disease; in addition, RotaTeq has been shown to protect against physician office visits and mild disease. This is an important clarification, especially for Europe, as there are a small number of deaths due to rotavirus. These data are available in Vesikari et al. NEJM 2006 article.	Remove sentence or re-phase to say that the main objective of vaccination is to protect against any severity of disease, including office visits, hospitalisations and deaths.	The main objectives for public-health-funded programmes are commonly to protect against hospitalisation and deaths due to infectious disease. The sentence has been adapted in accordance with the comment provided. Furthermore, results from a meta-analysis assessing RVGE of any severity in RCTs are presented on page 30 in the Efficacy chapter.
	Executive Summary	1, 214	The AIM should include an explanation on why it has taken 10 years to come out with an opinion of rotavirus vaccination in Europe	Include information on why there has been a 10 year lag	This Expert Opinion is a review of evidence available on burden of severe disease leading to hospitalisation, rotavirus vaccine efficacy, herd-protection, effectiveness, safety, cost-effectiveness, and attitudes to rotavirus vaccination. Recommendations for inclusion of any vaccine lie with each EU/EEA Member State. The task of ECDC is to compile and summarise scientific evidence to support Member State decisions. ECDC has not had the capacity to develop expert opinions for all childhood vaccines, or other vaccines available for introduction into national immunisation programmes. Rotavirus vaccination has been prioritised to

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					support the decision-making process in EU/EEA Member States.
	Executive Summary	1, 229	Why just against severe disease?	Based on face that rotavirus vaccines have shown protection against any severity of disease, it makes more sense for Europe to describe the burden of all severity of disease.	See comment above.
	Executive Summary	1, 253	Clarify if these data are for both vaccines.		Expert Opinion updated in line with proposal
	Executive Summary	2, 262	More accurate terminology is 'herd protection' of 'indirect effects'. Technically, herd immunity refers to immunity gathered from contact	General: change 'herd immunity' to 'herd protection'	Herd immunity and herd protection were used inconsistently. Herd immunity re-placed by herd protection throughout the document.
	Executive Summary	2, 265	Additional data exists for RotaTeq showing statistically significant protection through 24 years of life with a trend for protection through 65 years (Lopman et al. JID 2011).	Current section on herd protection is very limited; suggest including more data on this topic and explaining difference of data obtained on RV5 and RV1 separately.	Expert Opinion updated in line with proposal
	Executive Summary	2, 276	'indicate that rotavirus vaccines carry an increased risk' this is not true for all studies, for example, several evaluations conducted by the CDC using VSD data have not found an association of IS with RV5.	Change the sentence to include the word 'may'	The wording used in this document follows the European SPCs and cannot therefore be changed.
	Executive Summary	2, 280	'Possibly due to small sample size' is not the conclusion for all these papers. The studies that saw an increased risk were SCCS analyses, where the ones that didn't where a different type of analysis, e.g. historical or concurrent controls.	Remove 'possibly due to small sample size'	The statement '*possibly due to*' is vague but sample size could be the reason why no increased risk was observed in the earlier studies, although perhaps not the only reason.
	Executive Summary	2, 288	Risk minimisation strategies.	Need to outline what these strategies are.	Expert Opinion updated in line with proposal.
	Executive Summary	2, 292-294	Transmit vaccine virus to severe immunocompromised individuals is not a contraindication to vaccination based on the vaccines' labels.	Clarify that this is a precaution and not a contraindication to vaccination.	SCID is a contra-indication in the two European SPCs. The second sentence discusses avoiding contact between newly vaccinated infants and severely immunocompromised individuals and is therefore not a contraindication.
	Executive Summary, Cost-effectiveness	Page 2 Line 298-299	The sentence 'the inclusion of societal costs significantly affects the estimating cost-saving threshold' is technically incorrect. In economic evaluation, threshold is defined to assess cost-effectiveness – not cost-savings. A threshold analysis provides the maximum price for which the assessed intervention (vaccination programme) is estimated to be cost-effective (or cost-saving), for a given value of the willingness	*'The inclusion of societal costs and/or positive indirect benefits of the vaccines such as herd immunity, significantly affect the level of price at which the vaccines are cost-effective. Majority of studies, particularly those that do not take into account societal costs and/or herd immunity conclude (…)'*	Expert Opinion updated in line with proposal.

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			to pay for a QALY or the health outcome of interest. Also, The level of price at which the vaccines are cost-effective is sensitive not only to societal costs but also to whether authors accounted for positive indirect benefits from the vaccines, such as herd immunity. This parameter has been considered in more recent economic evaluation on RV vaccination (post 2011). The range of price from the comparative analysis is only provided in the executive summary and not in the main core of the document (cf section 'Cost-effectiveness studies in EU/EEA p 43)		
	Executive Summary, Cost-effectiveness	Page 2 Line 301 - 303	▸ The term 'meta-analysis' is incorrectly used. A meta-analysis is a statistical analysis that combines the results of multiple scientific studies. The study referred here for the 5 EU Member states is a comparative analysis performed for these 5 countries => provide scenarios for each country. ▸ The price provided is per dose and not per course	*A comparative analysis of rotavirus vaccination in five European Union countries (Belgium, England and Wales, Finland, France and the Netherlands) using a single model, estimated a threshold price per dose for rotavirus vaccination to be cost-effective ranging between EUR 28-52.*	Expert Opinion updated in line with proposal.
	Executive Summary	P2 Line 304	Missing information related to current implementation of RV immunisation programmes. We suggest integrating a section entitled 'Rotavirus immunisation programmes in EU/EEA' into the executive summary, between the sections 'Cost-effectiveness' and 'Attitude to rotavirus vaccination among parents and healthcare workers'	*'Rotavirus immunisation programmes in EU/EEA'* *As of March 2016, twelve EU/EEA Member States were recommending vaccination against rotavirus-induced gastroenteritis in their national paediatric immunisation programmes and had initiated or were about to initiate the programme.'*	Expert Opinion updated in line with proposal.
	Conclusion and possible implications for public health practice and research	Page 3, line 320	Up to six additional IS cases have been observed **within a risk window of 7 days after vaccination**.	A risk of up to six additional intussusception cases per 100 000 infants **within 7 days of vaccination** has been identified.	Expert Opinion updated in line with proposal.
	Executive Summary, Conclusion	P3 Line323	Development and use of Specific communication tools related to symptoms recognition and treatment of intussusception towards healthcare professionals and parents by the ECDC should be mentioned here and also later in the document (p41) in the 'risk mitigation strategies'	*'Training material for vaccinators/healthcare personnel is needed to educate parents on IS risk, symptom recognitions and emergency measures to run.'* *'Training material for vaccinators/healthcare personnel is needed to ensure adequate and*	Expert Opinion updated in line with proposal.

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				prompt treatment, should an IS case be encountered.'	
	Conclusion and possible implications for public health practice and research	Page 3, line 333	When investigating breakthrough cases in vaccinated individuals, the detection of pathogens others than rotavirus that may be responsible for GE cases should be performed (i.e. norovirus, adenovirus, sapovirus, …) is important	Investigation and reporting of hospitalised breakthrough rotavirus diseases in vaccinated individuals (including genotyping and detection of other GE pathogens, i.e. norovirus, adenovirus, sapovirus, …)	Expert Opinion updated in line with proposal.
	Executive Summary, Conclusion	P3 Line349	The executive summary ends on the possible EU–level joint procurement option. However in the case of non-pandemic/non-outbreaks, vaccinations such as the rotavirus vaccines in Europe where only two suppliers exist, a joint public procurement (likely to be based on price driven criteria), may result in unsustainable vaccine supply and market distortion. Structured negotiations must be performed not solely on price but also on quality and innovation aspects of the vaccines to ensure sustainability of the market supply.	Finally, sharing available health outcomes (…) *EU/EEA countries interested and new procurement options (including joint procurement) allowing structured negotiations based not solely on price but also on quality and innovation aspects of the vaccines should be explored.*	The option of joint procurement has been deleted since there is no experience with this new mechanism or its implications.
	Background	4, 364	New global disease burden data available.	Update ~527 000 with new data by Tate et al. CID 2016.	Expert Opinion updated in line with proposal.
	Rotavirus disease	5, 393	Figure 1	The last Eurorotanet report has data until 2015. Please update this figure according to this last version of the report.	Expert Opinion updated in line with proposal.
	Infectious dose and virus shedding	Page 7, line 466	Extended virus shedding after an episode of GE was described by Richardson et al, Lancet, 1998 'Extended excretion of RV after severe diarrhea in young children'	Add the reference: Richardson et al, Lancet, 1998 'Extended excretion of RV after severe diarrhea in young children'	Expert Opinion updated in line with proposal.
	EU dose recommendations	8, 524	The other reason why the vaccines were administered early in the clinical trials was to ensure that all doses would be provided before rotavirus disease peaked in seriousness: ~6 months of age.	Add additional reason why series should be completed at young age.	Expert Opinion updated in line with proposal.
	Vaccination of infants with other underlying medical disorder	10, 592-597	This section is missing key information from this article, such as RV5 being able to be tolerated, able to generate a robust immune response and that the majority of the AEs were considered to be not vaccine-related, but rather due to the underlying medical conditions.	Add the following information: In this population, infants were able to tolerate oral RV5 and mount an immune response with a statistically significant three-fold rise in anti-rotavirus serum IgA GMT from baseline, a response similar to their age-matched controls and the vaccine was well-tolerated with few vaccine-related AEs.	Proposal too detailed to be included. Interested clinicians are expected to read the reference.

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	Interchangeability	10, 608-628	This section needs to be updated with the new literature available.	Add information from the following recently published literature: Mohammed et al. Vaccine 2015 Payne et al. JAMA Peds 2016 Libster et al. Pediatrics 2016	Expert Opinion updated in line with proposal. See page 10.
	Vaccine induced immunity	11, 632	For RV5, serum anti-rotavirus IgA is only one of the makers that were used to assess immunogenicity, along with serum neutralisation assays to each of the reassortants in the vaccine	Clarify that additional assays than just IgA have been used for RV5 trials to assess immunity. Based a poster from ESPID 2014 and a presentation at International Rotavirus Symposium 2015, on Sabin website (both by Goveia), actually RV5 correlates best with Postdose 3 G1 SNA GMT at the individual and population level evaluations.	Expert Opinion updated in line with proposal.
	Storage	12, 648	Both vaccines are stored at 2-8C	Add that RV5 also is stored at 2-8C	Expert Opinion updated in line with proposal.
	Storage	12, 648	Data available showing safety, tolerability and immunogenicity of RV5 manufactured by a modified process (stability at 37)		Expert Opinion updated in line with proposal.
	Contamination of RV1 and RV5 vaccines with porcine circovirus	Page 12, line 651	….PCV genome fragments was identified in both rotavirus vaccines. PCV genome fragments were identified in RotaTeq whereas PCV whole virus was identified in Rotarix.	This should be rectified: DNA from PCV1 and PCV2 were identified in RotaTeq. PCV1 whole virus was identified in Rotarix.	Expert Opinion updated in line with proposal.
	Contamination of RV1 and RV5 with PCV	12, 657	No regulatory definition has been provided for what PCV-free actually means and thus guidelines have been provided. Currently RV5 is already using a different trypsin source and enhanced screening technics to ensure vaccine does not have PCV.	Remove: develop PCV-free vaccines which will become available shortly. This sentence is not accurate. Please refer to article by Ranucci et al. PDA J Pharm Sci and Tech 2011, for more information about RV5 and PCV.	Expert Opinion updated in line with proposal.
	Rotavirus vaccines authorised in non-EU/EEA countries	Page 12 Lines 661-662	An additional rotavirus vaccine seems to be licensed for use in Vietnam by POLYVAC. Ref: Burnett, Yen, Tate & Parashar – Table 3.	Three additional rotavirus vaccines are authorised in China, India and Vietnam and several vaccine candidates are at various developmental stages.	Expert Opinion updated in line with proposal.
	RV vaccines in non-EU/EEA countries	12, 661	There is a vaccine called Rotavin licensed in Vietnam.	Add information about Rotavin	Expert Opinion updated in line with proposal.
	Overview of human rotaviruses	14, 724	The end of the last sentence in the yellow box is missing.	Please ended the sentence.	Expert Opinion updated in line with proposal.
	Rotavirus strain diversity	Page 15, line 751	The EuroRotaNet 7th year report is cited here. This information should be updated with a link to the EuroRotaNet 9th year report currently available on the EuroRotaNet website	The information extracted from the 7th year report should be updated by information from the 9th year report http://www.eurorotanet.net/	Expert Opinion updated with the latest information available (to 2016) in line with proposal.

Comments provided by	Section of document	Page and line number	Comment and rationale	Proposed change	Assessment by ECDC and, where appropriate, change implemented
	RV strain diversity	16, 766	Additional effectiveness data against G12 is now in the EU label for RV5	Add information about protection against G12, based on EU label.	Expert Opinion updated in line with proposal.
	RV immunisation programme in EU/EEA countries	17, 789	Recommend to update this section at time of publication as currently as of 'March 2016'.	Update section at time of publication	Updated at the time of publication, May 2017
	Rotavirus vaccination programmes in EU/EEA countries	Page 17 Line 802	Austria: Rotavirus vaccination was recommended in 2006 but vaccination was initiated in 2007. Ref: Weil-Olivier,Millier, Toumi & Trichard - Figure 3.	Austria: Rotavirus vaccination was initiated in 2007.	Expert Opinion updated in line with proposal.
	Rotavirus vaccination programmes in EU/EEA countries	Page 17 Line 806-808	BELGIUM: Rotavirus vaccination is not included in the vaccination programmes at regional level, however it is nationally recommended and partially reimbursed since 2006. Ref: Eurosurveillance - Braeckman, Theeten, Lernout, Hens, Roelants, Hoppenbrouwers , Van Damme . Rotavirus vaccination coverage and adherence to recommended age among infants in Flanders (Belgium) in 2012.	BELGIUM: Rotavirus vaccination was recommended and partially reimbursed at national level in 2006. Unlike other infant vaccines in the national immunisation schedule, rotavirus vaccination is not offered fully free of charge by the government, nor included in the vaccination programmes at regional level. If parents wish to have their child vaccinated against rotavirus, they need a prescription for the vaccine via a well-baby clinic, general practitioner or paediatrician. Rotavirus vaccination is systematically offered during preventive consultations organised by the government agency 'well-baby clinics' at regional level.	Expert Opinion updated in line with proposal.
	Rotavirus vaccination programmes in EU/EEA countries	Page 17 Line 820-821	GREECE: Rotavirus vaccination was recommended in 2011 and initiated in 2012. Ref: Weil-Olivier,Millier, Toumi & Trichard – Figure 3 & page 5	GREECE: Rotavirus vaccination was initiated in 2012.	Expert Opinion updated in line with proposal.
	Background Rotavirus immunisation programmes	P17 Line 822	Before Latvia, it should be Italy, forgotten in the list of country with regional implementation		Expert Opinion updated in line with proposal.
	Table 4. Current status of rotavirus immunisation programmes in EU/EEA countries	Page 19	Year of introduction into national immunisation programmes To be corrected for Greece: 2012 instead of 2015. Ref: Weil-Olivier,Millier, Toumi & Trichard – Figure 3 & page 5	Year of introduction into national immunisation programmes, Greece: 2012	Expert Opinion updated in line with proposal.

Comments provided by	Section of document	Page and line number	Comment and rationale	Proposed change	Assessment by ECDC and, where appropriate, change implemented
	Table 4. Current status of rotavirus immunisation programmes in EU/EEA countries	Page 19	Age group recommended: Germany : different from STIKO recommendation (D1 at 6 weeks, D2 at 2 months, D3 at 3-4 months) Greece: National vaccination calendar states D1 at 2 months, D2 at 4 months, D3 at 6 months, both being in accordance with below reference Ref: http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx	Germany: D1 6 weeks D2 2 months D3 3-4 months Greece: D1 2 months D2 4 months D3 6 months.	Expert Opinion updated in line with proposal.
	Methodology used for evaluating rotavirus vaccine effectiveness	Page 21, line 894	...effectiveness of either RV1 or RV2... RV2 should be replaced by RV5	...effectiveness of either RV1 or RV5...	Expert Opinion updated in line with proposal.
	Methodology used for evaluating rotavirus vaccine safety	Page 22, line 935	...safety of either RV1 or RV2.... RV2 should be replaced by RV5	...safety of either RV1 or RV5...	Expert Opinion updated in line with proposal.
	Results	24, 995	Recommend to include more information about any severity of disease, including office visits and family impact, as the number of deaths and severe disease is relatively low in Europe, yet significant burden from the disease exists.	Include additional information about any severity of disease in Europe.	Public health focuses on interventions to prevent severe disease, leading to hospitalisations and deaths. However, we acknowledge that the rotavirus vaccines have an impact on all severity and have included information from the RCTs on protection against any severity in the Efficacy chapter.
	Cross-protection against other genotypes	Page 29, line 1167	'However, the number of cases with G2P4 has been very limited and the confidence intervals are wide.'	This sentence is difficult to understand and related to Rotarix vaccine as protection of Rotateq against G2P[4] is direct protection. This should be clarified.	Expert Opinion updated in line with proposal.
	Cross-protection against other genotypes	29, 1168	Statement about no data available on new serotypes is not true, actually effectiveness data against these serotypes exist in both vaccines' EU labels	Update this sentence with data from literature and SmPCs.	Expert Opinion updated in line with proposal.
	Identified knowledge gaps and needs for capacity	Page 29, line 1180	'Efficacy data for G2P4-induced infections is limited and is entirely missing for cases induces by new emerging rotavirus genotypes such as G10 and G12.' The information on limited efficacy data only concerns Rotarix vaccine. Moreover, Rotateq has proven effectiveness against G12P[8]. (Payne et al, Clinical Infectious Diseases, 2015 'Long-term Consistency in Rotavirus Vaccine Protection: RV5 and RV1 Vaccine Effectiveness in US Children, 2012-2013')	'Rotarix efficacy data for G2P[4] induced infections is limited.' Rotateq has proven effectiveness against G12P[8]. Efficacy data of both vaccines against G10 strains are missing, however those strains are very scarce in Europe.	Expert Opinion updated in line with proposal.

Comments provided by	Section of document	Page and line number	Comment and rationale	Proposed change	Assessment by ECDC and, where appropriate, change implemented
			It is right that effectiveness data against G10 are missing, however it should be added that G10 strains are very scarce in Europe (see EurRotaNet 9th year report: http://www.eurorotanet.net/		
	Identified knowledge gaps and needs for capacity	Page 29, line 1181	'Observational studies should be conducted for G10, G12 or any other….'	G12 effectiveness data are available from observational studies as mentioned above. Please refer to Payne 2016 study	Expert Opinion updated in line with proposal.
	Rotavirus vaccine effectiveness	Page 29, 1196	'Studies were conducted between 2010 and 2013 and assessed effectiveness over 2-3 winter seasons.' This section should be updated with recent Finnish data where effectiveness of Rotateq was evaluated over 4 seasons: Hemming-Harlo et al, Journal of the Pediatric Infectious Diseases Society, 2016: Sustained high effectiveness of RotaTeq on hospitalisations attributable to rotavirus-associated gastroenteritis during a 4-year period in Finland.'	Please update this section with the indicated reference.	Expert Opinion updated in line with proposal.
	Other studies of interest	31, 1241	New data on impact on mortality is available from Mexico	Update the current reference to Sanchez-Uribe et al. CID 2016	Expert Opinion updated in line with proposal.
	Other studies of interest	31, 1242-1245	There are additional studies from Spain showing a reduction in seizures from RV vaccination use.	Update this section with additional literature	Expert Opinion updated in line with proposal.
	Other studies of interest	31, 1246-1247	New data from Payne et al. CID 2015 showing protection of RV5 through 7th year of life. These data are in RV5 EU label	This information should be updated: i.e. Payne et al demonstrated sustained effectiveness of RotaTeq in children up to seven years of age and this is reflected in the RotaTeq EU SPC.	Expert Opinion updated in line with proposal.
	Other studies of interest	31, 1238	Finland 5 year data now available (Hemming-Harlo 2016).		Expert Opinion updated in line with proposal.
	Herd immunity	32, 1297	Data available for Africa as well (Rwanda Fidele Ngabo, Jacqueline E Tate 2016)		Expert Opinion updated in line with proposal.
	Rotavirus vaccine safety	Page 32, line 1318	This section should be updated with information on vaccine shedding from recent work: ‣ Rotateq vaccine strains were identified in children hospitalised for respiratory diseases in Finland (Markkula et al, PIDJ, 2014: 'Detection of Vaccine-Derived Rotavirus Strains in Non-Immunocompromised Children up to 3-6 Months after RotaTeq® Vaccination' ‣ In the UK a significant number of vaccine derived strains were detected post-vaccine introduction in 2014/15. Of these 91% were in infants under the age of 6 months. These children aged 2 to 6 months (in line with	This section should be updated with recent data	Expert Opinion updated in line with proposal.

Comments provided by	Section of document	Page and line number	Comment and rationale	Proposed change	Assessment by ECDC and, where appropriate, change implemented
			RotarixTM vaccine schedule) are likely to be shedding vaccine strain post-vaccination and may have gastroenteritis symptoms caused by other gastroenteritis causing pathogens or non-infectious aetiologies. Consequently, in order to better understand these cases the impact of greater sensitivity of detection due to the introduction of molecular tests for front-line diagnostics and the potential role of other co-infecting pathogens is currently being investigated. Furthermore, work to establish case vaccine status will allow investigation of the potential and extent of horizontal transmission (EuroRotaNet 9th year report, available under: http://www.eurorotanet.net/		
	Assessment of reports of intussusception following routine use of second generation ….	Page 36, line 1467	'… two cases of intussusception with fatal outcome in rotavirus-vaccinated infants were subsequently reported from France in 2015'. Please check the indicated reference '13' which seems not to be the right reference here		Reference was made to footnote no. 16 and not reference no. 16.
	Results – Rotavirus vaccine safety – Identified knowledge gaps and needs for capacity building	P42 Line 1610-1626	To provide healthcare professionals with tools to explain to parents RV-vaccination IS low risk, IS time window, IS symptom recognition etc.	*Training material for vaccinators/healthcare personnel is needed to educate parents on IS risk, symptom recognitions and emergency measures to run.*	Expert Opinion updated in line with proposal.
	Cost-effectiveness studies performed in EU/EEA countries	P43 Line 1656-1657	JCVI is the HTA body which assess the vaccination program, so better to mention JCVI adopts the threshold of intervention from NICE.	The Joint Committee on Vaccination and Immunisation (JCVI) as an independent body to assess the vaccination programme in the UK adopts the threshold of interventions from NICE. Ref:https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/224864/JCVI_Code_of_Practice_revision_2013_-_final.pdf	Expert Opinion updated in line with proposal.
	Results cost-effectiveness studies in EU/EEA	P43 Line 1670-1674 and P45-46 table 10	A total of 15 cost-effectiveness studies were identified in the review – however in an exhaustive literature review on all economic analysis on RV vaccination performed for the period up to 2011 by Aballea et al. (A critical literature review of health economic evaluations of rotavirus vaccination. Hum Vaccin Immunother. 2013 Jun 1; 9(6): 1272–1288). In		Expert Opinion updated in line with proposal.

Comments provided by	Section of document	Page and line number	Comment and rationale	Proposed change	Assessment by ECDC and, where appropriate, change implemented
			all, 32 economic analyses on RV vaccination in EU were found and analysed. Other economic studies have been done between 2011 and 2014 and seem missing from the review such as: ‣ Atkins KE et al. The cost-effectiveness of pentavalent rotavirus vaccination in England and Wales. ‣ Vaccine. 2012 Nov 6;30(48):6766-76. From these references, it appears differences between studies are also related to vaccine herd immunity assumptions and utility used for QALY assessment. Also, The level of price at which the vaccines are cost-effective is sensitive not only to societal costs but also to whether authors accounted for positive indirect benefits from the vaccines, such as herd immunity. This parameter has been considered in more recent economic evaluation on RV vaccination (post 2011). The range of price from the comparative analysis (Jit et al. 2010) is only provided in the executive summary and not in the main core of the document (cf section 'Cost-effectiveness studies in EU/EEA p 43). We suggest ECDC to update the evidence review with these references adding the impact of Quality of life assumptions and herd immunity on the cost-effectiveness results and add the comparative analysis from Jit et al. to ensure consistency with information provided in the executive summary.		
	Cost-effectiveness studies in EU/EEA	P44 Line 1724	We should also mention that all listed studies applied only static model which did not account the effect of herd protection.	None of listed studies assessed the cost-effectiveness of rotavirus vaccination using dynamic model to account for effect of herd protection.	Expert Opinion updated in line with proposal.
	Conclusions	P 44 line 1727 - 1729	The sentence 'the inclusion of societal costs significantly affects the estimating cost-saving threshold' is technically incorrect. In economic evaluation, threshold is defined to assess cost-effectiveness – not cost-savings. A threshold analysis provides the maximum price for which the assessed intervention (vaccination programme) is estimated to be cost-effective (or cost-saving), for a given value of the willingness to pay for a QALY or the health outcome of interest.	'The inclusion of societal costs and/or positive indirect benefits of the vaccines such as herd immunity, significantly affect the level of price at which the vaccines are cost-effective (…) '	The topic has been re-discussed and a decision was taken to stay with a concluding sentence that health-economic moels of cost-effectiveness for rotavirus vaccination should be shared so that they and be used by those EU/EEA countries interested.

Comments provided by	Section of document	Page and line number	Comment and rationale	Proposed change	Assessment by ECDC and, where appropriate, change implemented
	Results Cost-effectiveness studies in EU/EEA – Identified knowledge gaps and needs for capacity building	P 44 Line 1738 - 1740	Option for an EU-level joint level procurement is cited for the first time without explanation neither reference on the topic. We suggest having a specific short section dedicated to National funding system for rotavirus vaccines and New option of an EU-level joint procurement for MS providing: definition, references, benefits and risks of such an option. The vaccine market is characterised by a very limited number of suppliers, particularly with regard to some specific vaccines. It is crucial that joint procurement arrangements need to be carefully considered to maintain sustainability of vaccine supply and avoid creating market distortion or any concentration of demand, which could jeopardise the ability to respond to the Member States needs. In markets functioning by public procurement, a supplier who loses a public bid thereby loses all or nearly all access to the market for the duration of the tender (generally many years). The decrease in demand resulting from this exclusion may push a supplier below the level of production necessary to sustain the high fixed costs of continued production. The aggregation of demand could potentially magnify these elements and drive some suppliers completely out of the market. Thus the concentration of demand is likely to increase the risks inherent in the vaccines business and endanger the sector's sustainability. The experience of other joint procurement arrangements implemented in other regions of the world (e.g. UNICEF, PAHO) has shown that the buying power of pooled procurement can shift market balances and result in a shrinking supplier base overall (Ref: The World Bank and GAVI alliance 2010 - The vaccine market pooled procurement. http://www.who.int/immunization/programmes_systems/financing/analyses/Brief_12_Pooled_Procurement.pdf). For example an analysis of UNICEF procurement of measles vaccines over the period 1992-2001 has shown a drastic reduction of the number of suppliers from 10 to 3. *(ref: Susan McKinney & Steve Jarrett (2002) SAGE meeting update on vaccine security)*	Title: 'EU-level joint procurement for Member States'. *The objective of the joint procurement of medical countermeasures is to ensure availability in sufficient quantities, guarantee access and treat equally all the Member States involved.* (Reference: http://ec.europa.eu/health/preparedness_response/joint_procurement/jpa_signature_en.htm) *In the case of non-pandemic /non-outbreak vaccines such as rotavirus vaccines in Europe, provided by only two suppliers, a joint public procurement likely to be based on price driven-criteria, may result in unsustainable vaccine supply and market distortion.* *Structured negotiations must be performed not solely on price but also on quality and innovation aspects of the vaccines to ensure sustainability of the market supply.* *Vaccines are high-technology products with limited interchangeability and a potentially varying impact in terms of health outcome. Their acquisition therefore constitutes a highly technical and complex topic, which requires specialist procurement expertise.* *New procurement options (including joint procurement) allowing structured negotiations based not solely on price but also on quality and innovation aspects of the vaccines should be explored.*	This topic has been re-discussed and a decision taken to remove it.
	Monitoring of short-term	Page 49, line 1845	'A potential shift of the disease to older age groups….' Is it correct to speak about a 'shift of		It is common for epidemiologists to talk about a shift in the pattern of age groups

Comments provided by	Section of document	Page and line number	Comment and rationale	Proposed change	Assessment by ECDC and, where appropriate, change implemented
	rotavirus vaccine effectiveness		disease' here. As the cases in older children are not expected to be higher than in the pre-vaccination period, but rather remaining cases in children who were not targeted by the vaccination programme.		affected. Sentence updated in Expert Opinion.
	Annexes	52, 1940	Clark does not have a 'e' at the end of the name in table	Correct spelling	Expert Opinion updated in line with proposal.
GSK vaccines Belgium *Volker Vetter*	Executive Summary – Vaccine effectiveness	Page 2 , Line 257, 258	Belgium is not included in the text though the Belgian RotaBEL study has been included in the references.	Add Belgium (Rotarix, Rotateq)	Expert Opinion updated in line with proposal.
	Rotavirus vaccines available in EU/EEA countries	Page 8, line 508	Both vaccines are described as attenuated vaccines which is not true.	Two live ~~attenuated~~ vaccines…	Expert Opinion updated in line with proposal.
	Rotavirus vaccines available in EU/EEA countries	Page 8, line 509	Comment on text: 'Rotarix, a monovalent vaccine developed from a human rotavirus strain attenuated through serial passage in cell culture ' Rationale: Rotarix is not a monovalent vaccine. Valency is defined as the number of antibody binding sites [TheFreeDictionary's Medical dictionary, available online at http://medical-dictionary.thefreedictionary.com, accessed 14 November 2016]. A single Rotavirus strain consists of multiple binding sites. Therefore an immune answer, even to a single Rotavirus strain, is per definition polyvalent and thus Rotarix does not qualify as a monovalent vaccine.	Rotarix, a live attenuated human rotavirus vaccine	It is common that vaccines containing one vaccine strain/component, such as Rotarix, are named as monovalent whereas RV5 is a pentavalent vaccine.
	Rotavirus vaccines available in EU/EEA countries	Page 8, line 509 and 511	To describe the two vaccines as RV1 and RV5 does not reflect the fundamentally different concept of the two vaccines.	human-bovine rotavirus reassortants (e.g. HBR) vs. Human rotavirus RIX4414 strain (e.g. HRV)	The abbreviations RV1 and RV5 are being used widely and are helpful to distinguish them but at the same time they do not differentiate the vaccines too much.
		Page 8, 541	Apnea is reported for both vaccines not only for the HRV.	Apnoea has been reported in younger infants for both vaccines	Expert Opinion updated in line with proposal.
		Page 8, Table 1	RV5 is not a live attenuated vaccine.	human-bovine rotavirus reassortant	Expert Opinion updated in line with proposal.
	Vaccination of Premature Infants	Page 8 – Line 556-557	Table 1. In row of excipients for RV1 – Lyophilised Rotarix presentation after reconstitution contains sucrose 9 mg and sorbitol 13.5 mg and Liquid Rotarix presentation contains sucrose 1073 mg.	Please add the sugar content for both presentations of Rotarix: 'Lyophilised Rotarix presentation after reconstitution contains sucrose 9 mg	Expert Opinion updated in line with proposal.

Comments provided by	Section of document	Page and line number	Comment and rationale	Proposed change	Assessment by ECDC and, where appropriate, change implemented
				and sorbitol 13.5 mg and Liquid Rotarix contains sucrose 1073 mg'	
	Inter-changeability	Page 10 – Line 607	US study data on Rotavirus Vaccine Interchangeability has not been added - Libster R, McNeal M, Walter EB, et al. Safety and immunogenicity of sequential rotavirus vaccine schedules. Pediatrics. 2016;137(2):e20152603.	Findings from Libster R, McNeal M, Walter EB, et al. Safety and immunogenicity of sequential rotavirus vaccine schedules. Pediatrics. 2016;137(2):e20152603 study to be included .	Expert Opinion updated in line with proposal.
	Inter-changeability	Page 10-11 Line 614-619	Comment text: 'monovalent vaccine' Rationale: Rotarix is not a monovalent vaccine Cfr rationale earlier comment	Human vaccine	See rationale above for keeping the wording 'monovalent'.
	Inter-changeability	Page 11 Line 626	Comment on text: 'monovalent vaccine' Rationale: Rotarix is not a monovalent vaccine Cfr rationale earlier comment	Human vaccine	See rationale above for keeping the wording 'monovalent'.
	Inter-changeability	Page 11 Line 626	Comment on text: 'monovalent vaccine' Rationale: Rotarix is not a monovalent vaccine Cfr rationale earlier comment	Human vaccine	See rationale for keeping the wording 'monovalent'.
	Vaccine-induced immunity	Page 11 Line 642	Comment on title Table 3: Table 3. Percentage of seropositive RV5-vaccinated subjects developing at least a threefold rise in serum rotavirus-specific IgA antibodies from baseline 42 days post-immunisation, using different EU immunisation schedules. Rationale: The table presents the percentage of vaccinated subjects seropositive after vaccination.	Table 3. Percentage of human-bovine rotavirus reassortant vaccine-vaccinated subjects developing at least a threefold rise in serum rotavirus-specific IgA antibodies from baseline 42 days post-immunisation, using different EU immunisation schedules	See rationale for keeping the wording 'RV5'. Deleted 'seropositive' in title.
	Contamination of RV1 and RV5 vaccines with porcine circovirus	Page 12 Line 656-657	Comment on text: However, manufacturers were instructed to develop PCV-free vaccines which will become available shortly Rationale: the wording 'shortly' is misleading.	However, manufacturers were instructed to develop PCV-free vaccines.	Expert Opinion updated in line with proposal.
		Page 12, 670	The 116 E strain has not been attenuated it is considered as naturally attenuated	Furthermore, an oral, live ~~attenuated monovalent~~ human-bovine reassortant rotavirus vaccine	Expert Opinion updated in line with proposal.
	Overview of human rotaviruses	Page 14 Line 724	Comment on text: Determination of the potential development of protective immunity after vaccination to current and emerging new rotavirus. Rationale: the sentence is not complete	Determination of the potential development of protective immunity after vaccination to current and emerging new rotavirus …. Please complete sentence.	Expert Opinion updated in line with proposal.
	Rotavirus strain surveillance in the EU/EEA	Page 15 Line 753	Comment on sentence: This network was established by both vaccine producers of the RV1 and RV5 vaccines. Rationale: the network was not established by the vaccine producers	This network is supported by both vaccine producers of the human attenuated rotavirus and the human-bovine rotavirus reassortant vaccines	Expert Opinion updated in line with proposal.

Comments provided by	Section of document	Page and line number	Comment and rationale	Proposed change	Assessment by ECDC and, where appropriate, change implemented
	Rotavirus strain surveillance in the EU/EEA	Page 15 Line 746-748	Comment on sentence: The requirements from EMA subsided in 2015 and it is unknown whether the vaccine producers will continue to fund the network. Rationale: The requirements from EMA for the manufacturer of RV1 have not subsided. The manufacturer of RV1 will support EuroRotaNet until August 2017	The producer of the human attenuated rotavirus vaccine will support the network until August 2017.	Expert Opinion updated in line with proposal.
	Rotavirus strain diversity	Page 16 Line 758	Source: Eurorotanet 7th annual report, www.eurorota.net	The 9th Annual report is available on www.eurorotanet.be, describing data until Aug 2015. Please align the description of the EuroRotaNet data with the 9th report.	Expert Opinion updated in line with proposal with data until end of 2016.
	Rotavirus strain diversity	Page 16 Line 759-761	Comment on sentence: The vast majority of human cases within EU/EEA and worldwide are caused by six genotypes within serogroup A rotaviruses and are responsible for > 90% of all human rotavirus disease, namely G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8]. Rationale: the sentence only mentions 5 genotypes	The vast majority of human cases within EU/EEA and worldwide are caused by five genotypes within serogroup A rotaviruses and are responsible for > 90% of all human rotavirus disease, namely G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8].	Changed to six since Figure 5 displays six genotypes.
	Rotavirus strain diversity	Page 17 Line 786-787	Comment on text and in the context of differences in distribution of genotypes according to age. Rationale: distribution of genotypes can also vary substantially in different rotavirus seasons	and in the context of differences in distribution of genotypes according to age and seasonality	Expert Opinion updated in line with proposal.
	Rotavirus immunisation programmes in EU/EEA countries	Page 20 - Table 4 – last line of table for UK , 5th column	The UK coverage data is available from https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/555048/hpr3216_rtvrs_VC.pdf Preliminary estimates show average rotavirus vaccine coverage in England at six months of age is 94.1% for one dose and 89.7% for two doses, for the period February 2016 to July 2016. These figures show a continuation of the high coverage trends observed since February 2014	To add coverage estimates form UK Public health website . 'Preliminary estimates show average rotavirus vaccine coverage in England at six months of age is 94.1% for one dose and 89.7% for two doses, for the period February 2016 to July 2016. These figures show a continuation of the high coverage trends observed since February 2014'	Expert Opinion updated in line with proposal.
	Methodology used for evaluating rotavirus vaccine effectiveness	Page 21 Line 894	Comment on text: effectiveness of either RV1 or RV2 Rationale: typographical error	effectiveness of either the human attenuated rotavirus vaccine or the human-bovine rotavirus reassortant vaccine	Expert Opinion updated in line with proposal.
	Methodology used for evaluating rotavirus	Page 21 – Line 896	Belgium is not included in the text though the Belgian RotaBEL study has been included in the references	Add Belgium in the bracket- (Europe, Australia, Canada, USA, Latin America and Asia).	Belgium is part of Europe, so not specified separately.

Comments provided by	Section of document	Page and line number	Comment and rationale	Proposed change	Assessment by ECDC and, where appropriate, change implemented
	vaccine effectiveness				
	Methodology used for evaluating rotavirus vaccine effectiveness	Page 22 Line 906	Comment on text: The pooled RR or were used Rationale: typographical error	The pooled RR or were used	Expert Opinion updated in line with proposal.
	Methodology used for evaluating rotavirus vaccine safety	Page 22 Line 935	Comment on text: either RV1 or RV2 Rationale: typographical error	Please see proposal on nomenclature	Typographical error corrected to RV5, the nomenclature is maintained.
	Nosocomial infections	Page 26 , Table 5	The data for last column in Table 5 i.e. Median duration of hospitalisation (days) is not provided for Belgium .	To add median number of hospitalsation days from Belgium studies - i.e. Bilcke et al states 4.4 days (*Bilcke J, Van Damme P, De Smet F, Hanquet G, Van Ranst M, Beutels P. The health and economic burden of rotavirus disease in Belgium. Eur J Pediatr . 2008;167:1409–1419. doi: 10.1007/s00431-008-0684-3*) 7.62 days in 2005 *(Infect Dis Ther. 2016 Oct 6. [Epub ahead of print] The Sustained Rotavirus Vaccination Impact on Nosocomial Infection, Duration of Hospital Stay, and Age: The RotaBIS Study (2005-2012). Standaert B1, Strens D2, Li X3, Schecroun N4, Raes M5)*	Expert Opinion updated in line with proposal.
	Rotavirus vaccine efficacy	Page 26 Line 1121	3 year efficacy data from Asia of Rotarix should be added . (Vaccine. 2012 Jun 22;30(30):4552-7. doi: 10.1016/j.vaccine.2012.03.030. Epub 2012 Apr 10. Rotavirus vaccine RIX4414 efficacy sustained during the third year of life: a randomised clinical trial in an Asian population. Phua KB et al).	To add Asian data for 3rd year efficacy – 'Efficacy was 100% (67.5-100) in the third-year for Rotarix'	Expert Opinion updated in line with proposal.
	Cross-protection against other genotypes	Page 29 . Line 1171	Effectiveness data on additional serotypes should be added here for Rotarix	To add cross protection data from effectiveness data *'VE has been demonstrated against rotavirus of both common (G1P[8], G2P[4], G3P[8] and G9P[8]) and less common (G9P[6] and G9P[4]) genotypes'*	Expert Opinion updated in line with proposal.
	Rotavirus vaccine effectiveness	Page 29 – Line 1186	Need to update data as of Sept 2016 from -Sept 2016 IVAC view – Hub report	88 Rotavirus Vaccine introduction (81 National and 8 Subnational)	Expert Opinion updated in line with proposal.

Comments provided by	Section of document	Page and line number	Comment and rationale	Proposed change	Assessment by ECDC and, where appropriate, change implemented
	Vaccination with first generation of oral live attenuated rotavirus vaccine	Page 35 Line 1401	Comment on text: >70 000 children were included in the randomised clinical trials conducted Rationale: Randomised clinical trial conducted for intussusception after Rotarix vaccination enrolled 63225 subjects	>60 000 children were included in the randomised clinical trials conducted	Expert Opinion updated in line with proposal.
	Cost effectiveness	Page 42, line 1627	General comments on cost effectiveness: • The vaccines may offer a broader economic value by improving quality of care in hospitals during peak seasons • Herd effects are huge at the start of the programme (UK) for which dynamic or semi-dynamic models have to be introduced • The vaccines have been launched with a lot of modelling exercises and uncertainties; today we have the vaccine launched in different countries in Europe and the question now is about the differences between model prediction and observed data. (e.g. much bigger herd effect observed in the UK as predicted).	Consideration of these point in the discussion	Expert Opinion updated in line with proposal.
	Cost effectiveness	Page 44, line 1725	The list of cost-effectiveness analysis studies is incomplete (one study of France, one of Italy and one of Germany not included)	Knoll et al. Health Economics Review 2013 2013, 3:27 Standaert et al. Pharmacoeconomics 2008, 10: 23-35 Standaert at al. Appl Health Econ Health Policy 2008; 6 (4): 1-18	Expert Opinion updated in line with proposal.
World Health Organization Regional Office for Europe *Danni Daniels*	Executive Summary Results (rotavirus vaccine efficacy) Results (identified gaps) Options (monitoring short-term effectiveness) Conclusions	p 3 (ln 332-333) p 28 (ln 1144-1145) p 31 (ln 1262-1264) p 49 (ln 1832-1833) p 50 (ln 1882-1883)	There are several references to reporting of hospitalised breakthrough rotavirus disease in vaccinated individuals. However, there is no mention that this is expected given the effectiveness of rotavirus vaccines. An example of how to calculate the 'expected' number of children hospitalised for rotavirus disease given the effectiveness of rotavirus vaccine should be provided in the document. If the observed number of cases exceeds the expected number of cases among fully rotavirus-vaccinated children, an investigation should be encouraged.	Mention that hospitalised rotavirus disease is expected among fully-vaccinated children due to the effectiveness of the rotavirus vaccines. Provide an example of how to calculate the expected number of children hospitalised with rotavirus disease among fully-vaccinated children based on the effectiveness of the rotavirus vaccines. Recommend that an investigation be conducted if the observed number exceeds the expected number of children hospitalised for rotavirus disease among the fully vaccinated with rotavirus vaccine.	Expert Opinion updated in line with proposal.