THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Little P, Francis NA, Stuart B, et al. Antibiotics for lower respiratory tract infection in children presenting in primary care in England (ARTIC PC): a double-blind, randomised, placebo-controlled trial. *Lancet* 2021; published online Sept 22. http://dx.doi.org/10.1016/S0140-6736(21)01431-8.

Appendix.

Table 6. Description of attendances or admissions to hospital

Placebo	Antibiotics
Hospital admission - Worsening of symptoms/'Viral-Induced' wheeze	Hospital admission - stridor, floppy episode and febrile convulsion, croup, Short of breath
Hospital admission - Shortness of breath. Bronchiolitis, increased work of breathing requiring optiflow and NG feeding	Persistent symptoms of fever, increasing breathlessness, oxygen sats 91%, respiratory rate 32/min, expiratory wheeze; admission to hospital (not overnight)
Exacerbation of cough and phlegm/ cough getting worse, vomiting overnight, decreased feeding – not admitted overnight	Hospital admission - Bronchiolitis
Hospital admission - no further information available	Gastro-intestinal symptoms: hospital admission - not overnight
	Temp 38.5, 'rattle in throat/chest', stomach pain

7. Hospital admissions (overnight) by STARWAVe prediction rule

	Placebo	Antibiotics
STARWAVe		
Very low risk	1/104 (1.0%)	0/118 (0.0%)
Normal risk	2/94 (2.1%)	2/89 (2.2%)
High risk	0/6 (0.0%)	0/4 (0.0%)

Adherence.

Among those who reported adherence, most (95%) started taking their medication on day 1, adherence was maintained in the antibiotics arm over days 1 to 5, but decreased gradually to 84% by day 5 in the placebo arm. Reported adherence was higher for longer prior duration of illness (OR 1.08, 95% CI 1.01 to 1.16) adjusting for group and other prespecified covariates. Among those who thought their child was receiving antibiotics, 68 (85%) adhered to their medication, and among those who thought their child was receiving placebo 82 (82%) adhered to their medication. There was little evidence for clustering by GP practice, intra-cluster correlation ICC 0.01 (95% CI 0.00 to 0.99).

Adherence sensitivity analyses

In order to provide a lower bound to the adherence, we assume that all those who completed the diary but did not fill in medication dosage did not adhere to their medication. Under this assumption, 98/161 (60.9%) in the Antibiotics group and 87/156 (55.8%) in the Placebo group adhered to their medication. In order to provide an upper bound to the adherence, we assume all those who completed the diary but did not fill in medication dosage did adhere. Under this assumption, adherence was 140/161 (87.0%) in the antibiotics arm and 130/156 (83.3%) in the placebo arm. If adherence is low, the ITT effect of antibiotics on duration will be diluted. Therefore, as a sensitivity analysis, assuming all those who completed the diary but did not fill in medication dosage did not adhere in the antibiotics arm.

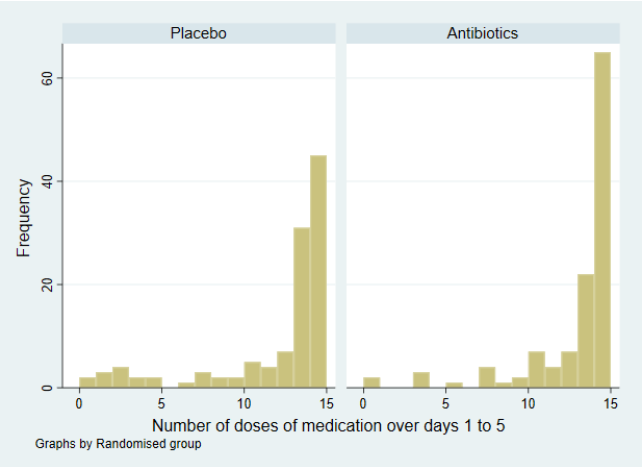

Figure 2. Number of doses of medication over days 1 to 5

	Medication taken (n, %)	
Day	Placebo	Antibiotics
1	108 (95.6%)	112 (94.1%)
2	103 (92.0%)	117 (98.3%)
3	99 (88.4%)	116 (97.5%)
4	94 (84.7%)	110 (93.2%)
5	93 (83.8%)	108 (91.5%)

Table 8. Effectiveness of antibiotics in primary and secondary outcomes (complete cases analysis)

	Number analysed	Placebo	Antibiotics	Adjusted* treatment estimate (95% CI)
Duration of moderately bad or worse symptoms in days (median, IQR)	317	6 (4, 15)	5 (4, 11)	HR 1.15 (0.91, 1.46)
Symptom severity (mean, SD)	298	2.1 (1.1)	1.8 (1.0)	Diff -0.29 (-0.53, -0.04)
Duration of symptoms until very little problem in days (median, IQR)	317	8 (5, 20)	7 (4, 17)	HR 1.10 (0.85, 1.40)
Return with new or worsening symptoms (n, %)	401	76 (38.2)	60 (29.7)	OR 0.71 (0.46, 1.08) RR 0.78 (0.61, 1.04)
Complications (n, %)	415	4 (2.0)	5 (2.4)	OR 1.21 (0.31, 4.67) RR 1.18 (0.33, 4.26)
Side effects (n, %)	310	52 (34.0)	60 (38.2)	OR 1.32 (0.81, 2.15) RR 1.19 (0.64, 1.56)

*Adjusted for prior duration of illness, baseline severity, age, and comorbidity

Table 9. Duration of moderately bad or worse symptoms by subgroup (complete cases analysis)

Subgroup	N	Placebo	Antibiotics	Interaction term (99% CI)**	Adjusted *hazard ratio (99% CI)**
Abnormal chest signs					
Yes	106	6 (4, 16)	6 (4, 15)	0.82 (0.49, 1.36)	0.91 (0.59, 1.41)
No	211	7 (4, 15)	5 (3, 11)		1.25 (0.93, 1.68)
Sputum					
Yes	239	7 (4, 16)	5 (4,14)	1.20 (0.58, 2.49)	1.22 (0.85, 1.75)
No	77	5 (4, 14)	5 (3, 10)		0.95 (0.47, 1.90)
Fever					
Yes	246	6 (4, 16)	5 (3,10)	1.63 (0.74, 3.58)	1.28 (0.90, 1.83)
No	71	7 (4, 13)	7 (4, 26)		0.65 (0.30, 1.42)
Physician rating of unwell					
Yes	205	6 (4, 15.5)	5 (3, 10)	1.43 (0.74, 2.76)	1.33 (0.89, 1.98)
No	112	8 (4, 14.5)	6 (4, 16)		0.92 (0.54, 1.57)
Shortness of breath					
Yes	148	6 (4,11)	5 (3, 14)	1.07 (0.56, 2.02)	1.24 (0.78, 1.99)
No	169	7 (4, 18.5)	5.5 (4, 11)		1.16 (0.75, 1.81)
Oxygen saturation low					
Yes	15	11 (6, 18)	8 (4, 20)	0.80 (0.18, 3.55)	1.45 (0.25, 8.46)
No	235	6 (4, 15)	5 (3.5, 10)		1.12 (0.78, 1.61)
STARWAVe					
Very low risk	171	7 (4, 17)	5 (4, 10		1.24 (0.89, 1.99)
Normal risk	137	6 (4, 11.5)	6 (3,14)	0.88 (0.46, 1.66)	1.09 (0.67, 1.78)
High risk	9	-***	-	-	-

*Adjusted for prior duration of illness, baseline severity, age, and comorbidity; **95% CI for the abnormal chest signs subgroup. ***too few data to obtain reliable estimates

Table 10. Duration of moderately bad or worse symptoms by subgroup (adjusted for other subgroups)

Subgroup	N	Placebo	Antibiotics	Interaction term (99% CI)**	Adjusted* Hazard ratio (99% CI)**
Abnormal chest signs					
Yes	106	6 (4, 16)	6 (4, 15)	0.83 (0.50, 1.40)	0.92 (0.59, 1.42)
No	211	7 (4, 15)	5 (3, 11)		1.27 (0.94, 1.71)
Sputum					
Yes	239	7 (4, 16)	5 (4,14)	1.24 (0.60, 2.58)	1.23 (0.86, 1.78)
No	77	5 (4, 14)	5 (3, 10)		0.93 (0.45, 1.89)
Fever					
Yes	246	6 (4, 16)	5 (3,10)	1.62 (0.74, 3.57)	1.30 (0.91, 1.87)
No	71	7 (4, 13)	7 (4, 26)		0.66 (0.30, 1.44)
Physician rating of unwell					
Yes	205	6 (4, 15.5)	5 (3, 10)	1.49 (0.76, 2.89)	1.35 (0.91, 2.02)
No	112	8 (4, 14.5)	6 (4, 16)		0.87 (0.50, 1.50)
Shortness of breath					
Yes	148	6 (4,11)	5 (3, 14)	1.07 (0.56, 2.03)	1.27 (0.79, 2.04)
No	169	7 (4, 18.5)	5.5 (4, 11)		1.20 (0.76, 1.88)
Oxygen saturation low					
Yes	15	11 (6, 18)	8 (4, 20)	0.80 (0.18, 3.53)	1.20 (0.24, 5.93)
No	235	6 (4, 15)	5 (3.5, 10)		1.15 (0.79, 1.66)
STARWAVe					
Very low risk	171	7 (4, 17)	5 (4, 10)		1.32 (0.86, 2.04)
Normal risk	137	6 (4, 11.5)	6 (3,14)	0.88 (0.65, 1.19)	1.12 (0.67, 1.88)
High risk	9	***-	-	-	-

*Adjusted for prior duration of illness, baseline severity, age, comorbidity, and all other subgroups; **95% CI for the abnormal chest signs subgroup. ***too few data to obtain reliable estimates

Table 11. Symptom severity by subgroup

	Placebo Mean (sd)	Antibiotics Mean (sd)	Interaction term (99% CI)	Adjusted* Mean difference (99% CI)
**Abnormal chest signs - yes	2.2 (1.2)	2.0 (0.9)	-0.01 (-0.70, 0.69)	-0.21 (-0.80, 0.38)
no	2.0 (1.1)	1.7 (1.1)		-0.27 (-0.67, 0.13)
Sputum - yes	2.1 (1.1)	1.8 (1.0)	-0.04 (-0.79, 0.73)	-0.30 (-0.65, 0.05)
no	2.0 (1.2)	1.8 (1.3)		-0.29 (-1.16, 0.59)
Fever - yes	2.2 (1.1)	1.8 (1.0)	-0.31 (-1.10, 0.48)	-0.36 (-0.71, -0.01)
no	1.6 (1.2)	1.6 (1.2)		-0.07 (-0.92, 0.79)
Unwell - yes	2.2 (1.1)	1.8 (1.1)	-0.22 (-0.90, 0.46)	-0.35 (-0.76, 0.07)
no	1.8 (1.2)	1.7 (0.9)		-0.12 (-0.67, 0.42)
Shortness of breath - yes	2.2 (1.1)	2.0 (1.1)	0.10 (-0.56, 0.76)	-0.14 (-0.64, 0.34)
no	1.9 (1.2)	1.6 (1.0)		-0.31 (-0.76, 0.14)
STARWAVe				
Very low risk	2.0 (1.2)	1.7 (1.1)		-0.25 (-0.71, 0.21)
Normal risk	2.2 (1.1)	1.8 (1.0)	-0.11 (-0.78, 0.55)	-0.37 (-0.85, 0.11)
High risk	2.2 (1.2)	2.4 (1.4)	0.65 (-1.38, 2.68)	1.73 (-4.71, 8.16)

*Adjusted for prior duration of illness, baseline severity, age, and comorbidity; **95% CI for the abnormal chest signs subgroup

Table 12. Re-consultation by subgroup

	Placebo n (%)	Antibiotics n (%)	Interaction term (99% CI)	Adjusted* Odds ratio (99% CI)	Adjusted* Risk ratio (99% CI)	NNT (99% CI)
Abnormal: yes chest signs**	31 (44.9)	26 (38.2)	1.37 (0.42, 4.48)	0.81 (0.31, 2.10)	0.89 (0.45, 1.40)	-15 (7, -4)
no	45 (34.6)	34 (25.4)		0.62 (0.30, 1.28)	0.72 (0.40, 1.17)	-9 (16, -4)
Sputum - yes	57 (39.3)	50 (32.7)	1.60 (0.56, 4.62)	0.77 (0.40, 1.46)	0.85 (0.52, 1.24)	-15 (13, -5)
no	18 (34.0)	9 (18.8)		0.45 (0.13, 1.58)	0.55 (0.18, 1.32)	-6 (17, -3)
Fever - yes	52 (34.2)	48 (29.8)	1.97 (0.70, 5.53)	0.82 (0.43, 1.56)	0.87 (0.53, 1.30)	-23 (11, -6)
no	24 (51.2)	12 (29.3)		0.41 (0.12, 1.41)	0.59 (0.22, 1.17)	-5 (20, -2)
Unwell - yes	52 (38.8)	40 (30.8)	1.25 (0.38, 4.12)	0.75 (0.37, 1.51)	0.83 (0.49, 1.26)	-12 (14, -4)
no	24 (36.9)	20 (27.8)		0.64 (0.24, 1.71)	0.74 (0.33, 1.35)	-11 (9, -3)
Shortness of breath - yes	33 (36.7)	37 (38.9)	2.81 (0.89, 8.92)	1.15 (0.51, 2.61)	1.09 (0.62, 1.64)	44 (5, -6)
no	43 (39.4)	23 (21.5)		0.42 (0.18, 0.95)	0.54 (0.26, 0.97)	-6 (-56, -3)
STARWAVe						
Very low risk	28 (27.2)	30 (26.6)		1.04 (0.47, 2.36)	1.03 (0.55, 1.72)	-157 (7, -6)
Normal risk	46 (51.1)	28 (32.9)	0.44 (0.14, 1.40)	0.43 (0.19, 1.01)	0.61 (0.32, 1.00)	-6 (99, -3)
High risk	2 (33.3)	2 (50.0)	-	-	-	-

*Adjusted for prior duration of illness, baseline severity, age, and comorbidity; **95% CI for the abnormal chest signs subgroup; - too few data to obtain reliable estimates

Table 13 Intervention and health service use costing between groups

Group	**Service**	**Mean cost (£, SD)**
Placebo N=211	Re-consultation	13.2 (25)
	medication	0.6 (1.6)
	Referral	5.7 (28.1)
	Hospitalisation	7 (58.5)
	Total NHS	25.8 (78.8)
	Societal	32.7 (105.8)
	NHS and societal	58.6 (128.9)
Antibiotics N=221	Re-consultation	9.4 (20.4)
	medication	0.3 (1.2)
	Referral	7.7 (33.2)
	Hospitalisation	9.1 (67.9)
	Intervention	3 (0)
	Total NHS	29.4 (86.2)
	Societal	32.9 (93)
	NHS and societal	62.3 (130.2)

Table 14. Potential pathogens

	Placebo (n=150)	Antibiotics (n=156)
[1]Bacterial pathogens potentially responsive to amoxicillin(n, %)	76 (50.7)	76 (48.7)
Bacterial pathogens not implicated in causing LRTI or not responsive to amoxicillin(n, %)	2 (1.3)	5 (3.2)
Viruses (n, %)	80 (53.3)	78 (50.0)
Carriage organisms (n, %)	63 (42.0)	61 (39.1)
Dual bacterial & viral infection (n, %)	49 (32.7)	47 (30.1)

Viruses – Adenovirus, Bocavirus, Coronavirus, Enterovirus, HMPV, Influenzae, Parainfluenza, Parechovirus, Rhinovirus, RSV

[1]Potential bacterial pathogens that could respond to amoxicillin: H Influenzae, M Catarrhalis, S pneumoniae

Bacterial pathogens either not implicated in LRTI or would not respond to amoxicillin (B pertussis, C Pneumoniae, F Necrophorum, , S Pyogenes, M Pneumoniae,) were found among 7 children (2 placebo group, 5 antibiotic group):

Carriage organisms – CN Staph, Staph NUC, Staph PVL, MecA resistance, N Meningiditis

Table 15. Duration of moderately bad or worse symptoms by pathogen subgroups

Subgroup	Placebo N	Placebo	Antibiotics N	Antibiotics	Unadjusted interaction term (99% CI)	Unadjusted median difference (99% CI)	Adjusted* interaction term (99% CI)	Adjusted* median difference (99% CI)
Bacteria[1]								
Yes	57	6 (4, 5)	57	4 (3, 10)	-1 (-6.8, 4.8)	-2 (-6.6, 2.6)	-1.2 (-7.6, 5.1)	-1.8 (-7.5, 3.8)
No	54	7 (4, 17)	61	6 (4,10)		-1 (-5.5, 3.5)		-0.6 (-5.3, 4.0)

*Adjusted for age, baseline severity, comorbidity and prior duration of illness

[1]Potentially amoxicillin sensitive bacteria - H Influenzae, M Catarrhalis, S Pneumoniae

Table 16. Characteristics of observational and randomised participants

		Observational Overall (N=312)	RCT Overall (N=432)
Male (n, %)		168 (53.9)	233 (53.9)
Age in years (median, IQR)		3.1 (1.6, 5.0)	3.2 (1.6, 5.7)
Comorbidity (n, %)		35 (11.2)	55 (12.7)
Asthma (n, %)		19 (6.1)	45 (10.4)
Long term illness (n/N, %)		19/196 (9.7)	20/231 (8.6)
Hay fever/eczema (n/N, %)		69/195 (35.4)	83/232 (35.8)
Family history of asthma (n/N, %)		114/196 (58.2)	147/229 (64.2)
Breast fed at 3 months (n/N, %)		98/192 (51.4)	114/230 (49.6)
Mother age (mean, SD, N)		35.6 (6.1) (N=182)	34.9 (6.8) (N=219)
Number of times had cough in last 12 months (mean, SD, N)		2.3 (1.9) (N=184)	2.6 (2.6) (N=222)
Prior influenza vaccine in last 12 months (n/N, %)		195/268 (72.8)	114/401 (21.4)
Prior pneumococcal vaccine (booster) in last 12 months (n/N, %)		182/266 (68.2)	125/401 (31.2)
Smoker in household (n, %)			
	Yes	60 (19.3)	94 (21.8)
	No	242 (77.8)	331 (76.6)
	Don’t know	9 (2.9)	7 (1.6)
Number of children in home (n, %)			
	1	118 (37.8)	173 (40.1)
	2	131 (42.0)	168 (38.9)
	3	47 (15.1)	60 (13.9)
	4	13 (4.2)	20 (4.6)
	5 or more	3 (0.9)	11 (2.5)
Parent highest qualification (n, %)			
	Degree	131 (42.0)	159 (36.8)
	Diploma	46 (14.7)	50 (11.6)
	A-level	26 (8.3)	39 (9.0)
	GCSE/O-level	30 (9.6)	47 (10.9)
	None	5 (1.6)	17 (3.9)
	Not given	63 (20.2)	95 (22.0)

	Other	11 (3.5)	25 (5.8)
Ethnic group (n, %)			
	British/Irish/Other white	275 (88.2)	371 (85.9)
	Mixed	12 (3.8)	19 (4.4)
	South Asian	16 (5.1)	29 (6.7)
	Other	2 (0.6)	9 (2.1)
	Prefer not to say	6 (1.9)	3 (0.7)

Table 17. Illness presentation of observational and randomised participants

		Observational Overall (N=312)	RCT Overall (N=432)
Baseline severity* (mean, SD)		1.6 (0.4)	1.6 (0.3)
Cough severity (mean, SD)		1.8 (1.0)	1.9 (1.1)
Duration of illness in days (median, IQR)		5 (3, 8)	5 (3, 10)
Abnormal chest signs* (n, %)		164 (52.6)	150 (34.7)
Sputum/rattly chest (n/N, %)		243 (78.4)	325/429 (75.8)
Fever during illness (n, %)		241 (77.2)	338 (78.2)
Unwell (according to physician) (n, %)		204 (65.8)	284 (65.7)
Shortness of breath (Yes/No) (n, %)		166 (53.2)	199 (46.1)
Oxygen saturation low (n/N, %)		35/237 (14.8)	22/336 (6.6)
STARWAVe* (n, %)			
	Very low risk	154 (49.4)	233 (53.9)
	Normal risk	137 (43.9)	189 (43.8)
	High risk	21 (6.7)	10 (2.3)
Physician rating unwell* (mean, SD)		5.6 (1.9)	5.5 (1.6)
Parent rating of unwell* (mean, SD)		4.3 (1.9)	3.7 (1.7)
Temperature (mean, SD, N)		37.3 (0.8) (N=309)	37.3 (0.8) (N=428)
Oxygen saturation (mean, SD, N)		96.8 (2.1) (N=237)	97.3 (1.6) (N=336)
Heart rate (beats per min) (mean, SD, N)		117.6 (21.3) (N=305)	111.9 (19.1) (N=420)
Respiratory rate (breaths per min) (mean, SD, N)		27.4 (9.6) (N=295)	25.1 (7.0) (N=411)
Tachypnoea (n/N, %)		59/293 (20.1)	55/411 (13.4)
Capillary refill >3 seconds (n, %)		4/301 (1.3)	5 (1.2)
Consciousness (%)	Normal	292 (94.5)	417 (96.8)
	Irritable	12 (3.9)	13 (3.0)
	Drowsy	5 (1.6)	1 (0.2)
Ill appearance (n, %)		88 (28.2)	95 (22.0)
Number of days unwell before seeing general practitioner (median, IQR, N)		5 (3, 7) (N=193)	5 (3, 9) (N=227)
Treated with OTC medication (n/N, %)		173/195 (88.7)	212/232 (91.4)

*Baseline severity on a scale 1 to 4: 1=none, 2=mild, 3=moderate, 4=severe; Abnormal chest signs include wheeze, stridor, grunting, nasal flaring, inter/subcostal recession, crackles/crepitations, bronchial breathing; STARWAVe prediction rule(39) for hospital admission (short illness, temperature, age, recession, wheeze, asthma, vomiting); Physician and parent rating of unwell on a scale 0 to 10

Search Strategy for Cochrane Systematic review:

The authors searched for primary research of randomised controlled trials with no language restrictions in CENTRAL 2016, Issue 11 (accessed 13 January 2017), MEDLINE (1966 to January week 1, 2017), Embase (1974 to 13 January 2017), and LILACS (1982 to 13 January 2017); andsearched the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov on 5 April 2017. The search terms used were: 1 exp Bronchitis/
2 bronchit*.tw.
3 (bronchial adj2 infect*).tw.
4 exp Respiratory Tract Infections/
5 or/1-4
6 exp Anti-Bacterial Agents/
7 exp Lactams/
8 exp Tetracyclines/
9 exp Aminoglycosides/
10 exp Glycopeptides/
11 exp Macrolides/
12 antibiotic*.tw.
13 (alamethicin or amdinocillin* or amikacin or amoxicillin* or ampicillin or aurodox or azithromycin or azlocillin or aztreonam or bacitracin or bacteriocin* or brefeldin* or butirosin* or candicidin or carbenicillin or carfecillin or cefaclor or cefadroxil or cefamandole or cefazolin or cefixime or cefmenoxime or cefmetazole or cefonicid or cefoperazone or cefotaxime or cefotetan or cefotiam or cefoxitin or cefsulodin or ceftazidime or ceftizoxime or ceftriaxone or cefuroxime or cephacetrile or cephalexin or cephaloglycin or cephaloridine or cephalosporin* or cephalothin or cephapirin or cephradine or chloramphenicol or chlortetracycline or citrinin or clarithromycin or clavulanic acid* or clindamycin or cloxacillin or colistin or cyclacillin or dactinomycin or daptomycin or demeclocycline or dibekacin or dicloxacillin or dihydrostreptomycin* or distamycin* or doxycycline or echinomycin or edeine or erythromycin* or floxacillin or framycetin or fusidic acid or gentamicin* or gramicidin or imipenem or lactam* or lasalocid or leucomycins or lymecycline or mepartricin or methacycline or methicillin or mezlocillin or mikamycin or minocycline or miocamycin or moxalactam or mupirocin or mycobacillin or nafcillin or nebramycin or enigericin or nisin or novobiocin or nystatin or ofloxacin or oligomycins or oxacillin or oxytetracycline or penicillanic acid or penicillic acid or penicillin* or piperacillin or pivampicillin or polymyxin* or pristinamycin* or prodigiosin or rifabutin or ristocetin or rolitetracycline or roxarsone or rutamycin or sirolimus or sisomicin or spectinomycin or streptogramin* or streptovaricin or sulbactam or sulbenicillin or talampicillin or teicoplanin or tetracycline or thiamphenicol or thiostrepton or ticarcillin or tobramycin or troleandomycin or tylosin or tyrocidine or tyrothricin or valinomycin or vancomycin or vernamycin* or viomycin* or virginiamycin* or beta-lactam*).tw,nm.
14 or/6-13
15 5 and 14
The MEDLINE search was combined with the Cochrane Highly Sensitive Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2011).