The burden of Group B *Streptococcus* worldwide for pregnant women, stillbirths and children

Paper 7: Risk of early-onset neonatal group B *Streptococcus* disease with maternal colonization worldwide: systematic review and meta-analyses

Supplementary information

Contents

Supplementary Table S1: Search strategy and sources of data

- Maternal colonisation search (see Paper 2 of this Supplement)
  - No date restrictions *(including high income >10yrs old)*
  - Including all studies with a cohort of more than 200 GBS colonised mothers which report on neonatal outcomes with availability of blood and csf culture
- Recent systematic review of prevalence of early-onset neonatal infection among newborns of mothers with colonisation/infection (including but not limited to studies on GBS) (Chan et al 2015)
- Cochrane reviews
  - IAP for maternal colonisation (2014)
  - Chlorhexidine for prevention of neonatal GBS disease (2014)
- UK cost effectiveness review (Colbourn et al 2007)
- Reference lists of above
- *Review of risk of neonatal disease in US before CDC recommendations adopted (Benitz 1999) – papers included above*
- Unpublished, anonymised data provided by investigator group

Supplementary Table S2: Assessment of potential for bias in studies

Category	Risk grading	Example
Selection bias	High risk	Selection based on risk factors
	Moderate risk	Swabs taken after 35 weeks' gestation
	Low risk	Unselected representative sample
	Unclear risk	Selection inadequately described
Misclassification of exposure	High risk	PCR detection Non vaginal swabs Mothers tested for GBS colonization after diagnosis of newborn
	Moderate risk	Non selective culture methods
	Low risk	Selective enrichment
	Unclear risk	Methods of GBS detection in mothers not described
Loss to follow-up of outcome	High risk	Newborns of GBS colonized mothers not all followed up
	Moderate risk	Follow up < 3 days
	Low risk	Follow up 3-6 days
	Unclear risk	No description of length of follow up
Overrepresentation of high risk mothers	High risk	High prevalence of any risk factor (>30%)
	Moderate risk	Moderately high prevalence of a risk factor (10-30%)
	Low risk	Representative prevalence of risk factors
	Unclear risk	No description of risk factors
Misclassification of outcome	High risk	Culture diagnosis not available EOD cases not from within the original cohort of GBS colonized mothers
	Moderate risk	Non-selective culture methods
	Low risk	Selective enrichment Automated culture
	Unclear risk	Methods not described

Supplementary Table S3: Characteristics of included studies

Country	Author	Year	Design *	Exclusions	IAP policy for GBS colonization?	Intra-partum antibiotic** (%)	GBS colonized mothers (n)	EOGBS cases	Any risk factors	Risk of bias#	Direction of bias##
Qatar	Al taher[1]	2008	Obsv		Y	80	550	0	Y	Mod	Under
Italy	Berardi[2]	2014	Obsv	<35 wks, Planned elective c section, non-Ampicillin IAP	Y	92	499	0	Y	Mod	Under
Spain	Bosch Mestres[3]	1997	Obsv		Y	93	551	2	Y	Low	Unc
USA	Boyer[4]	1983	Obsv		N	20	281	4	N	Unc	Unc
USA	Boyer[5]	1983	Obsv		N	16	495	5	Y	Unc	Unc
Sweden	Burman[6]	1992	RCT	<37wks, planned elective c-section, multiple pregnancy, congenital abnormality, previous infant with GBS, antibiotics within 2 weeks of swab	N	0	797	2	Y	Mod	Under
Italy	Cantoni[7]	2013	Obsv	preterm	Y	83	3010	0	Y	Mod	Under
SouthAfrica	Cutland[8] Secondary Analysis	2009	RCT	Planned c-section, APH, Congenital Malformation, IUD, Age<15, chlorhex allergy, face, gen warts, full cervical dilatation	RCT	0	825	10	Y		
Spain	De Cueto[9]	1998	Obsv	none	Y	44	454	1	Y	Unc	Unc
Italy	Della Morte[10]	1996	Obsv	?	Y	76	376	4	Y	Unc	Unc
USA	Dillon[11]	1987	Obsv		N	0	1523	24	Y	Mod	Under
Italy	Facchinetti[12]	2002	RCT	<37 weeks, multiple pregnancy, ROM >6 hrs, C section	RCT	50	217	2	Y	Mod	Under
USA	Faro[13]	2010	Obsv		Y	95	552	3	Y	Mod	Under
Germany	Grischke[14]	1992	Obsv	?	N	21	218	6	N	Unc	Unc
Austria	Hafner[15]	1998	Obsv	< 33 weeks	Y	91	520	0	N	Mod	Under

Sweden	Hakansson[16]	2008	Obsv	none	N	28	327	0	Y	Low	Unc
Israel	Hashavya[17]	2011	Obsv		Y	92	3819	2	N	Mod	Unc
USA	Katz[18]	1994	Obsv		Y	92	237	0	Y	Low/ Mod	Unc /Under
Poland	Kociszewska-Najman[19]	2010	Obsv		Y	80	250	1	N	Low	Under
Gambia	Le Doare[20]	2016	Obsv	not planning to breastfeed, HIV positive	N		253	1	N	Mod	Under
Taiwan	Lin[21]	2011	Obsv		Y	90	447	2	Y	Mod	Under
USA	Lin[22]	2011	Obsv	<32 weeks	Y	69	904	1	Y	Mod	Under
USA	Morales[23]	1986	RCT	<36 weeks, planned elective c-section	RCT	51	263	2	Y	Mod	Under
USA	Pass[24]	1979	Obsv		N	0	216	7	Y	Unc	Unc
USA	Pylipow[25]	1994	Obsv		N	21	331	11	Y	Low/ mod	Under
Kenya	Seale[26] (secondary analysis)	2016	Obsv	none	N	0	608	3	Y	Mod	Under
Poland	Szymusik[27]	2014	Obsv	none	Y	79	220	0	Y	Mod	Under
France	Thibaudon Baveux[28]	2008	Obsv		Y	90	283	0	Y	Mod	Under
Finland	Tuppurainen[29]	1989	RCT	c-section	RCT	23	377	7	N	Mod	Over
Italy	Zuppa[30]	2014	Obsv	planned elective c-section	Y	92	676	0	Y	Mod	Under

*Design: Obsv=observational, RCT=Randomized controlled trial

**Includes any intravenous antibiotics, either in the context of a policy of IAP for GBS colonization, or as treatment of a suspected infection, or in response to risk factors.

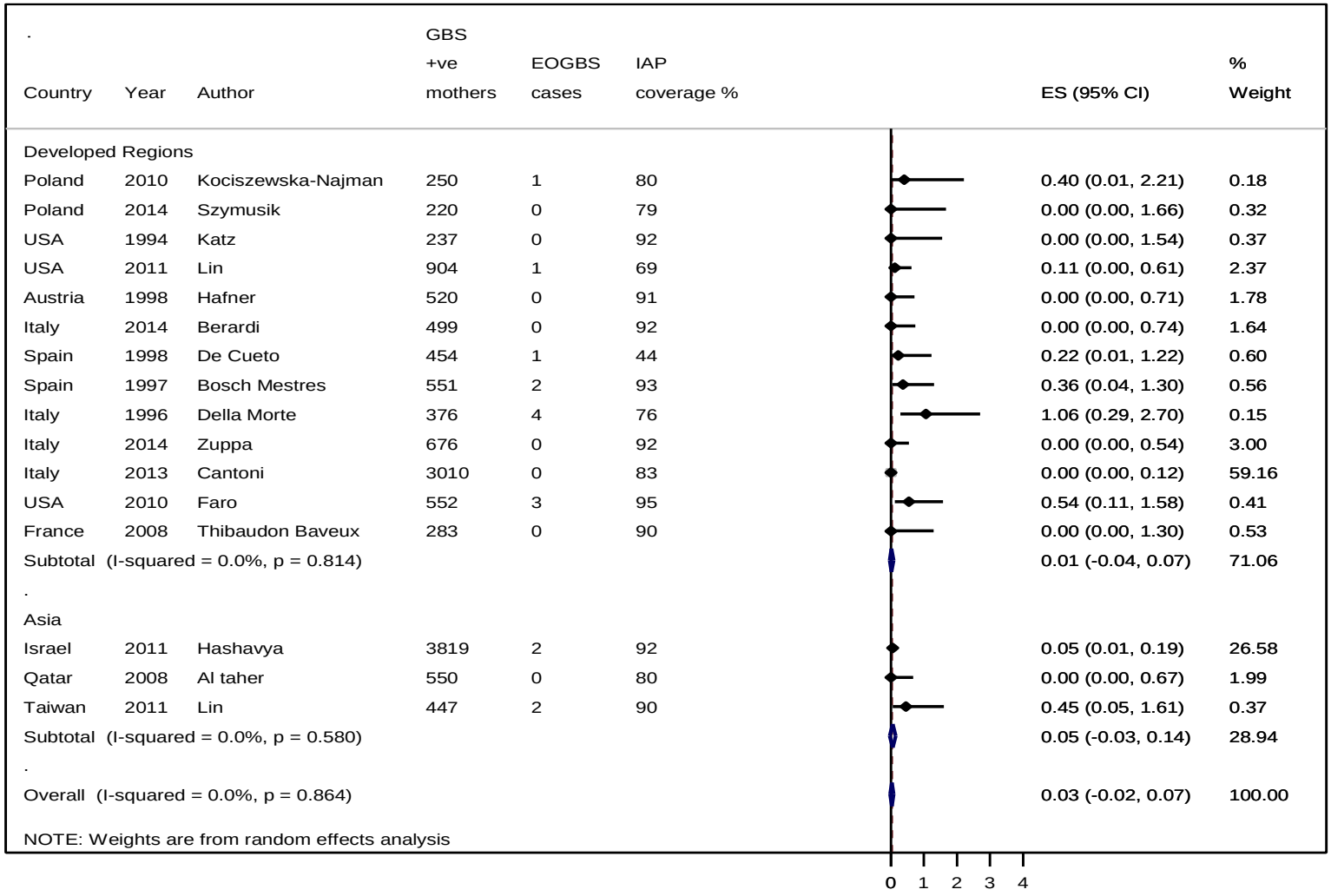
#Risk of bias: Unc=Unclear, Mod=moderate

##Direction of bias: Under=Underestimate, Over=overestimate, Unc=Unclear

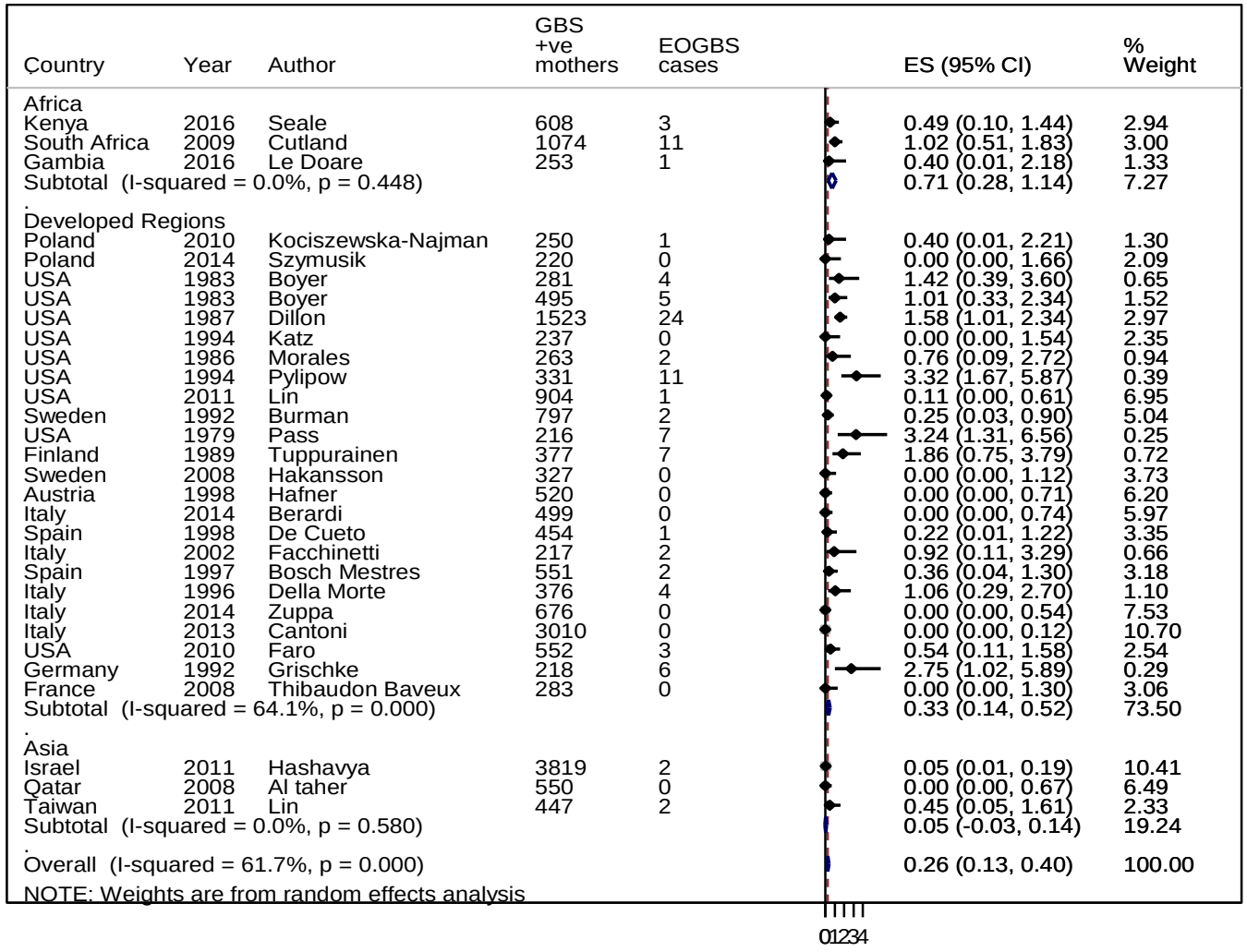
Supplementary Table S4: Summary of risk of EOD in different IAP policy contexts and in the presence of risk factors (sensitivity analyses)

Meta-analysis	Risk %	Risk if any risk factor described	Risk only if gestation described	Risk if PROM described	Risk if maternal fever described
All studies	0.26%(0.13-0.40)	0.32(0.14-0.50)	0.29(0.08-0.51)	0.32(0.0-0.65)	0.52(0.04-1.00)
No IAP policy	1.05 (0.58-1.51)	0.89 (0.41-1.37)	0.88 (0.23-1.53)	0.78 (0.48-1.49)	1.36 (0.43-2.29)
IAP policy (varying coverage)	0.03 (0-0.07)	0.03(0-0.07)	0.01(0-0.07)	0.04(0-0.24)	0.04(0-0.25)

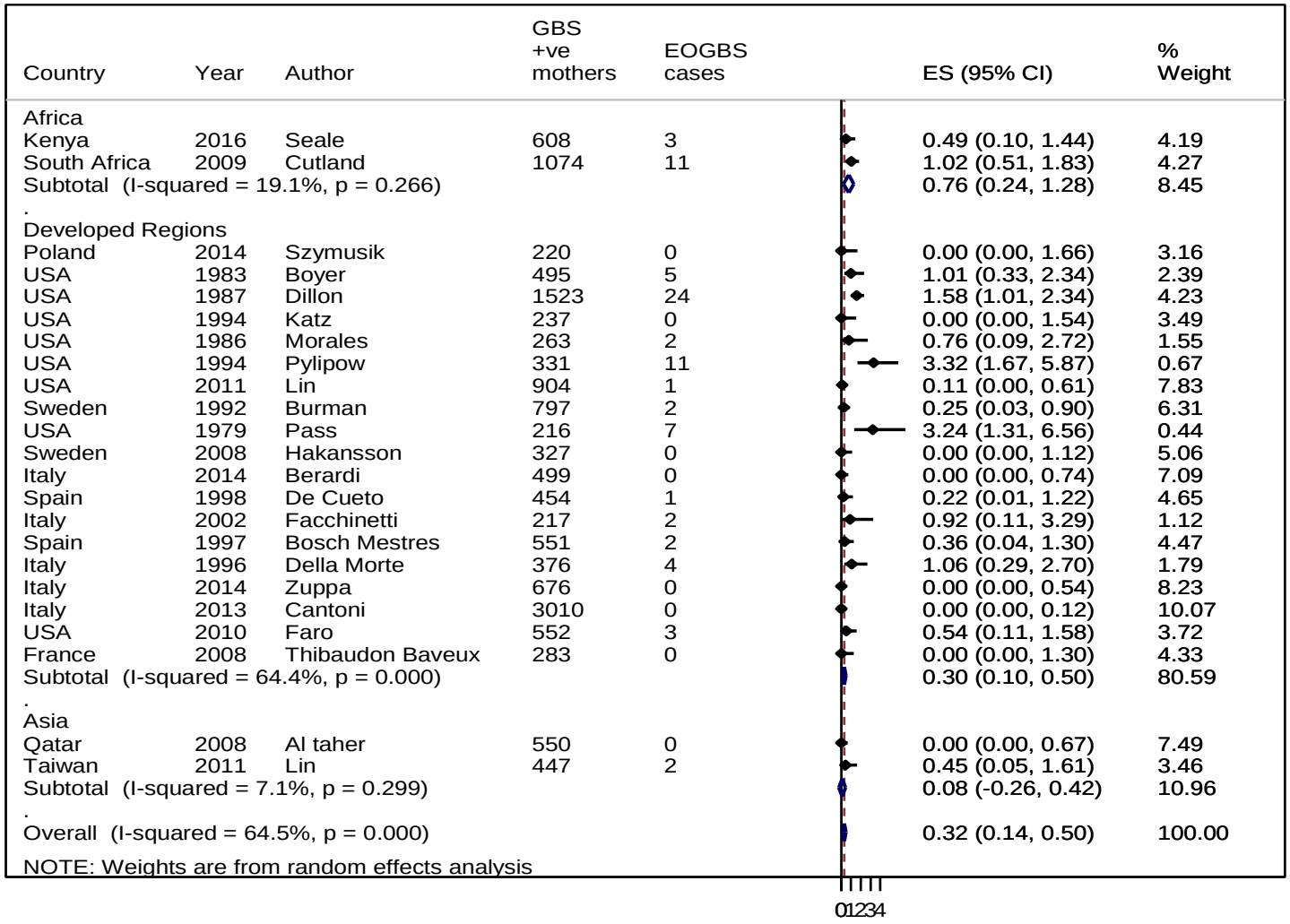
Supplementary Figure S1: Meta-analysis of risk of EOD with a policy of IAP for GBS colonized mothers



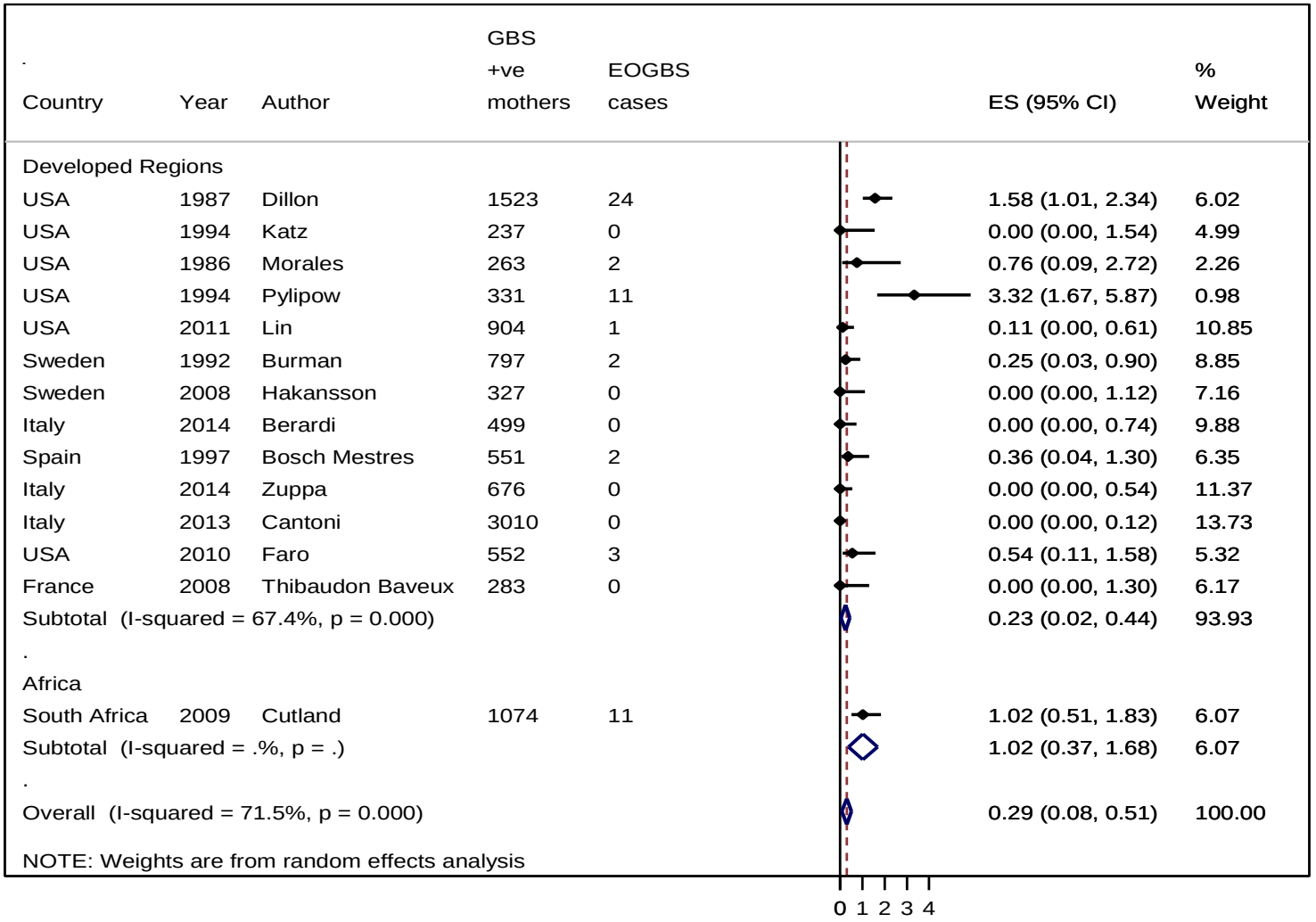
Supplementary Figure S2: Meta-analysis of risk of EOGBS (all studies regardless of IAP policy)



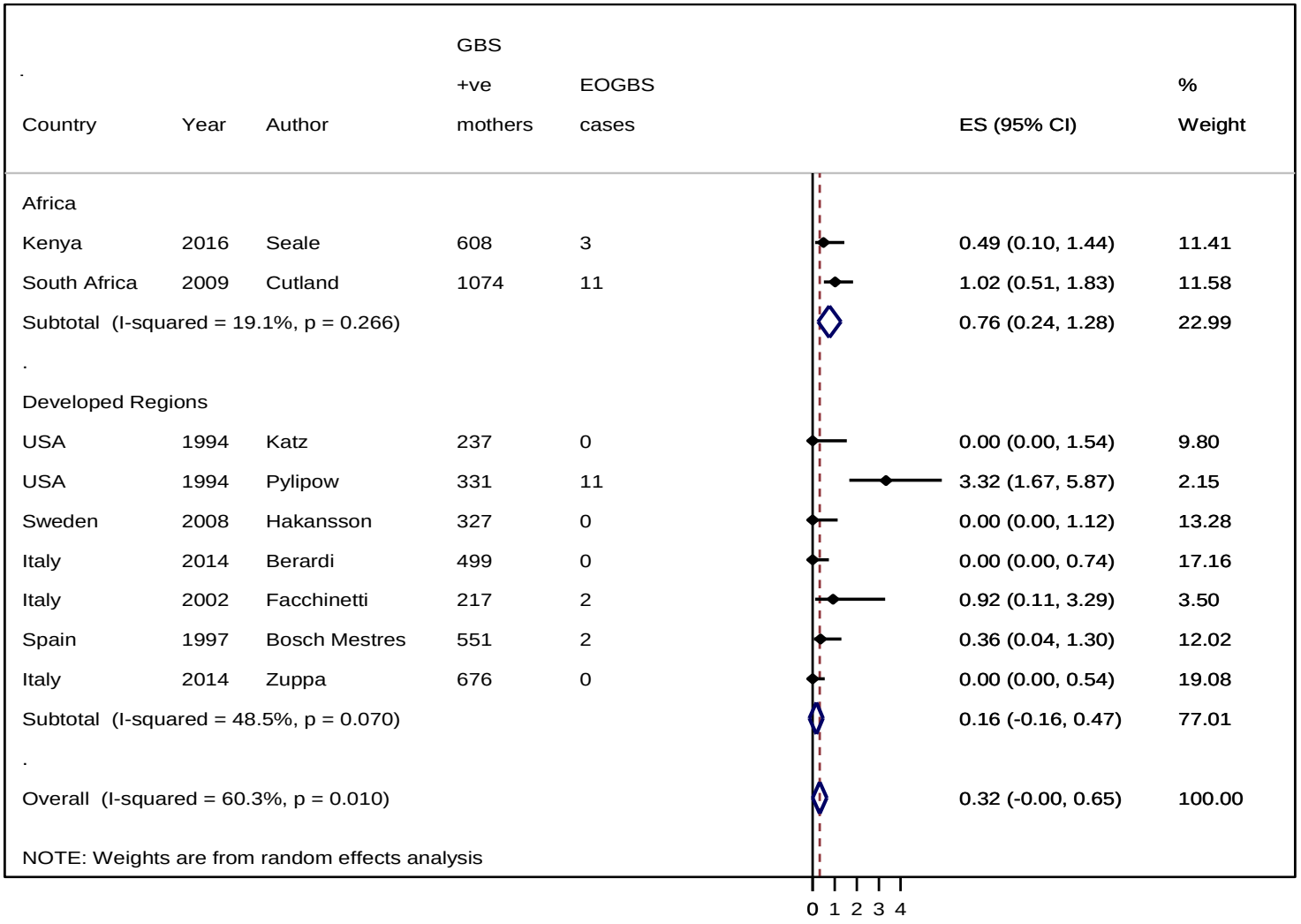
Supplementary Figure S3: Meta-analysis of studies describing any risk factor (regardless of IAP policy)



Supplementary Figure S4: Meta-analysis of studies describing gestational age (regardless of IAP policy)



Supplementary Figure S5: Meta-analysis of studies describing prolonged rupture of membranes (regardless of IAP policy)



Supplementary Figure S6: Meta-analysis of studies describing maternal fever (regardless of IAP policy)