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Community-based antibiotic delivery for possible serious bacterial infections in neonates in low- and middle-income countries (Review)

Duby J, Lassi ZS, Bhutta ZA

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Community-based antibiotic delivery for possible serious bacterial infections in neonates in low- and middle-income countries (Review)

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[Intervention Review]

Community-based antibiotic delivery for possible serious bacterial infections in neonates in low- and middle-income countries

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ABSTRACT

Background

The recommended management for neonates with a possible serious bacterial infection (PSBI) is hospitalisation and treatment with intravenous antibiotics, such as ampicillin plus gentamicin. However, hospitalisation is often not feasible for neonates in low- and middle-income countries (LMICs). Therefore, alternative options for the management of neonatal PSBI in LMICs needs to be evaluated.

Objectives

To assess the effects of community-based antibiotics for neonatal PSBI in LMICs on neonatal mortality and to assess whether the effects of community-based antibiotics for neonatal PSBI differ according to the antibiotic regimen administered.

Search methods

We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL 2018, Issue 3), MEDLINE via PubMed (1966 to 16 April 2018), Embase (1980 to 16 April 2018), and CINAHL (1982 to 16 April 2018). We also searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomised controlled trials (RCTs) and quasi-randomised trials.

Selection criteria

We included randomised, quasi-randomised and cluster-randomised trials. For the first comparison, we included trials that compared antibiotics which were initiated and completed in the community to the standard hospital referral for neonatal PSBI in LMICs. For the second comparison, we included trials that compared simplified antibiotic regimens which relied more on oral antibiotics than intravenous antibiotics to the standard regimen of seven to 10 days of injectable penicillin/ampicillin with an injectable aminoglycoside delivered in the community to treat neonatal PSBI.

Data collection and analysis

We extracted data using the standard methods of the Cochrane Neonatal Group. The primary outcomes were all-cause neonatal mortality and sepsis-specific neonatal mortality. We used the GRADE approach to assess the quality of evidence.

Main results

For the first comparison, five studies met the inclusion criteria. Community-based antibiotic delivery for neonatal PSBI reduced neonatal mortality when compared to hospital referral only (typical risk ratio (RR) 0.82, 95% confidence interval (CI) 0.68 to 0.99; 5 studies, $n = 125,134$; low-quality evidence). There was, however, a high level of statistical heterogeneity ($I^2 = 87\%$) likely, due to the heterogenous nature of the study settings as well as the fact that four of the studies provided various co-interventions in conjunction with community-based antibiotics. Community-based antibiotic delivery for neonatal PSBI showed a possible effect on reducing sepsis-specific neonatal mortality (typical RR 0.78, 95% CI 0.60 to 1.00; 2 studies, $n = 40,233$; low-quality evidence).

For the second comparison, five studies met the inclusion criteria. Using a simplified antibiotic approach resulted in similar rates of neonatal mortality when compared to the standard regimen of seven days of injectable procaine benzylpenicillin and injectable procaine benzylpenicillin and injectable gentamicin delivered in community-settings for neonatal PSBI (typical RR 0.81, 95% CI 0.44 to 1.50; 3 studies, $n = 3476$; moderate-quality evidence). In subgroup analysis, the simplified antibiotic regimen of seven days of oral amoxicillin and injectable gentamicin showed no difference in neonatal mortality (typical RR 0.84, 95% CI 0.47 to 1.51; 3 studies, $n = 2001$; moderate-quality evidence). Two days of injectable benzylpenicillin and injectable gentamicin followed by five days of oral amoxicillin showed no difference in neonatal mortality (typical RR 0.88, 95% CI 0.29 to 2.65; 3 studies, $n = 2036$; low-quality evidence). Two days of injectable gentamicin and oral amoxicillin followed by five days of oral amoxicillin showed no difference in neonatal mortality (RR 0.67, 95% CI 0.24 to 1.85; 1 study, $n = 893$; moderate-quality evidence). For fast breathing alone, seven days of oral amoxicillin resulted in no difference in neonatal mortality (RR 0.99, 95% CI 0.20 to 4.91; 1 study, $n = 1406$; low-quality evidence). None of the studies in the second comparison reported the effect of a simplified antibiotic regimen on sepsis-specific neonatal mortality.

Authors' conclusions

Low-quality data demonstrated that community-based antibiotics reduced neonatal mortality when compared to the standard hospital referral for neonatal PSBI in resource-limited settings. The use of co-interventions, however, prevent disentanglement of the contribution from community-based antibiotics. Moderate-quality evidence showed that simplified, community-based treatment of PSBI using regimens which rely on the combination of oral and injectable antibiotics did not result in increased neonatal mortality when compared to the standard treatment of using only injectable antibiotics. Overall, the evidence suggests that simplified, community-based antibiotics may be efficacious to treat neonatal PSBI when hospitalisation is not feasible. However, implementation research is recommended to study the effectiveness and scale-up of simplified, community-based antibiotics in resource-limited settings.

PLAIN LANGUAGE SUMMARY

Antibiotics delivered in the home or clinic for newborns with suspected, serious infections in low- and middle-income countries

Review question

In low- and middle-income countries, are antibiotics delivered in the home or clinic an effective method for treating newborns with suspected, serious bacterial infections?

Background

Given their fragility, newborns with a suspected, serious bacterial infection are advised to be admitted to a hospital and receive intravenous antibiotics. However, hospital admission is often not possible for families who live in countries with limited resources. Therefore, alternative methods of delivering antibiotics to sick newborns have been studied. Treating a newborn outside of the hospital relies on a community health worker with limited, but targeted training, to diagnose the infection, dispense medication, and follow-up the newborn's response, either at home or in a clinic. Also, antibiotics may be provided orally so that parents can administer at home, but oral antibiotics may be less potent than intravenous antibiotics.

Study characteristics

We searched medical databases and found two types of studies that addressed our review question. One group of five trials studied communities in which sick newborns were offered antibiotics in the home or ambulatory clinics and compared them to communities in which sick newborns received only the standard referral to a hospital. The second group of five trials treated sick newborns in the home or clinic with either the intravenous antibiotics that are typically administered in the hospital or with simpler antibiotic regimens that relied more on oral antibiotics. The trials were conducted in a variety of countries within sub-Saharan Africa and South Asia. The evidence is up to date as of 16 April 2018.

Key results

There is reduced risk of newborn death when sick newborns are given antibiotics in the home or clinic compared to sick newborns who are only referred to a hospital, but this result is based on low-quality evidence. In addition, the majority of the studies that examined home- or clinic-based antibiotics included other interventions, such as improved care at birth, that may have influenced the findings.

Moderate-quality evidence showed that antibiotic regimens that involve fewer injections and can be administered in the home or clinic do not result in more newborn deaths when compared to the typically administered antibiotic regimens that rely solely on injections. Based on this result, simpler antibiotic regimens delivered in the home or clinic may be considered as an alternative treatment for sick newborns that cannot access a hospital. However, it is important to remember that the studies were conducted under ideal conditions with a high level of patient monitoring. Additional research in real-world settings with limited resources are recommended to determine if the results hold true.

Quality of evidence

The quality of evidence ranged from low to moderate quality.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Comparison 1: community-based antibiotic delivery compared to standard care for the management of neonatal possible serious bacterial infection

Primary outcomes with no subgroups for comparison 1

Patient or population: neonates with sepsis

Setting: community

Intervention: management of neonatal sepsis

Comparison: standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with all outcomes with no subgroups				
Neonatal mortality	Study population		RR 0.82 (0.68 to 0.99)	125,134 (5 RCTs)	⊕⊕⊕⊖ Low	We downgraded the evidence by one level for a high level of heterogeneity ($I^2 = 87\%$). The evidence was downgraded by one level for indirectness as the intervention studied was broader than the review question (i.e. use of cointerventions) for four studies.
	44 per 1000	36 per 1000 (30 to 43)				
Early neonatal mortality	Study population		RR 0.74 (0.65 to 0.85)	40,299 (2 RCTs)	⊕⊕⊕⊖ Moderate	We downgraded the evidence by one level for indirectness as the intervention studied was broader than the review question (i.e. use of cointerventions) for both studies.
	44 per 1000	33 per 1000 (30 to 37)				
Late neonatal mortality	Study population		RR 0.73 (0.55 to 0.96)	40,142 (2 RCTs)	⊕⊕⊕⊖ Moderate	We downgraded the evidence by one level for indirectness as the intervention studied was broader than the review question (i.e. use of cointerventions) for both studies.
	9 per 1000	7 per 1000 (6 to 9)				
Sepsis-specific mortality	Study population		RR 0.78 (0.60 to 1.00)	40,233 (2 RCTs)	⊕⊕⊕⊖ Low	We downgraded the evidence by one level for imprecision of results as the 95% CI includes an appreciable effect (relative risk reduction greater than 25%) and no effect. We downgraded the evidence by one level for indirectness as the intervention studied was broader than the review question (i.e. use of cointerventions) for both studies.
	7 per 1000	5 per 1000 (4 to 7)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: we are very uncertain about the estimate

Summary of findings 2. Comparison 1: referral or full course of antibiotics compared to standard care for health problem or population

Referral compared to full course for health problem or population

Patient or population: neonates with sepsis

Setting: community

Intervention: management of neonatal sepsis - antibiotics: first dose and referral or full course

Comparison: standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with full course	Risk with referral				
Neonatal mortality - first dose and referral	Study population		RR 0.57 (0.38 to 0.83)	3355 (1 RCT)	⊕⊕⊕⊖ Low	We downgraded the evidence by one level for imprecision as there were less than 300 events. We downgraded the evidence by one level for indirectness as the intervention studied was broader than the review question (i.e. use of co-interventions).
	40 per 1000	23 per 1000 (15 to 33)				
Neonatal mortality - full course	Study population		RR 0.87 (0.72 to 1.04)	121,779 (4 RCTs)	⊕⊕⊕⊖ Very low	We downgraded the evidence by one level for heterogeneity ($I^2=88\%$). We downgraded the evidence by one level for imprecision as the 95% CI includes both an appreciable benefit (relative risk reduction greater than 25%) and overlaps with no effect.
	44 per 1000	38 per 1000 (31 to 45)				

We downgraded the evidence by one level for indirectness as the intervention studied was broader than the review question (i.e. use of co-interventions) for three of the studies.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

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Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: we are very uncertain about the estimate

Summary of findings 3. Comparison 1: route of antibiotic compared to standard care for the management of neonatal sepsis

Route of antibiotic compared to placebo for health problem or population

Patient or population: neonates with sepsis

Setting: community

Intervention: management of neonatal sepsis - antibiotics (route of antibiotics)

Comparison: standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with route of antibiotic				
Neonatal mortality - oral antibiotic	Study population		RR 0.70 (0.54 to 0.90)	40,223 (2 RCTs)	⊕⊕⊕○ Low	We downgraded the evidence by one level for heterogeneity ($I^2 = 52\%$). We downgraded the evidence by one level for indirectness as the intervention studied was broader than the review question (i.e. use of co-interventions) for both of the studies.
	54 per 1000	38 per 1000 (29 to 48)				
Neonatal mortality - injectable antibiotic	Study population		RR 0.67 (0.51 to 0.88)	5684 (1 RCT)	⊕⊕⊕○ Moderate	We downgrade the evidence by one level for indirectness as the intervention studied was broader than the review question (i.e. use of co-interventions).
	44 per 1000	29 per 1000 (22 to 38)				

Neonatal mortality - oral + injectable antibiotics	Study population		RR 0.99 (0.92 to 1.06)	79,227 (2 RCTs)	⊕⊕⊕⊖ Moderate	We downgraded the evidence by one level for indirectness as the intervention studied in one study was broader than the review question (i.e. use of co-interventions).
	38 per 1000	38 per 1000 (35 to 41)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

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Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: we are very uncertain about the estimate

Summary of findings 4. Comparison 1: antibiotic alone or antibiotic with other newborn care interventions compared to standard care for the management of neonatal sepsis

Referral compared to full course for health problem or population

Patient or population: neonates with sepsis

Setting: community

Intervention: management of neonatal sepsis - antibiotics alone or antibiotics with other newborn care interventions

Comparison: standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with full course	Risk with referral				
Neonatal mortality - antibiotics alone	Study population		RR 1.07 (0.89 to 1.29)	18,747 (1 RCT)	⊕⊕⊕⊖ Moderate	We downgraded the evidence by one level for imprecision as the 95% CI includes both an appreciable harm (relative risk increase greater than 25%) and overlaps with no effect.
	23 per 1000	24 per 1000 (20 to 29)				
Neonatal mortality - antibiotics with other newborn care interventions	Study population		RR 0.76 (0.62 to 0.94)	106,387 (4 RCTs)	⊕⊕⊕⊖ Moderate	We downgraded the evidence by one level for heterogeneity ($I^2 = 88\%$)
	47 per 1000	36 per 1000 (29 to 44)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

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Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: we are very uncertain about the estimate

Summary of findings 5. Comparison 2: any simplified antibiotic regimen compared to the standard antibiotic regimen (7 days injectable benzylpenicillin + injectable gentamicin)

Any simplified antibiotic regimen compared with the standard antibiotic regimen for neonates with possible serious bacterial infection in low- and middle-income countries

Patient or population: neonates with possible serious bacterial infection

Settings: low- and middle-income countries

Intervention: any simplified antibiotic regimen

Comparison: standard antibiotic regimen (7 days injectable benzylpenicillin + injectable gentamicin)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with standard antibiotic regimen (7 days benzylpenicillin + gentamicin)	Risk with any simplified antibiotic regimen				
Neonatal mortality	Study population		RR 0.81 (0.44 to 1.50)	3476 (3 RCTs)	⊕⊕⊕⊖ Moderate	We downgraded the evidence by one level due to imprecision based on a wide 95% CI which includes an appreciable benefit (relative risk reduction greater than 25%), overlaps no effect and includes an appreciable harm (relative risk increase greater than 25%).
	24 per 1000	19 per 1000 (11 to 36)				
Treatment failure	Study population		RR 0.86 (0.67 to 1.10)	3476 (3 RCTs)	⊕⊕⊕⊖ Moderate	We downgraded the evidence by one level due to imprecision based on a wide 95% CI which includes an appreciable benefit (relative risk reduction greater than 25%) and overlaps no effect.
	83 per 1000	71 per 1000				

	(56 to 91)					
Adverse events	Study population		RR 1.38 (0.79 to 2.41)	3476 (3 RCTs)	⊕⊕⊕⊖ Moderate	We downgraded the evidence by one level due to imprecision based on a wide 95% CI which includes no effect and appreciable harm (relative risk increase greater than 25%).
	16 per 1000	22 per 1000 (13 to 39)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

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Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: we are very uncertain about the estimate

Summary of findings 6. Comparison 2: 7 days oral amoxicillin + injectable gentamicin compared to 7 days injectable benzylpenicillin + injectable gentamicin

Seven days oral amoxicillin + injectable gentamicin compared to seven days injectable benzylpenicillin + injectable gentamicin for neonates with possible serious bacterial infection in low- and middle-income countries

Patient or population: possible serious bacterial infections in neonates

Setting: low- and middle-income countries

Intervention: 7 days oral amoxicillin + injectable gentamicin

Comparison: 7 days injectable benzylpenicillin + injectable gentamicin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with standard regimen (7 days benzylpenicillin + gentamicin)	Risk with simplified regimen (7 days amoxicillin + gentamicin)				
Neonatal mortality	Study population		RR 0.84 (0.47 to 1.51)	2001 (3 RCTs)	⊕⊕⊕⊖ Moderate	We downgraded the evidence by one level due to imprecision based on a wide 95% CI which includes an appreciable benefit (relative risk reduction greater than 25%), overlaps
	24 per 1000	20 per 1000 (11 to 36)				

		no effect and includes an appreciable harm (relative risk increase greater than 25%).				
Early neonatal mortality	No evidence was available for this outcome					
Late neonatal mortality	No evidence was available for this outcome					
Sepsis-specific neonatal mortality	No evidence was available for this outcome					
Treatment failure	Study population		RR 0.82 (0.60 to 1.11)	2001 (3 RCTs)	⊕⊕⊕⊖ Moderate	We downgraded the evidence by one level due to imprecision based on a wide 95% CI which includes an appreciable benefit (relative risk reduction greater than 25%) and overlaps no effect.
	84 per 1000	68 per 1000 (41 to 76)				
Adverse events	Study population		RR 1.35 (0.72 to 2.53)	2001 (3 RCTs)	⊕⊕⊕⊖ Moderate	We downgraded the evidence by one level due to imprecision based on a wide 95% CI which includes an appreciable benefit (relative risk reduction greater than 25%), overlaps no effect and includes an appreciable harm (relative risk increase greater than 25%).
	16 per 1000	22 per 1000 (12 to 40)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

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Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: we are very uncertain about the estimate

Summary of findings 7. Comparison 2: 2 days injectable benzylpenicillin + injectable gentamicin followed by 5 days oral amoxicillin compared to 7 days injectable benzylpenicillin + injectable gentamicin

Two days injectable benzylpenicillin + injectable gentamicin followed by five days oral amoxicillin compared to seven days injectable benzylpenicillin + injectable gentamicin for neonates with possible serious bacterial infections in low- and middle-income countries

Patient or population: neonates with possible serious bacterial infections

Setting: low- and middle-income countries
Intervention: 2 days benzylpenicillin + gentamicin followed by 5 days amoxicillin
Comparison: 7 days benzylpenicillin + gentamicin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with standard regimen (7 days benzylpenicillin + gentamicin)	Risk with simplified regimen (2 days benzylpenicillin + gentamicin followed by 5 days amoxicillin)				
Neonatal mortality	Study population		RR 0.88 (0.29 to 2.65)	2036 (3 RCTs)	⊕⊕○○ Low	We downgraded the evidence by one level for a high level of heterogeneity (I = 67%). We downgraded the evidence by one level due to imprecision based on a wide 95% CI which includes an appreciable benefit (relative risk reduction greater than 25%), overlaps no effect and includes an appreciable harm (relative risk increase greater than 25%).
	24 per 1000	21 per 1000 (7 to 63)				
Early neonatal mortality	No evidence was available for this outcome					
Late neonatal mortality	No evidence was available for this outcome					
Sepsis-specific neonatal mortality	No evidence was available for this outcome					
Treatment failure	Study population		RR 0.93 (0.70 to 1.25)	2036 (3 RCTs)	⊕⊕⊕○ Moderate	We downgraded the evidence by one level due to imprecision based on a wide 95% CI which includes an appreciable benefit (relative risk reduction greater than 25%) and overlaps no effect.
	83 per 1000	77 per 1000 (58 to 104)				
Adverse events	Study population		RR 1.39 (0.67 to 2.87)	2036 (3 RCTs)	⊕⊕⊕○ Moderate	We downgraded the evidence by one level due to imprecision based on a wide 95% CI which includes an appreciable benefit (relative risk reduction greater than 25%), overlaps no effect and includes an appreciable harm (relative risk increase greater than 25%).
	16 per 1000	22 per 1000 (11 to 46)				

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

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Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: we are very uncertain about the estimate

Summary of findings 8. Comparison 2: 2 days oral amoxicillin + injectable gentamicin followed by 5 days oral amoxicillin compared to 7 days injectable benzylpenicillin + injectable gentamicin

Two days oral amoxicillin + injectable gentamicin followed by five days oral amoxicillin compared to seven days injectable benzylpenicillin + injectable gentamicin for neonates with possible serious bacterial infections in low- and middle-income countries

Patient or population: neonates with possible serious bacterial infection

Setting: low- and middle-income countries

Intervention: 2 days amoxicillin + gentamicin followed by 5 days amoxicillin

Comparison: 7 days benzylpenicillin + gentamicin

Outcomes	Anticipated absolute effects* (95% CI)		Relative ef- fect (95% CI)	Nº of partici- pants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with stan- dard regimen (7 days benzylpeni- cillin + gentam- icin)	Risk with simplified reg- imen (2 days benzylpeni- cillin + gentamicin fol- lowed by 5 days amoxi- cillin)				
Neonatal mortality	Study population		RR 0.67 (0.24 to 1.85)	893 (1 RCT)	⊕⊕⊕⊖ Moderate	We downgraded the evidence by one level due to imprecision based on a wide 95% CI which includes an appreciable benefit (relative risk reduction greater than 25%), overlaps no effect and includes an appreciable harm (relative risk increase greater than 25%).
	20 per 1000	13 per 1000 (5 to 37)				
Early neonatal mortality	No evidence was available for this outcome					
Late neonatal mortality	No evidence was available for this outcome					

Sepsis-specific neonatal mortality	No evidence was available for this outcome				
Treatment failure	Study population		RR 0.67 (0.24 to 1.85)	893 (1 RCT)	⊕⊕⊕⊖ Moderate
	52 per 1000	34 per 1000 (18 to 64)	We downgraded the evidence by one level due to imprecision based on a wide 95% CI which includes an appreciable benefit (relative risk reduction greater than 25%), overlaps no effect and includes an appreciable harm (relative risk increase greater than 25%).		
Adverse events	Study population		Not estimable	893 (1 RCT)	⊕⊕⊕⊕ High
	0 per 1000	0 per 1000 (0 to 0)			

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: we are very uncertain about the estimate

Summary of findings 9. Comparison 2: 7 days oral amoxicillin compared to 7 days injectable benzylpenicillin + injectable gentamicin for fast breathing alone

Seven days oral amoxicillin compared to seven days injectable benzylpenicillin + injectable gentamicin for neonates with fast breathing only in low- and middle-income countries

Patient or population: neonates with fast breathing alone

Setting: low- and middle-income countries

Intervention: 7 days amoxicillin

Comparison: 7 days benzylpenicillin + gentamicin

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
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	Risk with standard regimen (7 days benzylpenicillin + gentamicin)	Risk with simplified regimen (7 days amoxicillin)				
Neonatal mortality	Study population		RR 0.99 (0.20 to 4.91)	1406 (1 RCT)	⊕⊕⊕⊖ Low	We downgraded the evidence by one level due to imprecision based on a wide 95% CI which includes an appreciable benefit (relative risk reduction greater than 25%), overlaps no effect and includes an appreciable harm (relative risk increase greater than 25%).
	4 per 1000	4 per 1000 (1 to 20)				We downgraded the evidence by one level due to indirectness as the study population used a narrower inclusion criteria than the review question.
Early neonatal mortality	No evidence was available for this outcome					
Late neonatal mortality	No evidence was available for this outcome					
Sepsis-specific neonatal mortality	No evidence was available for this outcome					
Treatment failure	Study population		RR 0.83 (0.68 to 1.01)	1406 (1 RCT)	⊕⊕⊕⊖ Low	We downgraded the evidence by one level due to imprecision based on a wide 95% CI which includes an appreciable benefit (relative risk reduction greater than 25%) and overlaps no effect.
	245 per 1000	203 per 1000 (167 to 247)				We downgraded the evidence by one level due to indirectness as the study population used a narrower inclusion criteria than the review question.
Adverse events	Study population		Not estimable	1406 (1 RCT)	⊕⊕⊕⊖ Moderate	We downgraded the evidence by one level due to indirectness as the study population used a narrower inclusion criteria than the review question.
	0 per 1000	0 per 1000 (0 to 0)				
<p>*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>CI: confidence interval; RCT: randomised controlled trial; RR: risk ratio</p>						

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: we are very uncertain about the estimate

BACKGROUND

Description of the condition

Neonatal sepsis is a clinical syndrome resulting from a serious bacterial infection in the first month of life. It is the third-leading cause of neonatal mortality and accounts for over 500,000 deaths every year (Liu 2015). While a consensus definition is lacking (Wynn 2014), a diagnosis of possible serious bacterial infection (PSBI) in neonates likely includes any combination of temperature instability, poor feeding, difficulty breathing, convulsions, or altered level of consciousness in a newborn at risk of infection (WHO 2015). A positive culture from a sterile body site confirms the diagnosis of a serious bacterial infection but a negative blood culture cannot eliminate the suspicion of a serious bacterial infection, given its potential low negative predictive value (Garges 2006; Schelonka 1996).

Almost 99% of neonatal deaths occur in low- and middle-income countries (LMICs), and deaths from PSBI are no exception (UN-IGME 2017). In many LMICs, care for the mother and baby in the critical first few days after delivery are almost entirely lacking within the formal healthcare sector. Skilled birth attendant coverage is universal in high-income countries, but occurs in fewer than 50% of deliveries in low-income settings (Lawn 2012). Without the presence of a skilled birth attendant, deliveries often occur in settings with suboptimal hygiene in which non-sterile techniques may be used to cut the umbilical cord (Blencowe 2011). Numerous other factors, including preterm birth and birth asphyxia, are more prevalent in LMICs and are known to predispose neonates to infection (Darmstadt 2011).

For neonates and young infants with community-acquired PSBI in LMICs, the most common bacteria identified via blood culture are *Escherichia coli* (*E coli*), *Klebsiella* spp, and *Staphylococcus aureus* (*S aureus*) (Downie 2013; Saha 2018). Based on these organisms, the World Health Organization (WHO) recommends hospitalisation and empiric treatment with intravenous ampicillin (or penicillin) and gentamicin for neonates with PSBI (WHO 2017). In support of this treatment, the ANISA study – a 2018 multicentre observational cohort study in Bangladesh, India and Pakistan – found that 83% of neonatal blood culture isolates were susceptible to either monotherapy or combined therapy of ampicillin, penicillin and/or gentamicin (Saha 2018).

Description of the intervention

Although hospital admission with the administration of intravenous antibiotics remains the preferred approach for all infants under two months of age with PSBI, the WHO recently released guidelines for managing PSBI in young infants when referral is not feasible (WHO 2015). The guidelines recognise that families in many LMICs may have limited access to hospital-based facilities, financial constraints or sociocultural beliefs that either prevent them from seeking medical care for their newborn or lead them to refuse hospital admission when advised (Herbert 2012; Thaver 2009). Hence, there is a need for alternatives to hospital-based antibiotic administration to treat PSBI in neonates in LMICs.

Community-based antibiotic administration for PSBI in neonates involves community health workers (CHWs) who are members within the local community that provide basic preventative and curative health care (Bhutta 2008). Interventions delivered

by CHWs vary by region, but can include services such as immunisation, micronutrient supplementation to pregnant women and breastfeeding promotion (Bhutta 2010). CHWs play a vital role in improving the health outcomes of women and children in resource-limited settings, and it is estimated that an additional three million deaths worldwide could be prevented if CHW programmes were scaled up (Chou 2017).

In the context of neonatal illness, CHWs generally have limited formal education but are provided focused training on the signs and symptoms of neonatal PSBI (Gill 2012). CHWs visit the homes of newborns within their catchment area, identify those with PSBI, and administer a predetermined antibiotic therapy (Khanal 2011). Because effective treatment of PSBI requires multiple days of antibiotic administration, CHWs either make follow-up visits to administer subsequent doses or refer families to a nearby clinic that administers the required daily doses (Shrestha 2011).

How the intervention might work

The decentralisation of maternal and neonatal care from medical facilities to communities has been shown to improve health practices in LMICs. A recent Cochrane Review examined the impact of maternal and neonatal community-based packages that included interventions, such as home visits by CHWs and community support groups (Lassi 2015). The community-based packages improved uptake of tetanus immunisation, usage of clean delivery kits for home births, early initiation of breastfeeding, and maternal healthcare checking for illnesses related to their newborns. A similar community-based approach to antibiotic administration for PSBI in neonates could therefore operate within the existing infrastructure of community-based maternal and neonatal care in LMICs.

Moreover, a community-based approach for administering antibiotics has been shown to be effective for other paediatric infections in resource-limited settings (Perry 2014; Yeboah-Antwi 2010). CHWs in poor neighbourhoods of Peru administered home-based antibiotics to children with multidrug-resistant tuberculosis and produced a 95% rate of cure or probable cure (Drobac 2006). In Tigray, Ethiopia, a 40% reduction in child mortality was achieved by training mothers to identify malaria and provide home-based antimicrobials to their children (Kidane 2000).

Since community-based antibiotic therapy has succeeded for tuberculosis and malaria, it is reasonable to study whether a similar approach would be effective for PSBI in neonates. In this approach, CHWs would serve as the primary mechanism for diagnosing neonatal PSBI and delivering the antibiotics. Specifically, CHWs may either administer the antibiotics directly to the neonate in a community-based clinic or at the neonate's home. Alternatively, CHWs may distribute the antibiotic to the neonate's parents with education regarding administration.

Why it is important to do this review

Evaluating the delivery of antibiotics at the community level is important to establish whether CHWs are appropriate agents to diagnose and treat PSBI in neonates. The signs and symptoms of PSBI in neonates are subtle and nonspecific (Edwards 2003; WHO 2015). Although culture from a sterile body site remains the gold standard for directed therapy, the necessary laboratory services are often unavailable in resource-limited settings. In

local communities, this places the diagnostic burden on CHWs who have significantly less medical training than hospital-based clinicians and therefore have the potential to over- or under-diagnose PSBI, leading to excess mortality (Haines 2007). An additional complication is that the spectrum of neonatal pathogens within communities is not a fixed target and necessitates frequent evaluations regarding the efficacy and safety of a chosen antibiotic regimen (Darmstadt 2011; Zaidi 2005). Finally, there is the possibility that communities may not be receptive to community-based antibiotic treatment for neonatal PSBI.

The introduction of community-based antibiotics to manage PSBI in neonates has not been implemented in isolation. In addition to antibiotics, community strategies for newborn care may also involve home visits, maternal education, and/or assistance in other neonatal issues, including breastfeeding and temperature control (Darmstadt 2005). Prior reviews have analysed the impact of such community-based packages on neonatal health without isolating the role of antibiotic therapy (Bhutta 2005; Haws 2007; Lassi 2015). Hence, the current review seeks to focus on the effects of community-based antibiotic therapy for neonatal PSBI.

OBJECTIVES

To assess the effects of community-based antibiotics for neonatal PSBI in LMICs on neonatal mortality and to assess whether the effects of community-based antibiotics for neonatal PSBI differ according to the antibiotic regimen administered.

METHODS

Criteria for considering studies for this review

Types of studies

Individually-randomised, cluster-randomised and quasi-randomised trials were eligible for inclusion. We obtained disaggregated data for neonates for those trials conducted in neonates as well as in older age groups.

Types of participants

Neonates born at any gestational age enrolled at any time between 0 to 27 completed days of life with possible serious bacterial infection (PSBI), as defined by the World Health Organization (WHO; WHO 2015). Confirmation of a bacterial infection with a positive culture from a sterile body site, can be contributory, but is not necessary for inclusion.

Types of interventions

Comparison 1

Community-based programmes of newborn care that include the initiation of antibiotics in the community versus community-based programmes of newborn care that do not include the provision of community-based antibiotics for PSBI in low- and middle-income countries (LMICs). Community-based delivery of antibiotics include antibiotics delivered in the home or primary health centre/basic health unit. Basic health units provide care at the primary level, staffed primarily by either auxiliary nurses, auxiliary midwives, nurses, midwives, or community-health workers (WHO 2012).

Intervention

Community-based programmes of newborn care that include the initiation of antibiotics in the community for PSBI in LMICs.

Control

Community-based programmes of newborn care that do not include the provision of community-based antibiotics for PSBI in LMICs.

Although there is no international standard for community-based programmes of newborn care, such programmes may comprise some or all of the following.

1. Early identification of pregnancy.
2. Provision of focused antenatal care.
3. Promotion of institutional delivery.
4. Safe and clean delivery.
5. Recognition of asphyxia, initial stimulation and basic resuscitation of the newborn baby.
6. Prevention and management of hypothermia.
7. Management of preterm and low-birthweight neonates.
8. Education on neonatal care and signs of illness.

The frontline staff of community-based programmes of newborn care are community health workers (CHWs) who typically reside in the community they are serving and receive limited training on the interventions they are tasked to implement (WHO 2007).

Comparison 2

Community-based delivery of simplified antibiotic regimens versus community-based delivery of seven to 10 days of injectable penicillin/ampicillin and an injectable aminoglycoside for PSBI in neonates. Simplified antibiotic regimens are any antibiotic regimen that reduces the total number of injections compared to the standard treatment for neonatal PSBI of seven to 10 days of injectable penicillin/ampicillin and an injectable aminoglycoside. Simplified antibiotic regimens can include regimens with only a decreased number of injections or regimens with only oral antibiotics or regimens with both injections and oral antibiotics.

Intervention

Community-based delivery of simplified injectable antibiotics or oral antibiotics, or both for PSBI in neonates.

Control

Community-based delivery of seven to 10 days of injectable penicillin/ampicillin and an injectable aminoglycoside for PSBI in neonates.

Hospital-based delivery of injectable penicillin/ampicillin plus an injectable aminoglycoside is the standard of care for PSBI in neonates in LMICs (WHO 2013). Therefore, community-based delivery of these antibiotics serves as the control when comparing simplified community-based antibiotic regimens for PSBI in neonates.

Types of outcome measures

Primary outcomes

1. **Neonatal mortality** - the number of neonatal deaths from any cause among all neonates. For individually-randomised and quasi-randomised trials, neonatal mortality was calculated as the number of neonatal deaths divided by the total number of neonates enrolled in the trial. For cluster-randomised trials, neonatal mortality was calculated as the number of neonatal deaths divided by the total number of live births within each cluster during the trial period.
 - a. Early neonatal mortality: from birth through six completed days of life
 - b. Late neonatal mortality: between 7 and 27 completed days of life
2. **Sepsis-specific neonatal mortality** - the number of neonatal deaths secondary to PSBI among all neonates during the trial period. Similar calculation considerations applied to sepsis-specific mortality as neonatal mortality.
 - a. Early neonatal sepsis-specific mortality: from birth through six completed days of life
 - b. Late neonatal sepsis-specific mortality: between 7 and 27 completed days of life

Secondary outcomes

1. **Treatment failure** - defined as any one of the following: 1) death within seven days after enrolment; 2) hospital admission within seven days after enrolment due to clinical deterioration; 3) change of antibiotic regimen due to lack of improvement/clinical deterioration within seven days after enrolment
2. **Neonatal antibiotic-associated adverse events** - defined as occurrence of haematoma, bleeding or infection at an injection site, inability to pass urine for 12 hours, dehydration-associated severe diarrhoea, anaphylaxis, or development of rash within seven days of enrolment
3. **Total cost (in USD)** to manage all neonates with PSBI in the community during the trial period (including training, drug cost and delivery, and equipment)
4. **Cost of intervention (in USD) per neonate life saved** among all neonates with PSBI managed in the community during the trial period
5. **Acceptability of antibiotics** - defined as the number of mothers who accept community-based antibiotic treatment for their neonates among all mothers of neonates with PSBI identified during the trial period
6. **Antibiotic resistance** - defined as the number of cases in which there was isolation of bacteria resistant to penicillin/ampicillin and an aminoglycoside within 30 days after enrolment

Search methods for identification of studies

We used the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal [search strategy](#) for specialized register).

Electronic searches

We conducted a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL 2018, Issue 3) in the Cochrane Library; MEDLINE via PubMed (1966 to 16 April 2018); Embase (1980 to 16 April 2018); and CINAHL (1982 to 16 April

2018) using the following search terms: (Sepsis OR Septic OR Pneumonia) AND (Therapy OR Treatment OR Management OR Anti-Bacterial Agents OR antibiotic OR antibiotics) AND (basic health unit OR communit* OR county OR domiciliary OR developing OR disadvantaged OR facility OR home OR home-based OR impoverished OR peripheral OR poor OR rural OR slum OR underdeveloped OR underserved unit* OR village* OR residence characteristics OR rural population OR developing countries), plus database-specific limiters for RCTs and neonates (see [Appendix 1](#) for the full search strategies for each database). We did not apply language restrictions.

We searched clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov; the World Health Organization's International [Trials Registry](#) and Platform, and the [ISRCTN Registry](#)).

We have included relevant studies regardless of language or publication status (published, unpublished, in press, and in progress).

Searching other resources

We also searched the reference lists of any articles selected for inclusion in this review in order to identify additional relevant articles.

Data collection and analysis

We used the standard review methods of Cochrane ([Higgins 2011](#)), and of the Cochrane Neonatal Group.

Selection of studies

Two review authors (JD and ZSL) screened the titles and abstracts acquired from all sources listed above for relevance and retrieved the full text of all relevant and potentially relevant trials. The same review authors independently determined the eligibility of retrieved trials using predefined eligibility forms and resolved any disagreements through discussion. If these methods failed to clarify any doubts, we consulted a third review author (ZAB) or contacted the study authors, or both. We tabulated the excluded studies along with the reasons for excluding them. We also ensured that data from duplicate publications were entered only once in the review.

Data extraction and management

Two review authors (JD and ZSL) independently used a piloted data form to extract data. We compared data, corrected errors and resolved any disagreements by discussion or by consultation with the third review author (ZAB). We recorded information for each treatment arm, including newborn characteristics, sample size, time of onset of sepsis, causative organism (and its resistance pattern if available), risk factors identified, details of antibiotic used (class, dosage, frequency, route, and duration), cointerventions (such as education, maternal immunisation, basic newborn care etc.), details of essential newborn care in the control arm, the length of follow-up, and all outcomes mentioned above. We have attempted to contact study authors to obtain additional data or to clarify data.

Assessment of risk of bias in included studies

Two review authors (JD and ZSL) independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool for the following domains (Higgins 2017).

- Sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Any other bias.

Any disagreements were resolved by discussion or by a third review author (ZAB). See Appendix 2 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

For dichotomous data, we presented our results as summary risk ratios (RRs) with 95% confidence intervals (CIs).

Unit of analysis issues

We included cluster-randomised trials along with individually-randomised trials and quasi-randomised trials. For meta-analyses involving data from individually-randomised and cluster-randomised trials, we planned to incorporate the data of cluster-randomised trials using the generic inverse variance method in which logarithms of RR estimates were used along with the standard error of the logarithms of RR estimates. However, for comparison 1 we identified only cluster-randomised trials and for comparison 2 we identified only individually-RCTs. No additional considerations for unit of allocation were required because each comparison was analysed separately.

Dealing with missing data

For included studies, we noted levels of attrition. We planned to perform analyses on an intention-to-treat (ITT) basis, including all participants randomised to each group in the analyses. ITT analyses were possible for all meta-analyses for comparison 1. However, we were only able to obtain data for comparison 2 on a per-protocol basis.

Assessment of heterogeneity

We assessed heterogeneity between trials, if appropriate, using the I^2 statistic, the P value of the χ^2 statistic, and by the visual inspection of forest plots. When we identified high levels of heterogeneity among the trials and the visual inspection of forest plots was suggestive, we explored this further using a prespecified subgroup analysis

Assessment of reporting biases

We planned to assess possible publication bias and other biases using funnel plots where there were 10 or more studies in a meta-analysis. However, none of the performed meta-analyses identified 10 or more studies.

For included trials, we investigated the possible selective reporting of study outcomes by comparing the primary and secondary outcomes in the reports with the primary and secondary outcomes

proposed at trial registration, using information from the web sites clinicaltrials.gov, www.anzctr.org.au and www.isrctn.com. If we found such discrepancies, we contacted the primary investigators to obtain missing outcome data on outcomes prespecified at trial registration.

Data synthesis

When there were two or more sufficiently homogenous trials with disaggregated neonatal data for our defined outcomes, we performed meta-analyses using the Review Manager 5 software (Review Manager 2014). The current research question encompasses a wide range of study contexts and countries. Therefore, we used a random-effects model for all analyses to estimate the average treatment effect with corresponding 95% CIs.

Quality of evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of evidence of the following (clinically relevant) outcomes: all-cause neonatal mortality, early neonatal mortality, late neonatal mortality, and sepsis-specific neonatal mortality.

Two review authors (JD and ZSL) independently assessed the quality of the evidence for each of the outcomes above. We considered evidence from RCTs as high quality but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We used the GRADEpro GDT Guideline Development Tool to create nine 'Summary of findings' tables to report the quality of the evidence.

The GRADE approach results in an assessment of the quality of a body of evidence as one of four grades.

1. High quality: further research is very unlikely to change our confidence in the estimate of effect.
2. Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
3. Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
4. Very low quality: we are very uncertain about the estimate.

Subgroup analysis and investigation of heterogeneity

We planned to use the primary outcome to carry out the following prespecified subgroup analyses for comparison 1.

1. Method of diagnosis
2. Antibiotic class
3. Route of administration
4. Duration of antibiotic
5. Administrator of antibiotic
6. Location of antibiotic administration
7. Use of other cointerventions

However, based on the characteristics of the included studies, we only performed the following subgroup analyses for comparison 1.

1. Route of administration
2. Duration of antibiotic
3. Use of other cointerventions

Details regarding the included and excluded subgroup analyses can be found in the [Effects of interventions](#) section of the results.

We planned to use the primary outcome to carry out the following prespecified subgroup analyses for comparison 2.

1. Method of diagnosis
2. Type of simplified antibiotic regimen
3. Duration of antibiotic
4. Administrator of antibiotic
5. Location of antibiotic administration

However, based on the characteristics of the included studies, we only performed the following subgroup analyses for Comparison 2.

1. Type of simplified antibiotic regimen

Details regarding the reasons for excluding subgroup analyses for comparison 2 can be found in the [Effects of interventions](#) section of the results.

Sensitivity analysis

We planned to carry out sensitivity analyses to explore the effects of adequate allocation concealment, and other risk of bias components. However, each outcome was compromised of few studies, and all studies had high risk of performance bias as well as other biases. Therefore, we did not perform the planned sensitivity analyses.

RESULTS

Description of studies

See [Characteristics of included studies](#) and [Characteristics of excluded studies](#).

Results of the search

We identified a total of 3742 unique articles from database and supplementary searches. We excluded 3713 records following a review of titles and abstracts. We assessed the full text of 16 studies (29 papers) and excluded an additional six studies (10 articles). Ten trials (19 articles) met the inclusion criteria, including five trials (9 articles) for comparison 1 and five trials (10 articles) for comparison 2. We have presented the study flow diagram in [Figure 1](#).

Figure 1. Study flow diagram.

Figure 1. (Continued)

Included studies

Comparison 1

In the literature search to find trials comparing the initiation of community-based antibiotics to hospital referral and treatment, five studies met the inclusion criteria ([Baqui 2008](#); [Bhandari 2012](#); [Degefie 2017](#); [Gill 2011](#); [Soofi 2017](#)). A full description of the studies can be found in the [Characteristics of included studies](#).

Design

All of the studies were unblinded, parallel clustered-RCTs ([Baqui 2008](#); [Bhandari 2012](#); [Degefie 2017](#); [Gill 2011](#); [Soofi 2017](#)). In all of the trials, the interventions were administered by traditional birth attendants or community health workers (CHWs).

Sample sizes

The number of live births in the control clusters and intervention clusters varied between studies. The smallest studies included approximately 9000 live births and 1500 live births in each arm, respectively ([Degefie 2017](#); [Gill 2011](#)). [Bhandari 2012](#) had the largest sample size with approximately 30,000 live births in the control clusters and approximately 30,000 live births in the intervention clusters. [Baqui 2008](#) included approximately 15,000 births in each arm and [Soofi 2017](#) included approximately 20,000 live births in each arm.

Setting

The studies occurred in resource-limited regions of the following countries: Bangladesh ([Baqui 2008](#)), Ethiopia ([Degefie 2017](#)), India ([Bhandari 2012](#)), Pakistan ([Soofi 2017](#)), and Zambia ([Gill 2011](#)). Four of the studies were conducted in primarily rural regions with limited access to facility-based care ([Baqui 2008](#); [Degefie 2017](#); [Gill 2011](#); [Soofi 2017](#)), and one trial was undertaken in a large urban district ([Bhandari 2012](#)).

Participants

All neonates, aged 0 to 27 days, who resided in the study clusters were eligible for inclusion. Neonates who were diagnosed with a possible serious bacterial infection (PSBI), as defined by the study authors, were eligible for the intervention if they resided in the intervention clusters in three of the studies ([Baqui 2008](#); [Gill 2011](#); [Soofi 2017](#)). Two studies provided the intervention to neonates and infants up to two months of age with a diagnosis of PSBI, as defined by the study authors ([Bhandari 2012](#); [Degefie 2017](#)).

Interventions

Two of the studies provided community-delivered injectable benzylpenicillin and injectable gentamicin for seven to 10 days

to neonates with PSBI if hospital referral was refused ([Baqui 2008](#); [Bhandari 2012](#)). [Degefie 2017](#) provided seven days of oral amoxicillin and injectable gentamicin in the community if hospital referral was not feasible. [Soofi 2017](#) provided oral amoxicillin for seven days in the community if referral was not possible. For neonates with PSBI, [Gill 2011](#) only offered one dose of amoxicillin with referral to the nearest health facility.

Only one trial used community-based antibiotic delivery as the sole intervention ([Degefie 2017](#)). The other four trials offered other cointerventions ([Baqui 2008](#); [Bhandari 2012](#); [Gill 2011](#); [Soofi 2017](#)). Examples of cointerventions include antenatal and postnatal home visits, basic neonatal resuscitation and breastfeeding support.

Outcomes

All of the studies included all-cause neonatal mortality as a primary outcome ([Baqui 2008](#); [Bhandari 2012](#); [Degefie 2017](#); [Gill 2011](#); [Soofi 2017](#)). The two studies that included infants as participants also included infant mortality as a primary outcome ([Bhandari 2012](#); [Degefie 2017](#)). One study also included adherence to appropriate newborn care practices ([Bhandari 2012](#)).

Comparison 2

In the literature search to find trials comparing a simplified antibiotic regimen delivered in the community compared to the standard regimen of procaine benzylpenicillin and gentamicin in the community, five studies met the inclusion criteria ([AFRINEST\(1\) 2015](#); [AFRINEST\(2\) 2015](#); [Baqui 2015](#); [Mir 2017](#); [Zaidi 2012](#)). All of the studies published results that combined neonates and infants. Study authors were individually contacted and four of the five studies provided disaggregated neonatal data. A full description of the studies can be found in the [Characteristics of included studies](#) section.

Design

All studies were individually-randomised, open-label, equivalence trials ([AFRINEST\(1\) 2015](#); [AFRINEST\(2\) 2015](#); [Baqui 2015](#); [Mir 2017](#); [Zaidi 2012](#)).

Sample sizes

Four of the studies had similar sample sizes with a total of approximately 2000 to 3000 participants in each study ([AFRINEST\(1\) 2015](#); [AFRINEST\(2\) 2015](#); [Baqui 2015](#); [Mir 2017](#)). [Zaidi 2012](#) was a much smaller study with approximately 500 participants.

Setting

The studies occurred in resource-limited regions of the following countries: Bangladesh ([Baqui 2015](#)), Democratic Republic of Congo ([AFRINEST\(1\) 2015](#); [AFRINEST\(2\) 2015](#)), Kenya ([AFRINEST\(1\) 2015](#);

AFRINEST(2) 2015), Nigeria (AFRINEST(1) 2015; AFRINEST(2) 2015), and Pakistan (Mir 2017; Zaidi 2012). Study sites in each of the trials were a mix of rural, urban and peri-urban regions (AFRINEST(1) 2015; AFRINEST(2) 2015; Baqui 2015; Mir 2017; Zaidi 2012). In all study sites of Baqui 2015 and in the Nigerian study sites of AFRINEST(1) 2015 and AFRINEST(2) 2015, injectable and oral antibiotics were provided in the home setting. In all study sites of Zaidi 2012 and Mir 2017, in addition to the study sites in the Democratic Republic of Congo and Kenya of AFRINEST(1) 2015 and AFRINEST(2) 2015, injectable antibiotics were administered in an outpatient clinic and oral antibiotics were administered in the home.

Participants

All of the studies included neonates, 0 to 27 days of age, and infants up to two months of age (Zaidi 2012; AFRINEST(1) 2015; AFRINEST(2) 2015; Baqui 2015; Mir 2017). Four of the studies included participants with a diagnosis of PSBI, as defined by the study authors (AFRINEST(1) 2015; AFRINEST(2) 2015; Baqui 2015; Mir 2017; Zaidi 2012). AFRINEST(2) 2015 included participants who only had fast breathing which is one sign of PSBI. Neonates with any additional signs of PSBI were excluded from AFRINEST(2) 2015.

Interventions

All of the studies used seven days of injectable procaine benzylpenicillin and injectable gentamicin as their control arm (AFRINEST(1) 2015; AFRINEST(2) 2015; Baqui 2015; Mir 2017; Zaidi 2012). Three of the studies included one intervention arm that consisted of two days of procaine benzyl penicillin and gentamicin followed by five days of oral amoxicillin and another intervention arm that consisted of seven days of both gentamicin and amoxicillin

(AFRINEST(1) 2015; Baqui 2015; Mir 2017). AFRINEST(1) 2015 also included an additional intervention arm that administered amoxicillin for seven days and gentamicin for the first two days of treatment. The two intervention arms in Zaidi 2012 included treatment only with injectable ceftriaxone for seven days and another arm that consisted of injectable gentamicin and oral trimethoprim-sulphamethoxazole for seven days. The only intervention arm in AFRINEST(2) 2015 treated neonates and infants with fast breathing with seven days of amoxicillin.

Outcomes

All of the studies used treatment failure as a primary outcome although each study used a slightly different definition (AFRINEST(1) 2015; AFRINEST(2) 2015; Baqui 2015; Mir 2017; Zaidi 2012). All of the studies included death, some form of adverse event and some form of clinical deterioration as indications of treatment failure.

Excluded studies

We excluded six studies that did not satisfy the inclusion criteria. Four of the studies were non-RCTs (Bang 1990; Bang 1999; Khan 1990; Pandey 1991), and one trial was a cohort study (Bhandari 1996). One trial was a randomised trial but we excluded it due to an ill-defined inclusion criterion of an acute respiratory infection (Mtango 1986).

Risk of bias in included studies

Figure 2 and Figure 3 provide graphical summaries of the 'Risk of bias' assessment for the 10 included studies. As an aggregate body of evidence, we assessed the studies in both comparison 1 and comparison 2 to have an overall low risk of bias.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
AFRINEST(1) 2015	+	+	+	+	+	+	-
AFRINEST(2) 2015	+	+	+	+	+	+	-
Baqui 2008	+	+	+	?	+	+	-
Baqui 2015	+	+	+	+	+	+	-
Bhandari 2012	+	+	+	+	+	+	+
Degefe 2017	?	+	+	+	+	+	?
Gill 2011	-	+	+	?	+	+	+
Mir 2017	+	+	+	-	+	+	+
Soofi 2017	+	+	+	+	+	+	+
Zaidi 2012	+	+	+	-	+	+	-

Figure 3. (Continued)

Allocation

Comparison 1

All of the included studies were cluster-randomised trials and therefore all clusters were allocated at the same time (Baqui 2008; Bhandari 2012; Degefe 2017; Gill 2011; Soofi 2017). Three of the studies provided adequate explanation of their method for random sequence generation and we deemed them to be at low risk of bias (Baqui 2008; Bhandari 2012; Soofi 2017). Degefe 2017 did not describe the method for random sequence generation and we therefore deemed it to be of unclear risk. We assessed Gill 2011 as being at high risk for selection bias given that after randomisation, the study later added seven clusters into the control group that were not part of the original randomisation. In all of the trials, all of the clusters were randomised at the same time, which eliminates concern for lack of allocation concealment (Baqui 2008; Gill 2011; Bhandari 2012; Degefe 2017; Soofi 2017).

Comparison 2

All of the included studies used computer-generated random numbers to randomly assign individual participants (AFRINest(1) 2015; AFRINest(2) 2015; Baqui 2015; Mir 2017; Zaidi 2012). In addition, all of the studies used sealed, opaque envelopes to conceal allocation. Therefore, we deemed all studies to have a low risk of selection bias.

Blinding

Comparison 1

Given the nature of the interventions, it was not possible to blind the participants or the CHWs administering the intervention and would be unethical to give placebo injections to participants in the control arm. It was deemed that the outcomes were not likely to be influenced by the lack of blinding. Therefore, we deemed all studies to be at low risk of performance bias (Baqui 2008; Bhandari 2012; Degefe 2017; Gill 2011; Soofi 2017). In regards to detection bias, two of the studies did not report whether the outcome assessors were blinded and we deemed them to have an unclear risk (Baqui 2008; Gill 2011). We assessed the remaining three studies as low risk for detection bias given that they adequately blinded the outcome assessors (Bhandari 2012; Degefe 2017; Soofi 2017).

Comparison 2

Given the nature of the interventions, it was not possible to blind the participants or the personnel administering the intervention. It was deemed that the outcome was not likely to be influenced by the lack of blinding. Therefore, we deemed all studies to be at low risk of performance bias (AFRINest(1) 2015; AFRINest(2) 2015; Baqui 2015; Mir 2017; Zaidi 2012). Two of the studies ensured that the outcome assessment nurse was unaware of the participant's treatment allocation, leading to a low risk of detection bias (AFRINest(1) 2015; AFRINest(2) 2015). We deemed two studies to have a high risk of detection bias because the physicians who delivered the intervention were also responsible for being the

primary assessors of the outcome (Mir 2017; Zaidi 2012). In Baqui 2015, the primary assessor was not blinded but the clinic-based second physician was blinded to the intervention and we therefore deemed the study to be at low risk of detection bias.

Incomplete outcome data

Comparison 1

All of the studies had incomplete outcome data, however the attrition rates were similar in both the control and intervention arms in all studies (Baqui 2008; Gill 2011; Bhandari 2012; Degefe 2017; Soofi 2017). Therefore, we deemed all studies to have a low risk of attrition bias. It is worth noting that Degefe 2017 had incomplete monitoring of treatment adherence that only affected the intervention arm. However, this data did not affect the primary outcome of all-cause neonatal mortality and was therefore viewed as being irrelevant for bias concerns related to the primary analysis.

Comparison 2

All of the studies reported their incomplete outcome data (AFRINest(1) 2015; AFRINest(2) 2015; Baqui 2015; Mir 2017; Zaidi 2012). While there was differential attrition in Zaidi 2012 and AFRINest(2) 2015, the attrition rate was still 10% or less in each arm. The other three studies also had attrition rates of 10% or less in each arm with similar attrition rates between arms (AFRINest(1) 2015; Baqui 2015; Mir 2017). Attrition rates were secondary to protocol non-adherence or loss to follow-up. Therefore, we deemed all studies to be at low risk of attrition bias.

Selective reporting

Comparison 1

All of the trials were registered with a clinical trials registry and reported the outcomes identified in the study protocols (Baqui 2008; Bhandari 2012; Degefe 2017; Gill 2011; Soofi 2017). Therefore, we assessed these trials as having a low risk of reporting bias.

Comparison 2

All of the trials were registered with a clinical trials registry and reported the outcomes identified in the study protocols (AFRINest(1) 2015; AFRINest(2) 2015; Baqui 2015; Mir 2017; Zaidi 2012). Therefore, we assessed all trials as having a low risk of reporting bias.

Other potential sources of bias

Comparison 1

Contamination bias is another form of bias that is especially relevant for community-based, cluster-randomised controlled studies. Contamination bias occurs when members of the control group end up being exposed to the intervention. Baqui 2008 acknowledges the likelihood of contamination given that there seemed to be improved newborn care in the control areas and we deemed it to be at high risk for contamination. Bhandari 2012, Gill 2011 and Soofi 2017 report a low likelihood of contamination given

the nature of the organization of CHWs in their trials. [Degefie 2017](#) did not address the possibility of contamination and therefore has an unclear risk of contamination bias.

Comparison 2

Response bias, or the tendency for respondents to answer untruthfully, deserves to be assessed in these studies given the potential difference in methods for treatment adherence across arms. In [AFRINEST\(1\) 2015](#), [AFRINEST\(2\) 2015](#), [Baqui 2015](#) and [Zaidi 2012](#) all injectable medications were delivered by study personnel, but some or all doses of oral medications were administered by caregivers and adherence was based on caregiver report. Given that these studies performed per protocol analysis, there is a high risk of responder bias affecting only the arms in which oral medications were administered. We deemed [Mir 2017](#) to be at low risk of responder bias given that all doses of both oral and injectable medications were administered by health providers.

Effects of interventions

See: **Summary of findings for the main comparison** Comparison 1: community-based antibiotic delivery compared to standard care for the management of neonatal possible serious bacterial infection; **Summary of findings 2** Comparison 1: referral or full course of antibiotics compared to standard care for health problem or population; **Summary of findings 3** Comparison 1: route of antibiotic compared to standard care for the management of neonatal sepsis; **Summary of findings 4** Comparison 1: antibiotic alone or antibiotic with other newborn care interventions compared to standard care for the management of neonatal sepsis; **Summary of findings 5** Comparison 2: any simplified antibiotic

regimen compared to the standard antibiotic regimen (7 days injectable benzylpenicillin + injectable gentamicin); **Summary of findings 6** Comparison 2: 7 days oral amoxicillin + injectable gentamicin compared to 7 days injectable benzylpenicillin + injectable gentamicin; **Summary of findings 7** Comparison 2: 2 days injectable benzylpenicillin + injectable gentamicin followed by 5 days oral amoxicillin compared to 7 days injectable benzylpenicillin + injectable gentamicin; **Summary of findings 8** Comparison 2: 2 days oral amoxicillin + injectable gentamicin followed by 5 days oral amoxicillin compared to 7 days injectable benzylpenicillin + injectable gentamicin; **Summary of findings 9** Comparison 2: 7 days oral amoxicillin compared to 7 days injectable benzylpenicillin + injectable gentamicin for fast breathing alone

Comparison 1

Primary outcomes

Neonatal mortality

Five of the studies assessed neonatal mortality ([Baqui 2008](#); [Bhandari 2012](#); [Degefie 2017](#); [Gill 2011](#); [Soofi 2017](#)). Community-based antibiotic delivery for possible serious bacterial infection (PSBI) in neonates showed a possible effect on reducing neonatal mortality (typical risk ratio (RR) 0.82, 95% confidence interval (CI) 0.68 to 0.99; 5 studies, $n = 125,134$; random-effects, low-quality evidence). There was a high level of heterogeneity ($\text{Tau}^2 = 0.03$, $I^2 = 87\%$, $P < 0.0001$). We downgraded the evidence to low quality due to the high level of inconsistency across studies and indirectness of the evidence given that four of the studies tested an intervention much broader than the review question ([Analysis 1.1](#); [Figure 4](#); [Summary of findings for the main comparison](#)).

Figure 4. Forest plot of comparison: 1 Comparison 1: Full comparison (no subgroup), outcome: 1.1 Neonatal mortality.

Based on the high level of heterogeneity, we performed prespecified subgroup analyses. First, we performed a subgroup analysis based on antibiotic length. Specifically, we divided the studies into those that would provide a full course (7 to 10 days) of community-based antibiotics if hospital referral was refused and those studies that would only provide one dose of community-based antibiotics even if hospital referral was refused. Four of the five included studies provided a complete course of antibiotics if hospital referral was not possible ([Baqui 2008](#); [Bhandari 2012](#); [Degefie 2017](#); [Soofi 2017](#)). When analysis was limited to these four studies, there was no effect of community-based antibiotic delivery for PSBI (typical RR 0.87, 95% CI 0.72 to 1.04; 4 studies, $n = 121,779$; random-effects, very low-quality evidence) and heterogeneity remained high ($\text{Tau}^2 = 0.03$, $I^2 = 88\%$, $P < 0.01$). We rated this as very low-quality evidence due to a high level of heterogeneity as well as

due to the indirectness of the evidence ([Analysis 2.1](#); [Summary of findings 2](#)).

A second prespecified subgroup analysis partitioned studies into whether the antibiotics were injectable or oral. [Gill 2011](#) and [Soofi 2017](#) provided oral amoxicillin and found a possible reduction in neonatal mortality (typical RR 0.70, 95% CI 0.54 to 0.90; 2 studies, $n = 40,223$; random-effects, low-quality evidence) with a moderate level of heterogeneity ($\text{Tau}^2 = 0.02$, $I^2 = 52\%$, $P = 0.15$). [Baqui 2015](#) provided only injectable antibiotics and found a reduction on neonatal mortality (RR 0.67, 95% CI 0.51 to 0.88; 1 study, $n = 5684$; random-effects, moderate-quality evidence). [Bhandari 2012](#) and [Degefie 2017](#) provided a combination of injectable antibiotics and oral antibiotics and did not find a reduction in neonatal mortality

(RR 0.99, 95% CI 0.92 to 1.06; 2 studies, $n = 79,227$; random-effects, moderate-quality evidence; [Analysis 3.1](#); [Summary of findings 3](#)).

Four of the studies offered co-interventions, such as basic neonatal resuscitation, that may have influenced overall neonatal mortality ([Baqui 2008](#); [Bhandari 2012](#); [Gill 2011](#); [Soofi 2017](#)). Details regarding the specifics of co-interventions included in a trial's intervention arm but not the control arm are described in [Table 1](#). [Degefie 2017](#) was the only study that did not include co-interventions, and this study did not find an effect of community-based antibiotic delivery for PSBI on neonatal mortality (RR 1.07, 95% CI 0.89 to 1.29; 1 study, $n = 18,747$; random-effects, moderate-quality evidence). We downgraded [Degefie 2017](#) from high to moderate quality due to a wide 95% confidence interval. The studies that included co-interventions showed a possible reduction in neonatal mortality (typical RR 0.76, 95% CI 0.62 to 0.94; 4 studies, $n = 106,387$; random-effects, moderate-quality evidence; [Analysis 4.1](#); [Summary of findings 4](#)).

We planned the following subgroup analyses for comparison 1, but did not perform them for the indicated reasons.

1. Method of diagnosis - all trials used clinical diagnoses to establish infection.
2. Antibiotic class - all of the trials included in the meta-analyses administered either amoxicillin or benzylpenicillin as monotherapy or combined with an aminoglycoside. While both amoxicillin and benzylpenicillin fall into the penicillin class, they have different degrees of effectiveness and require different skills for administration. Therefore, subgroup analysis by antibiotic class had minimal clinical or public health relevance in the current review and was omitted.
3. Administrator of antibiotics - all trials either relied on a community health worker (CHW) to administer the antibiotics or did not specify the administrator of the antibiotic.
4. Location of antibiotic administration - given that healthcare workers administered all antibiotics, the location of administration (i.e. clinic versus home) likely had no clinical significance.

Comparing community-based antibiotics to standard care of referral to a health facility necessitates knowing how many families residing in the control clusters brought their sick neonates to a health facility either following a referral or independently. However, none of the five studies reported the number of neonates with PSBI in the control arm who were successfully referred to a health facility ([Baqui 2008](#); [Bhandari 2012](#); [Degefie 2017](#); [Gill 2011](#); [Soofi 2017](#)). To further understand the effect of community-based antibiotics, it is also helpful to know the number of neonates with PSBI in the intervention arm whose families accepted community-based antibiotics. In [Baqui 2008](#), 42% of neonates with PSBI in the

intervention arm were treated with community-based antibiotics while 32% accepted referral to a health facility. [Degefie 2017](#) and [Gill 2011](#) reported that over 90% of neonates with PSBI in the intervention arm were treated with community-based antibiotics. [Soofi 2017](#) reported that 16% of neonates with PSBI in the intervention arm were treated with community-based antibiotics; [Bhandari 2012](#) did not assess the number of neonates receiving community-based antibiotics.

Early neonatal mortality

Two studies assessed neonatal mortality within the first week of life ([Gill 2011](#); [Soofi 2017](#)). Community-based antibiotic delivery for PSBI in neonates showed a possible effect on reducing early neonatal mortality (typical RR 0.74, 95% CI 0.65 to 0.85; 2 studies, $n = 40,299$; random-effects, moderate-quality evidence). We identified a low level of heterogeneity ($I^2 = 10\%$, $P = 0.29$), although the small size of the meta-analysis may be inadequate to accurately measure heterogeneity. We downgraded the evidence from high to moderate quality due to the indirectness of evidence, given that the interventions studied were more comprehensive than the intervention in the review question ([Analysis 1.2](#); [Summary of findings for the main comparison](#)).

Late neonatal mortality

Two studies assessed neonatal mortality after the first week of life ([Gill 2011](#); [Soofi 2017](#)). Community-based antibiotic delivery for PSBI in neonates showed a possible effect on reducing late neonatal mortality (typical RR 0.73, 95% CI 0.55 to 0.96; 2 studies, $n = 40,142$; random-effects, moderate-quality evidence). We identified a low level of heterogeneity ($I^2 = 7\%$, $P = 0.30$) although the small size of the meta-analysis may be inadequate to accurately measure heterogeneity. We downgraded the evidence from high to moderate quality due to the indirectness of evidence, given that the interventions studied were more comprehensive than the intervention in the review question ([Analysis 1.3](#); [Summary of findings for the main comparison](#)).

Sepsis-specific mortality

Two studies assessed sepsis-specific mortality ([Gill 2011](#); [Soofi 2017](#)). Community-based antibiotic delivery for PSBI in neonates showed a possible effect on reducing sepsis-specific mortality (typical RR 0.78, 95% CI 0.60 to 1.00; 2 studies, $n = 40,233$; random-effects, low-quality evidence). We did not identify any heterogeneity ($I^2 = 0\%$, $P = 0.84$) although the small size of the meta-analysis may be inadequate to accurately measure heterogeneity. We downgraded evidence from high quality to low quality due to a wide 95% confidence interval and indirectness of evidence, given that the interventions studied were more comprehensive than the intervention in the review question ([Analysis 1.4](#); [Figure 5](#); [Summary of findings for the main comparison](#)).

Figure 5. Forest plot of comparison: 1 Full Comparison (No subgroup), outcome: 1.4 Sepsis-Specific Neonatal Mortality.

Secondary outcomes

None of the planned secondary outcomes were reported by the studies included in comparison 1.

Comparison 2

Primary outcomes

Neonatal mortality

Four of the five studies provided disaggregated neonatal data to assess neonatal mortality (AFRINEST(1) 2015; AFRINEST(2) 2015; Baqui 2015; Mir 2017). However, we excluded AFRINEST(2) 2015 from the primary meta-analysis, given that the study limited their participants to neonates who had fast breathing only and excluded neonates with other signs of PSBI. Each trial studied more than

one simplified antibiotic regimen, and every trial compared each simplified regimen to the study's control regimen. To examine the overall effects of a simplified, antibiotic approach, data from each intervention arm was initially aggregated and compared against the study's control arm. There was no difference in neonatal mortality when simplified, community-based treatment that combined oral and injectable antibiotics was compared to the standard regimen of injectable antibiotics (benzylpenicillin and gentamicin) only (typical RR 0.81, 95% CI 0.44 to 1.50; 3 studies, $n = 3476$; random-effects, moderate-quality evidence). We identified a low level of statistical heterogeneity ($I^2 = 33$, $P = 0.22$). We downgraded the evidence from high to moderate quality due to imprecision of results given the wide 95% confidence interval (Analysis 5.1; Figure 6; Summary of findings 5).

Figure 6. Forest plot of comparison: 5 Comparison 2: Simplified antibiotic regimen compared to standard antibiotic regime, outcome: 5.1 Neonatal mortality.

We then performed subgroup analyses based on the type of simplified, antibiotic regimen used in each intervention arm. Three studies provided disaggregated neonatal data to assess neonatal mortality when the simplified regimen of seven days of oral amoxicillin and injectable gentamicin was compared to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin for the treatment of PSBI (AFRINEST(1) 2015; Baqui 2015; Mir 2017). We did not find any difference in neonatal mortality for this comparison (typical RR 0.84, 95% CI 0.47 to 1.51; 3 studies, $n = 2001$; random-effects, moderate-quality evidence). We did not identify any statistical heterogeneity ($I^2 = 0\%$, $P = 0.65$). We downgraded the evidence from high to moderate quality due to imprecision of results given the wide 95% confidence interval (Analysis 6.1; Summary of findings 6).

Three studies examined neonatal mortality when the simplified regimen of two days of injectable gentamicin and injectable benzylpenicillin followed by five days of oral amoxicillin was compared to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin for the treatment of PSBI (AFRINEST(1) 2015; Baqui 2015; Mir 2017). We did not find any difference in neonatal mortality for this comparison (typical

RR 0.88, 95% CI 0.29 to 2.65; 3 studies, $n = 2036$; random-effects, low-quality evidence). There was a substantial level of statistical heterogeneity between studies ($I^2 = 67\%$, $P = 0.05$). We assessed the evidence as being of low quality due to imprecision and inconsistency among studies (Analysis 7.1; Summary of findings 7).

One study examined neonatal mortality when the simplified regimen of two days of injectable gentamicin and oral amoxicillin followed by five days of oral amoxicillin was compared to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin for the treatment of PSBI (AFRINEST(1) 2015). We did not find any difference in neonatal mortality for this comparison (RR 0.67, 95% CI 0.24 to 1.85; 1 study, $n = 893$, moderate-quality evidence). We downgraded the study to moderate quality due to imprecision of results given the wide 95% confidence interval (Analysis 8.1; Summary of findings 8).

We examined AFRINEST(2) 2015 separately, given that the study limited their inclusion criteria to neonates who had fast breathing only and excluded neonates with other signs of PSBI. We did not find any difference in neonatal mortality when the simplified regimen of seven days of oral amoxicillin was compared to the standard regimen of seven days of injectable benzylpenicillin and

injectable gentamicin (RR 0.99, 95% CI 0.20 to 4.91; 1 study, n = 1406, low-quality evidence). We downgraded the study to low quality due to imprecision of results (given the wide 95% confidence interval) and indirectness of evidence (given that the study population of neonates with fast breathing is a restricted version of the target population in the review question) ([Analysis 9.1](#); [Summary of findings 9](#)).

[Zaidi 2012](#) examined mortality for neonates and infants aged 0 to 59 days when the simplified regimen of seven days of injectable ceftriaxone was compared to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin for the treatment of PSBI. We did not find any difference in mortality for neonates and infants aged 0 to 59 days, but disaggregated neonatal data were not available. This study also compared the simplified regimen of seven days of injectable gentamicin and oral trimethoprim-sulphamethoxazole to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin. Again, we did not find any difference in mortality, but disaggregated neonatal data were not available.

We planned the following subgroup analyses for comparison 2, but did not perform them for the indicated reasons.

1. Method of diagnosis - all trials used clinical diagnoses to establish infection.
2. Duration of antibiotic - all trials used a seven day course.
3. Administrator of antibiotic - subgroup analysis was unable to be performed because each trial relied on more than one type of administrator to deliver the intervention. In addition, two of the trials ([AFRINEST\(1\) 2015](#); [AFRINEST\(2\) 2015](#)) had multiple study sites with different types of administrators but outcome data were not stratified by study site.
4. Location of antibiotic administration - subgroup analysis was unable to be performed because each trial except for [Baqui 2015](#) relied on more than one type of location for antibiotic administration. In addition, two of the trials had multiple study sites with different types of locations for antibiotic administration ([AFRINEST\(1\) 2015](#); [AFRINEST\(2\) 2015](#)), but outcome data were not stratified by study site.

Moreover, we did not identify any significant heterogeneity between the studies included in comparison 2 that merited subgroup analysis.

Early neonatal mortality

None of the studies provided data on early neonatal mortality.

Late neonatal mortality

None of the studies provided data on late neonatal mortality.

Sepsis-specific neonatal mortality

None of the studies provided data on sepsis-specific neonatal mortality.

Secondary outcomes

Treatment failure

Four of the five studies provided disaggregated neonatal data to assess treatment failure ([AFRINEST\(1\) 2015](#); [AFRINEST\(2\) 2015](#); [Baqui 2015](#); [Mir 2017](#)). However, we excluded [AFRINEST\(2\) 2015](#) from the meta-analysis, given that the study limited their

participants to neonates who had fast breathing only and excluded neonates with other signs of PSBI. There was no difference in treatment failure when simplified, community-based treatment that combined oral and injectable antibiotics was compared to the standard regimen of injectable antibiotics (benzylpenicillin and gentamicin) only (typical RR 0.86, 95% CI 0.67 to 1.10; 3 studies, n = 3476; random-effects, moderate-quality evidence). We did not identify any statistical heterogeneity ($I^2 = 0$, $P = 0.84$). We downgraded the evidence from high to moderate quality due to imprecision of results given the wide 95% confidence interval ([Analysis 5.2](#); [Summary of findings 5](#)).

We then performed subgroup analyses based on the type of simplified, antibiotic regimen used in each intervention arm. Three trials studied the outcome of treatment failure when the simplified regimen of seven days of oral amoxicillin and injectable gentamicin was compared to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin for the treatment of neonatal PSBI ([AFRINEST\(1\) 2015](#); [Baqui 2015](#); [Mir 2017](#)). We did not find any difference in treatment failure for this comparison (typical RR 0.82, 95% CI 0.60 to 1.11; 3 studies, n = 2001; random-effects, moderate-quality evidence). We did not identify any statistical heterogeneity ($I^2 = 0\%$, $P = 0.82$; [Analysis 6.2](#); [Summary of findings 6](#)).

Three studies examined the outcome of treatment failure when the simplified regimen of two days of injectable gentamicin and injectable benzylpenicillin followed by five days of oral amoxicillin was compared to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin for the treatment of neonatal PSBI ([AFRINEST\(1\) 2015](#); [Baqui 2015](#); [Mir 2017](#)). We did not find any difference in treatment failure for this comparison (typical RR 0.93, 95% CI 0.70 to 1.25; 3 studies, n = 2036; random-effects, moderate-quality evidence). There was no statistical heterogeneity between studies ($I^2 = 0\%$, $P = 0.66$; [Analysis 7.2](#); [Summary of findings 7](#)).

One study examined the outcome of treatment failure when the simplified regimen of two days of injectable gentamicin and oral amoxicillin followed by five days of oral amoxicillin was compared to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin for the treatment of neonatal PSBI ([AFRINEST\(1\) 2015](#)). We did not find any difference in treatment failure for this comparison (RR 0.65, 95% CI 0.34 to 1.13; 1 study, n = 893; moderate-quality evidence; [Analysis 8.1](#); [Summary of findings 8](#)).

We examined [AFRINEST\(2\) 2015](#) separately, given that the study limited their inclusion criteria to neonates who had fast breathing only and excluded neonates with other signs of PSBI. We did not find a difference in treatment failure when the simplified regimen of seven days of oral amoxicillin was compared to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin (RR 0.83, 95% CI 0.68 to 1.07; 1 study, n = 1406; low-quality evidence; [Analysis 9.2](#); [Summary of findings 9](#)).

[Zaidi 2012](#) examined treatment failure for neonates and infants aged 0 to 59 days when the simplified regimen of seven days of injectable ceftriaxone was compared to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin for the treatment of PSBI. We did not find any statistical difference in treatment for neonates and infants aged 0 to 59 days, but there was a trend toward higher failure rates with ceftriaxone. Disaggregated

neonatal data were not available. This study also compared the simplified regimen of seven days of injectable gentamicin and oral trimethoprim-sulphamethoxazole to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin. Neonates and infants aged 0 to 59 days who received seven days of injectable gentamicin and oral trimethoprim-sulphamethoxazole had higher treatment failure rates, but disaggregated neonatal data were not available.

Adverse events

Four of the five studies provided disaggregated neonatal data to assess treatment failure ([AFRINEST\(1\) 2015](#); [AFRINEST\(2\) 2015](#); [Baqui 2015](#); [Mir 2017](#)). However, we excluded [AFRINEST\(2\) 2015](#) from the meta-analysis, given that the study limited their participants to neonates who had fast breathing only and excluded neonates with other signs of PSBI. There was no difference in treatment failure when simplified, community-based treatment that combined oral and injectable antibiotics was compared to the standard regimen of injectable antibiotics (benzylpenicillin and gentamicin) only (typical RR 1.38, 95% CI 0.79 to 2.41; 3 studies, $n = 3476$; random-effects, moderate-quality evidence). We did not identify any statistical heterogeneity ($I^2 = 0$, $P = 0.32$). We downgraded the evidence from high to moderate quality due to imprecision of results given the wide 95% confidence interval ([Analysis 5.3](#); [Summary of findings 5](#)).

We then performed subgroup analyses based on the type of simplified, antibiotic regimen used in each intervention arm. Three trials studied the outcome of non-fatal adverse events when the simplified regimen of seven days of oral amoxicillin and injectable gentamicin was compared to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin for the treatment of neonatal PSBI ([AFRINEST\(1\) 2015](#); [Baqui 2015](#); [Mir 2017](#)). We did not find any difference in adverse events for this comparison (typical RR 1.35, 95% CI 0.72 to 2.53; 3 studies, $n = 2001$; random-effects, moderate-quality evidence). We did not identify any statistical heterogeneity ($I^2 = 0\%$, $P = 0.54$; [Analysis 6.3](#); [Summary of findings 6](#)).

Three studies examined the outcome of non-fatal adverse events when the simplified regimen of two days of injectable gentamicin and injectable benzylpenicillin followed by five days of oral amoxicillin was compared to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin for the treatment of neonatal PSBI ([AFRINEST\(1\) 2015](#); [Baqui 2015](#); [Mir 2017](#)). We did not find any difference in adverse events for this comparison (typical RR 1.39, 95% CI 0.67 to 2.87; 3 studies, $n = 2036$; random-effects, moderate-quality evidence). There was a low level of statistical heterogeneity between studies ($I^2 = 20\%$, $P = 0.26$; [Analysis 7.3](#); [Summary of findings 7](#)).

One study of high quality examined the outcome of non-fatal adverse events when the simplified regimen of two days of injectable gentamicin and oral amoxicillin followed by five days of oral amoxicillin was compared to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin for the treatment of neonatal PSBI ([AFRINEST\(1\) 2015](#)). There were no reported adverse events for neonates who received either the simplified regimen or the standard regimen ([Analysis 8.3](#); [Summary of findings 8](#)).

We examined [AFRINEST\(2\) 2015](#) separately, given that the study limited their inclusion criteria to neonates who had fast breathing only and excluded neonates with other signs of PSBI. There were no reported adverse events for neonates who received the simplified regimen or the standard regimen ([Analysis 9.3](#); [Summary of findings 9](#)).

[Zaidi 2012](#) examined non-fatal adverse events for neonates and infants aged 0 to 59 days when the simplified regimen of seven days of injectable ceftriaxone was compared to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin for the treatment of PSBI. There were no reported adverse events for neonates and infants aged 0 to 59 days who received the simplified regimen or the standard regimen, but disaggregated neonatal data were not available. This study also compared the simplified regimen of seven days of injectable gentamicin and oral trimethoprim-sulphamethoxazole to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin. Again, there were no reported adverse events for neonates and infants aged 0 to 59 days who received the simplified regimen or the standard regimen, but disaggregated neonatal data were not available.

Other secondary outcomes

None of the trials included in comparison 2 included data regarding cost, acceptability or antibiotic resistance.

DISCUSSION

Summary of main results

Comparison 1

We identified five cluster-randomised controlled trials (RCTs) evaluating the effectiveness of initiating community-based antibiotic delivery for neonatal possible serious bacterial infection (PSBI) in low- and middle-income countries (LMICs) ([Baqui 2008](#); [Bhandari 2012](#); [Degefie 2017](#); [Gill 2011](#); [Soofi 2017](#)). All of the studies included disaggregated neonatal data and were therefore included in the meta-analyses. The delivery of antibiotics in the community for neonates with PSBI showed a reduction in neonatal mortality compared to the standard hospital referral, although the evidence was of low quality. We downgraded the quality of evidence due to a high level of statistical heterogeneity and indirectness of the evidence, given that many of the trials included co-interventions in addition to the community-based antibiotics. The significant level of heterogeneity may be related to the differing antibiotic regimens, the various cointerventions that many of the studies offered, or both. Only one study did not offer any cointerventions, and this study did not find any change in neonatal mortality with community-based antibiotics for neonatal PSBI ([Degefie 2017](#)).

To isolate the effects of antibiotics from the other cointerventions, it is useful to examine the difference in neonatal mortality from sepsis. We found a potential reduction in sepsis-specific mortality. However, only two studies reported sepsis-specific mortality ([Gill 2011](#); [Soofi 2017](#)), and only one of these studies included provided a full course of antibiotics for neonatal PSBI ([Soofi 2017](#)).

Globally, infection is the leading cause of late neonatal mortality, whereas early neonatal mortality is more commonly the result of preterm birth or intrapartum complications ([Oza 2015](#)). Therefore, we hypothesised that community-based antibiotic delivery for

neonatal PSBI would result in a reduction in late neonatal mortality but not early neonatal mortality. Our review found a possible reduction in both early and late neonatal mortality. However, these findings should be viewed with caution as only two studies reported this outcome (Gill 2011; Soofi 2017). In addition, both studies included cointerventions, such as immediate newborn care by community health workers (CHWs), that may have influenced the findings.

Comparison 2

We identified five RCTs evaluating community-based delivery of simplified antibiotic regimens compared to community-based delivery of the standard regimen of injectable benzylpenicillin and injectable gentamicin for the treatment of neonatal PSBI in LMIC (AFRINEST(1) 2015; AFRINEST(2) 2015; Baqui 2015; Mir 2017; Zaidi 2012). All five RCTs included neonates and infants aged 0 to 59 days. Only four of the RCTs provided us with disaggregated neonatal data and were included in the meta-analyses.

Overall, a simplified approach to community-based antibiotics in which regimens rely more on oral antibiotics and less on injectable antibiotics did not find any significant differences in neonatal mortality, treatment failure or adverse events when compared to the standard regimen of seven days of injectable antibiotics only. This result was based on the findings of three studies, and the evidence was of moderate quality.

We then performed subgroup analyses based on the type of simplified, antibiotic regimen studied. The simplified regimen of seven days of oral amoxicillin and injectable gentamicin resulted in the similar rates of neonatal mortality, treatment failure and adverse events when compared to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin for the treatment of neonatal PSBI in LMICs. This result was based on the findings of three studies, and the evidence was of moderate quality.

The simplified regimen of two days of injectable benzylpenicillin and injectable gentamicin followed by five days of oral amoxicillin resulted in similar rates of neonatal mortality, treatment failure and adverse events when compared to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin for the treatment of neonatal PSBI in LMICs. This result was based on the findings of three studies, and the evidence was of low to moderate quality. When assessing the primary outcome of mortality, there was a substantial amount of statistical heterogeneity, reflecting the fact that Baqui 2015 found the simplified regimen to reduce the risk of neonatal mortality, whereas AFRINEST(1) 2015 and Mir 2017 found similar mortality rates for neonates who received the simplified regimen compared to the standard regimen. Given the underlying reason for the statistical heterogeneity, its finding should not detract from the interpretation that the simplified regimen did not result in higher rates of neonatal mortality compared to the standard regimen. Otherwise, the three studies had minimal clinical and methodological heterogeneity.

The simplified regimen of two days of injectable gentamicin and oral amoxicillin followed by five days of oral amoxicillin resulted in similar rates of neonatal, mortality, treatment failure and adverse events when compared to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin for the treatment of neonatal PSBI in LMICs. However, this finding was based on only one study which was of moderate quality.

One study examined a simplified regimen to treat fast breathing, which is one sign of PSBI (AFRINEST(2) 2015). This study found that the simplified regimen of seven days of oral amoxicillin resulted in similar rates of neonatal mortality, treatment failure and adverse events when compared to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin for the treatment of fast breathing in LMICs. This study was of low-quality evidence.

Zaidi 2012 met the inclusion criteria but the study included participants aged 0 to 59 days and disaggregated neonatal data were not available. For the simplified regimen of seven days of injectable ceftriaxone, this study found no difference in mortality, a trend towards higher rates of treatment failure and no difference in adverse events when compared to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin. For the simplified regimen of seven days of injectable gentamicin and oral trimethoprim-sulphamethoxazole, this study found no difference in mortality, higher rates of treatment failure and no difference in adverse events when compared to the standard regimen of seven days of injectable benzylpenicillin and injectable gentamicin.

Overall completeness and applicability of evidence

Comparison 1

Each study occurred in a different country within sub-Saharan Africa and South Asia, and all trials targeted communities with limited access to health facilities. In all of the studies, neonates were identified as having PSBI by CHWs or traditional birth attendants. While exact definitions of PSBI differed slightly between studies, all of the studies included easy-to-assess signs and symptoms related to feeding, breathing, state of consciousness and temperature. This method of diagnosis is highly applicable to low-resource settings in which skilled medical professionals and laboratory tests are often unavailable.

Two of the trials administered community-based injectable benzylpenicillin and injectable gentamicin for neonates with PSBI (Baqui 2008; Bhandari 2012), which is the same antibiotic regimen that the World Health Organization (WHO) recommends for neonates who are hospitalised with infection (WHO 2013). The remaining trials use various simplified antibiotic regimens. The one trial that administered the simplified antibiotic regimen endorsed by the 2015 WHO guidelines for community-based treatment of neonatal PSBI without any other cointerventions, did not find a reduction in neonatal mortality (Degefie 2017).

All of the studies included in the meta-analyses measured neonatal mortality as a primary outcome, but only two of the included studies measure sepsis-specific neonatal mortality. Given that most of the studies included cointerventions, the absence of sepsis-specific mortality measurements make it difficult to determine whether any reductions in neonatal mortality can be attributed to the introduction of community-based antibiotics for neonatal PSBI. Moreover, by virtue of the intervention, neonates living in the intervention cluster underwent higher levels of surveillance compared to those living in control clusters, making it impossible to discern if the measured effect is a result of community-based treatment of neonatal PSBI or simply a result of increased surveillance. Finally, none of the studies examined balancing

measures, such as adverse events or cost-effectiveness, which are important secondary outcomes to consider.

None of the studies assessed the number of neonates with PSBI who were successfully referred to a health facility in the control arm. Without this data, it is difficult to determine the reason behind any effect seen with the use of community-based antibiotics. Theoretically, the positive effect of community-based antibiotics is due to the failure of successful referral in LMICs as opposed to inadequate care in a health facility, but the evidence to confirm this relationship was not available.

Comparison 2

All of the studies were conducted in low-resource communities within sub-Saharan Africa and South Asia and relied only on standardised clinical criteria to establish a PSBI. All antibiotics were administered both at home and at nearby health clinics. All of the simplified regimens decreased the total number of injections the neonate would require and relied more on oral antibiotics in order to ease the treatment burden for both families and providers. Together, this methodology is very relevant to LMIC where sick neonates may go untreated because referral to an inpatient health facility is not feasible.

Nevertheless, all of the included studies were conducted under ideal conditions. Neonates in both the intervention and control arms were under higher levels of surveillance than typical for neonates residing in the study region. Physicians or nurses made the diagnosis of neonatal PSBI and administered the injectable antibiotics. In addition, the participants were monitored closely for evidence of treatment failure. These study conditions leave open the question of the results' external validity. The vast majority of LMICs that would take advantage of a simplified antibiotic regimen to treat neonatal PSBI in the community would rely on CHWs to enact surveillance for PSBI, diagnose PSBI and administer the treatment, rather than physicians or nurses. Moreover, these communities would likely not have the resources to track patients' responses in the detailed manner that was done in the trials. Because fewer resources are available in real-world settings compared to the trials' settings, the applicability of the results should be interpreted with caution.

Quality of the evidence

We assessed the quality of evidence included in this review using the GRADE criteria (Schünemann 2013).

Comparison 1

As an aggregate, the studies had an overall low risk of bias in both study design and implementation.

The quality of evidence used to assess neonatal mortality when comparing community-based antibiotics provided to neonates with PSBI to the standard hospital referral was low (Summary of findings for the main comparison). We downgraded the evidence due to a high level of heterogeneity and indirectness of the evidence. Given the low-quality evidence, the true effect of community-based antibiotics on neonatal mortality may be substantially different from the estimate of effect.

The evidence used to estimate sepsis-specific mortality, early neonatal mortality and late neonatal mortality was of low quality, and it should be noted that only two studies reported each of these

outcome measures (Gill 2011; Soofi 2017). We downgraded the evidence due to a wide confidence interval and the indirectness of evidence. Of these two studies, Soofi 2017 had a sample size more than seven times as large as Gill 2011, implying that the estimate of effect is primarily drawn from one study.

In the subgroup analysis separating antibiotic duration, we deemed the evidence to be of very low to low quality. We downgraded the evidence due to a high level of heterogeneity and indirectness of the evidence and we also downgraded the studies examining a full course of antibiotics for a wide confidence interval (Summary of findings 2). In the subgroup analysis examining the route of antibiotic administration, the evidence was of low to moderate quality (Summary of findings 3). We downgraded the evidence due to indirectness of evidence and the studies examining the delivery of oral antibiotics also had a high level of heterogeneity. In the subgroup analysis separating the studies with cointerventions, the evidence was of moderate quality. The evidence that included cointerventions had a high level of heterogeneity and the evidence without the use of cointerventions had a wide 95% confidence interval (Summary of findings 4).

Comparison 2

As an aggregate, the studies had an overall low risk of bias in both the study design and implementation. The quality of evidence examining the effect of using a simplified antibiotic approach compared to the standard approach in the community-treatment of neonatal PSBI was of moderate quality due to a wide 95% confidence interval (Summary of findings 5).

We then undertook a subgroup analysis based on the exact simplified antibiotic regimen. The quality of evidence used to compare the simplified antibiotic regimen of seven days of oral amoxicillin and injectable gentamicin to the standard regimen was of moderate quality due to a wide 95% confidence interval (Summary of findings 6). The quality of evidence used to compare the simplified antibiotic regimen of two days of injectable benzylpenicillin and injectable gentamicin followed by five days of oral amoxicillin to the standard regimen ranged from low to moderate quality due to heterogeneity and a wide confidence interval (Summary of findings 7). The evidence used to compare the simplified antibiotic regimen of two days of injectable gentamicin and oral amoxicillin followed by five days of oral amoxicillin to the standard regimen was of moderate to high quality due to a wide 95% confidence interval (Summary of findings 8). The evidence used to compare the simplified antibiotic regimen of seven days of oral amoxicillin to the standard regimen was of low quality (Summary of findings 9). We downgraded the evidence due to its indirectness, as the population of neonates with fast breathing is a restricted version of the population in the review question. We also downgraded the evidence due to a wide confidence interval.

Potential biases in the review process

Comparison 1

Zulfiqar A Bhutta (ZAB) is the senior author of this Cochrane Review and was also one of the authors of an included study (Soofi 2017). ZAB, however, was not among the review authors who selected the included studies or extracted the data for this review. He was consulted for any disagreements regarding data extraction and assessment, but no consultations were related to the data from Soofi 2017. We planned an a priori subgroup analysis for the

mortality outcome and the majority of the heterogeneity was found in neonatal mortality. Therefore, findings need to be interpreted with caution as the high level of heterogeneity may be related to methodological bias in the study designs. A number of subgroups showed significant statistical heterogeneity and the sources of this remain unclear.

Comparison 2

ZAB is the senior author of this Cochrane Review and was also one of the authors of an included study (Zaidi 2012). ZAB, however, was not one of the review authors who selected the included studies or extracted the data for this review. He was consulted for any disagreements regarding data extraction and assessment, but no consultations were related to the data from Zaidi 2012. Disaggregated neonatal data were not able to be extracted for Zaidi 2012. However, this study used simplified regimens that were unique from the regimens studied by the other trials. Therefore, the lack of the disaggregated data did not influence our analysis of the other simplified regimens.

Agreements and disagreements with other studies or reviews

Comparison 1

While not directly measured in the current Cochrane Review, the first step to reducing neonatal mortality from PSBI in a community-setting is ensuring an accurate diagnosis. Lee 2014 conducted a systematic review and meta-analysis of the ability of frontline healthcare workers, such as CHWs, to diagnosis PSBI in infants less than two months old. The authors found that compared to physicians, the frontline healthcare workers diagnosed PSBI with an average sensitivity of 82% (95% CI 76% to 88%) and specificity of 69% (95% CI 54% to 83%). Given that the risks of missing a PSBI are much greater than the risk of over treatment, the high sensitivity is reassuring and supports our findings that CHWs may be able to reduce neonatal mortality by treating PSBI in the community.

A 2011 review of community management for neonatal sepsis and pneumonia identified four non-RCTs that tested oral antibiotics for neonatal pneumonia. When analysed together, the authors found a reduction in both all-cause neonatal mortality and pneumonia-specific neonatal mortality (Zaidi 2011). While the clinical diagnosis of pneumonia falls under the scope of PSBI, the illness is usually less severe than more systemic forms of PSBI and therefore may be amenable to community-based oral antibiotics. When the authors analysed community-based antibiotics for neonatal sepsis, a systemic form of PSBI, they found a reduction in neonatal mortality in the one RCT and the one observational study that were included. However, this review was plagued by the same issues regarding the interpretation of the results as the current Cochrane Review, given the use of cointerventions in the included studies.

Comparison 2

The WHO's 2015 Guidelines for *Managing possible serious bacterial infection in young infants when referral is not feasible* includes a systematic review comparing various community-based antibiotic regimens for PSBI (WHO 2015). The review encompasses all infants aged 0 to 59 days and did not isolate neonates as the current review does. The WHO review examined all of the same studies

included in this Cochrane Review (AFRINEST(1) 2015; AFRINEST(2) 2015; Baqui 2015; Mir 2017; Zaidi 2012). The WHO reached similar mortality findings in their review for patients aged 0 to 59 days as we did in our review of only neonates. Based on their analysis, WHO guidelines conclude that there is a strong recommendation to use seven days of injectable gentamicin plus oral amoxicillin when treating infants with severe infection in the community, and this is based on moderate-quality evidence. An alternative regimen would be two days of injectable gentamicin and oral amoxicillin followed by five days of oral amoxicillin, but the quality of evidence is lower for this treatment. For infants with only fast breathing, the WHO makes a strong recommendation to use seven days of oral amoxicillin, and this is based on low-quality evidence.

AUTHORS' CONCLUSIONS

Implications for practice

Low quality data demonstrated that community-based antibiotics reduced neonatal mortality when compared to the standard hospital referral for neonatal PSBI in resource-limited settings. The use of cointerventions, however, prevent disentanglement of the contribution from community-based antibiotics. Moderate-quality evidence showed that simplified, community-based treatment of PSBI did not result in increased neonatal mortality when compared to the standard treatment of using only injectable antibiotics. Assessing the findings from both comparison 1 and comparison 2, it is reasonable to consider community-based antibiotics as an alternative treatment for neonatal PSBI in LMICs when hospital referral is not possible and adequate community-based monitoring is available. When treating neonatal PSBI in community-settings in LMICs, using a simplified, antibiotic regimen that combines both oral and injectable antibiotics is supported by the evidence. Ultimately, however, hospitalisation with parental antibiotics should remain the preferred treatment for neonatal PSBI due to the many limitations of the evidence presented in this review.

Implications for research

The efficacy of community-based, simplified antibiotics under ideal, trial conditions does not guarantee the effectiveness of such treatment for neonatal PSBI in real-world conditions of LMICs. Further implementation research is needed to verify whether community-based antibiotics can be scaled-up in LMICs, accepted by local communities and added to the ever-growing responsibilities of CHWs. Longer term, it will be important to study any changes in the pathogen landscape in LMICs following the introduction of community-based antibiotics for neonatal PSBI. The decentralisation of antibiotics has the potential to lead to the overuse or inappropriate use of antibiotics for non-bacterial serious illnesses, which could facilitate an increase in antibiotic resistance.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

AFRINEST(1) 2015

Methods	This study is an individually-randomised, multicentre, open-label equivalence trial conducted from 2011 to 2013. The study took place at five sites, one each in DR Congo and Kenya, and three in Nigeria (Ibadan, Ile-Ife, and Zaria). Community health workers identified cases of suspected neonatal sepsis which was confirmed by a treatment nurse. A treatment nurse at an outpatient health facility gave injections in DR Congo and Kenya, and a community health extension worker gave injections at the homes of enrolled infants in Nigeria. The treatment nurse gave the first dose every day when an oral antibiotic was scheduled. The mother gave the second dose of oral antibiotic per day, every day. Community health workers or community health extension workers, and their supervisors received training in the WHO and UNICEF's 'Caring for the Newborn at Home' course. Study nurses and their supervisors attended a 'Young Infant IMCI' course.
Participants	<p>Inclusion criteria: age 0 to 59 days, any sign of clinical severe infection (stopped feeding well (defined as poor feeding on observation), movement only when stimulated, severe chest indrawing, and axillary temperature $\geq 38.0^{\circ}\text{C}$ or $< 35.5^{\circ}\text{C}$), parents did not accept or could not access referral level care, parents gave consent to participate in the study.</p> <p>Exclusion criteria: critically ill - characterised by the presence of any of the following signs: unconsciousness, convulsions, unable to feed at all, apnoea, unable to cry, cyanosis, dehydration, bulging fontanelle, major congenital malformations inhibiting oral antibiotic intake, active bleeding requiring transfusion, surgical conditions needing hospital referral, and persistent vomiting defined as vomiting after three attempts to feed the baby within 30 min, very low weight (< 1500 grams at the time of presentation), and hospital admission for illness in the past two weeks or previously enrolled in the study</p>
Interventions	The reference treatment regimen was injectable gentamicin (4 mg/kg in the first week of life 7.5 mg/kg thereafter) and procaine benzylpenicillin (50,000 units/kg) for seven days which was compared with three simplified antibiotic regimens: injectable gentamicin and oral amoxicillin (75 mg/kg if < 2 kg and 100 mg/kg if > 2 kg) treatment for seven days; injectable procaine benzylpenicillin-gentamicin for two days, then oral amoxicillin for five days; and injectable gentamicin once per day for two days and oral amoxicillin for seven days
Outcomes	Primary outcome: treatment failure by the day eight post-enrolment visit. Treatment failure was defined as any one of: death, clinical deterioration, no improvement in clinical condition by day four, infant not cured by day eight, or development of a serious adverse event other than death that was thought to be related to the study antibiotics. The secondary outcomes were death between days 9 and 15 after enrolment, relapse, and adherence to the allocated treatment between days one and eight.
Notes	

AFRINEST(1) 2015 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "We stratified young infants aged 0 to 59 days with clinical signs of severe infection by age (0 to 6 days and 7 to 59 days) and we individually randomly assigned them within these strata to receive one of the four treatment regimens...an off-site person at WHO, who was not associated with the study, prepared randomisation lists. They generated randomisation lists for each site, for each of the two age strata, in a 1:1 ratio in blocks of eight using Stata 10."</p> <p>Comment: there was appropriate random sequence generation</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: "We sealed treatment allocation codes on a folded piece of card in two sets of sequentially numbered opaque colored envelopes, one color for each age stratum...The treatment allocation code remained concealed until after informed consent was obtained and the young infant enrolled in the study."</p> <p>Comment: there was appropriate allocation concealment</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "Treatment allocation was open to the parents and the treating health workers because it was deemed to be unethical to give placebo injections to young infants."</p> <p>Comment: the nature of the intervention made blinding of participants and personnel not feasible, but the outcome is not likely to be influenced by the lack of blinding</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote: "Outcome assessment nurses were unaware of the infant's treatment allocation."</p> <p>Comment: personnel assessing the outcomes were sufficiently blinded</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Quote: "Among all enrolled infants, 3364 (94%) fulfilled our treatment adherence and follow-up assessment criteria for inclusion in the per-protocol analysis"</p> <p>Comment: treatment adherence and follow-up assessment criteria was similar across all four treatment regimens (93%, 93%, 96%, 95%)</p>
Selective reporting (reporting bias)	Low risk	<p>Comment: The trial was registered with a clinical trials registry. In addition, the study protocol was published in <i>Pediatric Infectious Disease Journal</i> in 2013. The authors reported all outcomes described in the protocol.</p> <p>Australian New Zealand Clinical Trials Registry number: AC-TRN12610000286044</p>
Other bias	High risk	<p>Response bias - comment: all injectable medications were delivered by study personnel but some or all doses of oral medications were administered by caregivers and adherence was based on caregiver report. There is a high risk of responder bias affecting only the arms in which oral medications were administered.</p>

AFRINEST(2) 2015

Methods	This study is an individually-randomised, multicentre, open-label equivalence trial conducted from 2011 to 2013. The study took place at five sites, one each in DR Congo and Kenya, and three in Nigeria (Ibadan, Ile-Ife, and Zaria). Community health workers identified cases of suspected neonatal sep-
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AFRINEST(2) 2015 (Continued)

sis which was confirmed by a treatment nurse. A treatment nurse at an outpatient health facility gave injections in DR Congo and Kenya, and a community health extension worker gave injections at the homes of enrolled infants in Nigeria. The treatment nurse gave the first dose every day when an oral antibiotic was scheduled. The mother gave the second dose of oral antibiotic per day, every day. Community health workers or community health extension workers, and their supervisors received training in WHO and UNICEF's 'Caring for the Newborn at Home' course. Study nurses and their supervisors attended a 'Young Infant IMCI' course.

Participants	<p>Inclusion criteria: age 0 to 59 days, fast breathing (defined as respiratory rate of ≥ 60 breaths per min), parents did not accept or could not access referral level care, and parents gave consent to participate in the study.</p> <p>Exclusion criteria: signs of clinical severe infection (defined as poor feeding on observation, movement only when stimulated, severe chest indrawing, and axillary temperature $\geq 38.0^{\circ}\text{C}$ or $< 35.5^{\circ}\text{C}$), critical illness (characterised by presence of unconsciousness, convulsions, inability to feed at all, apnoea, inability to cry, cyanosis, dehydration, bulging fontanelle, major congenital malformations that inhibited oral antibiotic intake, active bleeding that necessitated transfusion, surgical conditions needing hospital referral, persistent vomiting (defined as vomiting after three attempts to feed the baby within 30 min)), very low weight (< 1500 grams at the time of presentation), and hospital admission for illness in the past two weeks or previous enrolment in the study</p>
Interventions	The reference treatment regimen was procaine benzylpenicillin (50,000 units/kg) intramuscularly daily and gentamicin (4 to 7.5 mg/kg) intramuscularly daily for seven days. This was compared to a regimen of oral amoxicillin suspension (75 mg/gram/day if < 2 kg or 100 mg/kg/day if > 2 kg) divided into two equal doses for seven days.
Outcomes	<p>Primary outcome: treatment failure by the day eight post-enrolment visit. Treatment failure was defined as any one of: death; clinical deterioration, persistence of fast breathing on day 4 or recurrence after day 4 up to day 8; and development of a serious adverse event</p> <p>Secondary outcomes: death 9 to 15 days after enrolment; relapse, and adherence to the study therapy on days 1 to 8</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "A member of staff at WHO, who was not involved with the study, used Stata 10 to prepare randomization lists for each age stratum at each site. We allocated infants in a 1:1 ratio in blocks of eight."</p> <p>Comment: there was appropriate random sequence generation</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: "We sealed treatment allocation codes on a folded piece of card in two sets of sequentially numbered, opaque, colored envelopes—with one color for each age stratum—to conceal allocation. The treatment allocation code remained concealed until after we had obtained informed consent and enrolled the infant in the study"</p> <p>Comment: there was appropriate allocation concealment</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: the nature of the intervention made blinding of participants and personnel not feasible, but the outcome is not likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The outcome assessment nurse was unaware of the infant's treatment allocation."

AFRINEST(2) 2015 (Continued)

All outcomes		Comment: personnel assessing the outcomes were sufficiently blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "2196 (94%) infants met the criteria for inclusion in the per-protocol analysis, with 1061 (91%) infants from the procaine benzylpenicillin-gentamicin group and 1135 (98%) infants from the oral amoxicillin group...The baseline characteristics of infants who were withdrawn from the study did not differ from those who were not withdrawn"
Selective reporting (reporting bias)	Low risk	Comment: The trial was registered with a clinical trials registry. In addition, the study protocol was published in <i>Pediatric Infectious Disease Journal</i> in 2013. The authors reported all outcomes described in the protocol. Australian New Zealand Clinical Trials Registry number: AC-TRN12610000286044
Other bias	High risk	Response bias - comment: all injectable medications were delivered by study personnel but some or all doses of oral medications were administered by caregivers and adherence was based on caregiver report. There is a high risk of responder bias affecting only the arms in which oral medications were administered.

Baqui 2008

Methods	The study was a cluster-randomised controlled trial conducted from July 2003 to December 2005. The study took place in three rural subdistricts of the Sylhet district of Bangladesh. These subdistricts have poor access to health care, approximately 15,000 live births per year and the ability for non-governmental organizations (NGOs) to scale-up the intervention. Twenty-four unions within the subdistricts were randomly assigned to one of two intervention arms (home care or community care) or to the comparison arm. The interventions in the home care arm were implemented by female community health workers who were responsible for a population of 4000. They received 6 weeks of supervised training about essential newborn care in a tertiary care hospital and in households. The community meetings in both the home care and the community care arm were implemented by male and female community mobilisers who were responsible for a population of 18,000. They were assisted by other volunteers who identified pregnant women and encouraged them to attend the events held by the community mobilisers.
Participants	Neonates (aged 0 to 27 days) in the home care arm were identified by community healthcare workers through routine household visits once every two months. Neonates with PSBI were identified if they had any one of the following: convulsions; unconsciousness; respiratory rate ≥ 60 breaths per minute; severe chest indrawing; $\geq 38.3^{\circ}\text{C}$ or $\leq 35.3^{\circ}\text{C}$; many or severe skin pustules or blisters on single large area; umbilical redness extending to the skin. Sepsis was also diagnosed if the neonate had any two of the following: history of convulsions; bulging fontanelle; vomiting after every feed; temperature 35.3°C to 36.4°C or 37.8°C to 38.4°C ; weak, abnormal or absent cry; lethargic; not able to feed; umbilicus discharging pus; umbilical redness not extending to the skin; some skin pustules; jaundiced palms or soles after one day of life.
Interventions	Neonates with PSBI in the home care arm were referred to subdistrict hospitals after receiving one dose of procaine benzylpenicillin and gentamicin intramuscularly. If families refused referral but consented to home treatment, the community healthcare workers continued treatment for 10 days. Neonates less than 2.0 kg received gentamicin 10 mg intramuscularly every other day and penicillin 80,000 units intramuscularly daily. Neonates between 2.0 kg and 2.5 kg received gentamicin 10 mg intramuscularly daily and penicillin 160,000 units intramuscularly daily. Neonates greater than 2.5 kg received gentamicin 13.5 mg intramuscularly daily and penicillin 160,000 units intramuscularly daily. Other interventions in the home care arm included community meetings to promote birth and newborn care preparedness, two antenatal home visits, provision of maternal iron and folic acid supplements, and three postnatal home visits.

Baqui 2008 (Continued)

The community care arm only included community meetings to promote birth and newborn care preparedness. Septic neonates were not identified, referred or treated in the community care arm.

The comparison arm received the usual health services provided by the government, NGOs, and private providers.

Refresher training sessions for the management of maternal and newborn complications were provided for government health workers in all three study arms. Adequate supply of antibiotics for treatment of newborn sepsis was ensured in the government subdistrict hospitals that served all three study arms.

Outcomes	Primary outcome: change in the rate or neonatal mortality, defined as death or a liveborn child within the first 27 completed days of life Secondary outcomes: changes in the number of antenatal visits from trained providers, use of iron and folic acid supplements, use of clean cord-cutting instruments, delays in the newborn's first bath, initiation of breastfeeding within one hour after birth and tetanus-toxoid immunisation coverage	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "24 clusters (unions)...were randomly assigned to one of two intervention arms—i.e. home-care or community-care—or to the comparison arm with computer-generated pseudo-random number sequence without stratification or matching...The computer-generated randomisation was implemented by a study investigator who had no role in the implementation of the study" Comment: there was appropriate random sequence generation
Allocation concealment (selection bias)	Low risk	Comment: since it was a cluster-randomised trial, all clusters were randomised at the same time
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: the nature of the intervention made blinding of participants and personnel not feasible, but the outcome is not likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: insufficient data to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Study supervisors and investigators reviewed data forms for accuracy, consistency, and completeness. Outcome assessors made additional field visits to clarify inconsistencies or obtain missing information as needed." Comment: percentage of participants absent at the time of survey was similar across all arms (home care 8.9%, community care 9.2%, comparison 9.5%). Percentage of participants who declined to participate was similar across all arms (home care 2.9%, community care 2.9%, comparison 3.3%)
Selective reporting (reporting bias)	Low risk	Comment: the trial was registered with a clinical trials registry and reported the outcomes identified in the study protocols Clinicaltrials.gov registry number: NCT00198705
Other bias	High risk	Contamination bias:

Baqui 2008 (Continued)

Quote: "The possibility of contamination is plausible...because the study clusters were geographically contiguous areas, with some degree of movement and communication among clusters"

Baqui 2015

Methods	The study was a randomised controlled trial conducted from 1 July 2009 to 30 June 2013. The study took place at 4 urban hospitals and one rural field site in Bangladesh. Study physicians diagnosed neonatal sepsis and administered all intramuscular injections. Family members administered all oral antibiotics.
Participants	<p>Infants aged 0 to 59 days in the outpatient departments of the 4 study hospitals who were diagnosed by a study physician with severe infection were eligible. In addition, female community health workers visited infants in the rural site days 0, 2, 6, 13, 20, 27, 34, 41, 48 and 59 after birth and referred potentially eligible participants to one of the outpatient departments where diagnosis of severe infection was determined by a study physician. Severe infection was defined as presence of one of the following signs: 1. severe chest indrawing; 2. temperature $\geq 38.0^{\circ}\text{C}$; 3. temperature $\leq 35.5^{\circ}\text{C}$; 4. lethargy; 5. feeding difficulty</p> <p>Infants were excluded if they had any 1 sign of critically severe infection: 1. unconsciousness; 2. convulsions; 3. inability to feed; 4. apnoea; 5. inability to cry; 6. cyanosis; 7. bulging fontanelle; 8. major congenital malformation; 9. major bleeding; 10. surgical condition; 11. persistent vomiting; 12. meningitis. Infants were also excluded if their weight < 1500 grams or had been hospitalised for illness in the previous two weeks. All infants with severe infection were first offered hospitalisation and were only enrolled in the study if parents refused admission.</p>
Interventions	Enrolled infants were assigned to one of three arms: A. intramuscular procaine-benzyl penicillin 4000 IU/kg to 5000 IU/kg and gentamicin 4 mg/kg to 6.5 mg/kg once daily for seven days; B. intramuscular gentamicin 4 mg/kg to 6.5 mg/kg once daily and oral amoxicillin 75 mg/kg/day to 100 mg/kg/day divided twice daily for seven days; C. intramuscular procaine benzylpenicillin and gentamicin once daily for two days followed by oral amoxicillin twice daily for five days
Outcomes	<p>Primary outcome: treatment failure in the 7 days after enrolment. Treatment failure was defined as death, clinical deterioration, need to alter antibiotic regiment, need for hospitalisation, occurrence of new clinical signs, persistence of initial clinical sign(s) on day four, or recurrence of initial clinical(s) on or after day five.</p> <p>Secondary outcomes: proportions of infants who died and of those who had non-fatal relapse</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "Infants are randomized to 1 of the 3 home treatment regimens using site- and age-specific (< 7 days or 7 to 59 days) computer-generated randomization sequences with varying random block sizes of 3, 6 and 12."</p> <p>Comment: there was appropriate random sequence generation</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: "The allocation sequence for each site and age groups is placed in serially numbered, sealed and opaque envelopes and delivered to each site. After consent and enrolment, the study physician selects the next envelope, and the treatment corresponding to the allocation code printed within the envelope is assigned to the infant"</p>

Baqui 2015 (Continued)

		Comment: there was appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "We did not deem it ethical to give placebo injections to such young infants and therefore, we were not able to mask the study participants or study physicians to treatment group allocation" Comment: the nature of the intervention made blinding of participants and personnel not feasible, but the outcome is not likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All surviving infants meeting clinical treatment failure criteria by study physicians on routine follow-ups are designated as provisional treatment failures and transported to the hospital accompanied by study personnel. At the hospital, the infant undergoes a repeat examination without history-taking by a second study physician. To the extent possible, the second physician assessor is blinded to the treatment allocation and prior history of the infant." Comment: although the physicians who delivered the intervention were also responsible for being the primary assessors of the outcome, the second physician at the hospital was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 35 infants (4.2%) from treatment arm A, 49 infants (5.9%) from treatment arm B and 39 infants (4.7%) from treatment arm C were excluded from analyses due to protocol violations
Selective reporting (reporting bias)	Low risk	Comment: The trial was registered with a clinical trials registry. In addition, the study protocol was published in <i>Pediatric Infectious Disease Journal</i> in 2013. The authors reported all outcomes described in the protocol Clinicaltrials.gov registry number: NCT00844337
Other bias	High risk	Response bias Comment: all injectable medications were delivered by study personnel but some or all doses of oral medications were administered by caregivers and adherence was based on caregiver report. There is a high risk of responder bias affecting only the arms in which oral medications were administered.

Bhandari 2012

Methods	The study was a cluster-randomised controlled trial conducted from July 2007 to April 2010. The study took place in 18 communities in the district of Faridabad, Haryana, India and each community was randomised to either the intervention arm or the control arm. The intervention involved many types of health practitioners including physicians, nurses, community health workers and traditional birth attendants
Participants	Neonates (0 to 27 days) and infants (28 days to one year of life) who resided in the 18 study communities were included
Interventions	The intervention was the introduction of The Integrated Management of Neonatal and Childhood Illness (IMNCI). IMNCI includes three main components: <ol style="list-style-type: none"> 1. Improvement in the case management skills of health staff 2. Improvement in the overall health system to support its performance, and 3. Improvement in family and community health care practices which include: prevention and management of hypothermia early initiation of breastfeeding and exclusive breastfeeding community-based care of low birth weight infants improved care-seeking for neonatal infections

Bhandari 2012 (Continued)

Neonates who lived in the intervention clusters and were identified as having a local infection (umbilicus red or draining pus, pus discharge from ear or skin pustules) were given five days of oral cotrimoxazole or amoxicillin. Those identified as having a PSBI were given the first dose of injectable benzylpenicillin and gentamicin by a community health worker and then referred to the hospital. If referral was not possible, efforts were made to continue antibiotic treatment in clinic or at home. The diagnosis of a PSBI was made if any of the following were present: convulsions; fast breathing; severe chest indrawing; grunting; nasal flaring; bulging fontanelle; multiple skin pustules; axillary temperature $> 37.5^{\circ}\text{C}$ or $< 35.5^{\circ}\text{C}$; lethargy; less than normal movement

Outcomes

Primary outcomes: neonatal mortality (deaths between birth and day 27 of life), mortality beyond the first 24 hours of birth (deaths between day 1 and day 27 of life), and infant mortality (deaths between birth and 1 year of life)

Secondary outcomes: newborn care practices and process of delivery of the intervention

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We divided the clusters into three strata containing six clusters each according to their baseline neonatal mortality rate. An independent epidemiologist generated 10 stratified randomization schemes to allocate the clusters to intervention or control groups. We excluded three of these schemes, which had large differences in neonatal mortality rate, proportion of home births, proportion of mothers who had never been to school, and population size. We selected one of the remaining seven allocation schemes by a computer generated random number." Comment: there was appropriate random sequence generation
Allocation concealment (selection bias)	Low risk	Comment: since it was cluster-randomised trial, all clusters were randomised at the same time
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: the nature of the intervention made blinding of participants and personnel not feasible, but the outcome is not likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The surveillance team was not told the intervention status of the community they were visiting." Comment: personnel assessing the outcomes were sufficiently blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: the intervention and control clusters had similar rates of attrition. In the intervention clusters, 37,741 pregnancies were identified of which 88% (33,091) of the outcomes were known. In the control clusters, 39,846 pregnancies were identified of which 86% (34,257) of the outcomes were known. In the intervention clusters, 29,782 live births were identified and less than 1% (115) were lost to follow-up. In the control clusters, 30,920 live births were identified and less than 1% (107) were lost to follow-up
Selective reporting (reporting bias)	Low risk	Comment: the trial was registered with a clinical trials registry and reported the outcomes identified in the study protocols Clinicaltrials.gov registry number: NCT00474981
Other bias	Low risk	Contamination bias:

Bhandari 2012 (Continued)

Quote: "Although contiguous, the 18 clusters are large and the way healthcare and worker responsibilities are organised within a primary health centre area makes the risk of contamination low."

Degefie 2017

Methods	The study was a cluster-randomised controlled trial conducted from July 2011 to June 2013. The study took place in three rural areas of Ethiopia. Twenty-two clusters, each with approximately 1000 births annually, were randomly assigned to the intervention or control arm. In both arms, postnatal home visits were conducted to provide counselling and neonatal assessment. In the intervention arm, infants with a PSBI received antibiotics at a health post if referral to a facility was refused, and infants with a PSBI in the control arm were only offered referral to a facility. The home visits and interventions were provided by health education workers who are women with 10 th grade education and additional one year of focused training.
Participants	Neonates (aged 0 to 27 days) were identified as having a PSBI in both arms by health education workers at health posts. Any one of the following classified an infant as having a PSBI: convulsions, poor feeding, fast breathing, respiratory distress, lethargy, hypo/hyperthermia.
Interventions	Neonates in both arms were referred to an inpatient facility. If families in the intervention arm refused, neonates were provided seven days of oral amoxicillin 40 mg/kg three times daily and intramuscular gentamicin 3 mg/kg to 7.5 mg/kg daily. The oral amoxicillin was administered by the neonate's caregivers and the intramuscular gentamicin was administered by health education workers.
Outcomes	Primary outcome: all-cause neonatal mortality, restricted to death on days 2 to 27 after birth. Neonatal mortality was measured by household survey data

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient explanation of randomisation process
Allocation concealment (selection bias)	Low risk	Comment: since it was a cluster-randomised trial, all clusters were randomised at the same time
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: the nature of the intervention made blinding of participants and personnel not feasible, but the outcome is not likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "...survey teams were blinded to minimize interviewer bias." Comment: personnel assessing the outcomes were sufficiently blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were similar rates of attrition in the intervention and control arm. In the intervention arm, 6% of allocated households were not included in the final analysis. In the control arm, 8% of allocated households were not included in the final analysis
Selective reporting (reporting bias)	Low risk	Comment: the trial was registered with a clinical trials registry and reported the outcomes identified in the study protocols Clinicaltrials.gov registry number: NCT00743691

Degefie 2017 (Continued)

Other bias	Unclear risk	Contamination bias: Comment: no information is provided about risk of contamination bias
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Gill 2011

Methods	The study was a cluster-randomised controlled trial conducted from June 2006 to November 2008. The study took place in Lufwanyama, Zambia, a district with 12 rural health centres staffed by nurse midwives or clinical officers. The district had no doctors and no hospital. There were 60 intervention clusters and 67 control clusters. Both intervention and control clusters were staffed with traditional birth attendants who were trained in basic obstetric and newborn care, including the use of clean delivery kits. Traditional birth attendants in the intervention clusters received an additional two weeks of training on basic newborn resuscitation and recognition and initial treatment of possible sepsis.
Participants	All neonates (aged 0 to 27 days) whose deliveries were attended by traditional birth attendants from the study area were included
Interventions	The intervention included basic newborn resuscitation and recognition and initial treatment of possible sepsis. Basic newborn resuscitation included drying, stimulating and positive pressure ventilation. Signs indicating a PSBI included chest retractions/coughing, poor/absent muscle tone, feeling too hot/too cold, inconsolability, unable to arouse, vomiting, swollen abdomen, refusal to feed, diarrhoea, redness around umbilical cord, convulsions or not making urine. If sepsis was suspected, the traditional birth attendant would administer one dose of oral amoxicillin 500 mg and refer the neonate and mother to the nearest health facility, ideally accompanying them.
Outcomes	Primary outcome: proportion of liveborn infants who died by 27 completed days after birth Secondary outcomes: proportion of stillbirth, mortality rates at different time points during the 27 days and cause-specific mortality
Notes	Both intervention and control birth attendants received one clean delivery kit per birth. Each kit contained a plastic delivery sheet, a cord cutter, cotton cord ties, one pair of latex gloves, soap, and a candle with matches.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Randomization was done by generating 120 allocation slips (60 intervention and 60 control), which were placed in an opaque container. During a public ceremony, witnessed by all the birth attendants and study staff, the participants individually took a slip from the box and the group allocation was announced to the whole group" Comment: an additional seven control birth attendants were included during the study without randomisation
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was done by generating 120 allocation slips (60 intervention and 60 control), which were placed in an opaque container. During a public ceremony, witnessed by all the birth attendants and study staff, the [birth attendants representing each cluster] individually took a slip from the box and the group allocation was announced to the whole group" Comment: since it was a cluster-randomised trial, all clusters were randomised at the same time

Gill 2011 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: the nature of the intervention made blinding of participants and personnel not feasible, but the outcome is not likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: there are insufficient data to determine whether the outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Before final vital status had been determined at 28 days, 76 infants (2.1%) were lost to follow-up: 34 of 2007 (1.7%) intervention deliveries and 42 of 1552 (2.7%) control deliveries" Quote: "Some of the reports from one data collector were found to have been falsified. Consequently, all of the data on deliveries from that data collector (including reports for intervention and control birth attendants) were excluded from the final analysis" Comment: this included 46 infants (2.3%) from the intervention arm and 16 infants (1.0%) from the control arm
Selective reporting (reporting bias)	Low risk	Comment: the trial was registered with a clinical trials registry and reported the outcomes identified in the study protocol Clinicaltrials.gov registry number: NCT00518856
Other bias	Low risk	Contamination bias: Comment: there is a low risk of contamination bias given the organisation of the CHWs

Mir 2017

Methods	The study was a randomised controlled trial from January 2010 to December 2013. The study took place in five low-income settlements in coastal Karachi, Pakistan (Rehri Goth, Ibrahim Hyderi, Ali Akbar Shah Goth, Bhains colony, and Bilal colony). Infants from the catchment area were either referred to a study clinic by community health workers during routine household surveillance or presented with their family at one of the five primary healthcare clinics, at which study clinicians screened them for eligibility to participate in the trial. Paramedics or study clinicians administered all intramuscular injections at study clinics; study personnel gave the morning dose of oral antibiotic at the clinic, and a community health worker visiting the child's household administered the evening dose.	
Participants	<p>Inclusion criteria: aged 0 to 59 days, living in the catchment area, refusal by family to be admitted to hospital, and at least one of any of the following signs of clinical severe infection: movement only when stimulated; not feeding well on observation; temperature $\geq 38^{\circ}\text{C}$ or $< 35.5^{\circ}\text{C}$; severe chest indrawing.</p> <p>Exclusion criteria: infants were excluded from the study if their family agreed to admission, weight at presentation < 1500 grams, major congenital malformations or suspected chromosomal abnormalities were present, surgical conditions needed hospital referral, they had been admitted for illness in the past two weeks, they had been included previously in the study, or they had one or more signs of critical illness (unconsciousness; convulsions; inability to feed; apnoea; inability to cry; cyanosis; bulging fontanelle; active bleeding needing transfusion; persistent vomiting)</p>	
Interventions	The reference treatment regimen was procaine benzylpenicillin (40,000 mg/kg to 60,000 units/kg) and gentamicin (4 mg/kg to 6.5 mg/kg), each administered intramuscularly once daily for seven days. The second regimen was gentamicin administered intramuscularly once daily and amoxicillin (75 mg/kg/day to 100 mg/kg/day) administered orally twice daily for seven days. The third regimen was procaine	

Mir 2017 (Continued)

benzylpenicillin and gentamicin administered intramuscularly once daily for two days followed by amoxicillin administered orally twice daily for five days.

Outcomes

Primary outcome: treatment failure within seven days of enrolment, which we defined as either: death; admission; clinical deterioration; change in antibiotic regimen because of infectious comorbidity; serious adverse event; occurrence of a new sign of clinical severe infection on or after day three; persistence of presenting signs at day four; or recurrence of initial signs of sepsis on or after day five

Among young infants who had treatment failure, **secondary outcomes** were: death within seven days of enrolment; death at any time before the day 14 to 15 assessment; and admission for any reason at any time within seven days of enrolment

Among children who did not have treatment failure, **secondary outcomes** were: admission at any time between the day eight and day 14 to 15 visits; death at any time between the day eight and day 14 to 15 visits; and non-fatal relapse at any time between the day eight and day 14 to 15 visits

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We used a site-specific and age-specific (< 7 days and 7 to 59 days) randomization sequence list generated by the London School of Hygiene & Tropical Medicine." Comment: there was appropriate random sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "The allocation sequence for every site and age group was placed in serially numbered, sealed, opaque envelopes by the Data Management Unit at Aga Khan University and delivered to every site. Study clinicians selected the next envelope and the treatment corresponding to the allocation code printed within was assigned to the infant." Comment: there was appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Study participants' families and study clinicians were not blinded to treatment allocation because giving placebo injections to sick young infants was judged unethical" Comment: the nature of the intervention made blinding of participants and personnel not feasible, but the outcome is not likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: The clinicians who delivered the intervention were also responsible for being the primary assessors of the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: of the 820 infants allocated to procaine benzylpenicillin and gentamicin, 9% (73) had inadequate follow-up and/or inadequate treatment and were excluded from analysis. Of the 816 allocated to amoxicillin and gentamicin 8% (65) had inadequate follow-up and/or inadequate treatment and were excluded from analysis. Of the 817 allocated to procaine benzylpenicillin, gentamicin and amoxicillin 8% (64) had inadequate follow-up and/or inadequate treatment and were excluded from analysis. Thus, all groups had similar rates of attrition.
Selective reporting (reporting bias)	Low risk	Comment: the trial was registered with a clinical trials registry. In addition, the study protocol was published in <i>Pediatric Infectious Disease Journal</i> in 2013. The authors reported all outcomes described in the protocol

Mir 2017 (Continued)

Clinicaltrials.gov registry number: NCT01027429

Other bias	Low risk	Response bias: all doses of both oral and injectable medications were administered and observed by health providers
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Soofi 2017

Methods	The study was a cluster-randomised controlled trial conducted from January 2009 to February 2011. The study took place in two subdistricts of Naushero Feroze, a rural district of Sind, Pakistan and included 34 clusters. Female health workers and traditional birth attendants in both the control and intervention underwent training.	
Participants	All neonates (aged 0 to 27 completed days) whose deliveries were attended by traditional birth attendants or female health workers from the study area were included.	
Interventions	In both arms, female health workers were trained to promote antenatal care, administer iron to pregnant women, provide immediate newborn care (including umbilical cord care) and promote breastfeeding. In the intervention clusters, female health workers were additionally trained to refer high risk pregnancies, recognise and provide initial resuscitation to birth asphyxiated neonates, enhance temperature control of low birth weight neonates, recognise and treat neonatal infection with amoxicillin. Referral for PSBI was encouraged but seven days of amoxicillin was provided if referral was not possible. In the control clusters, female health workers were advised to refer any sick newborns, but they were not provided with amoxicillin to treat the newborns. In both arms, traditional birth attendants, were trained to promote antenatal care, use clean delivery kits, provide immediate newborn care of delayed bathing and eye care. In the intervention clusters, traditional birth attendants were also trained to provide initial management to birth asphyxiated neonates and recognise signs of neonatal sepsis or pneumonia and refer to female health workers.	
Outcomes	<p>Primary outcomes: neonatal mortality rates and perinatal mortality rates</p> <p>Secondary outcomes: birth asphyxia-related neonatal mortality rates, neonatal mortality rates among low birth weight infants and neonatal mortality rates due to sepsis</p> <p>Additional process outcomes were also measured</p>	

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "This is a cluster randomize controlled trial and the randomization was based on computer generated blocks" Comment: there was appropriate random sequence generation
Allocation concealment (selection bias)	Low risk	Comment: since it was a cluster-randomised trial, all clusters were randomised at the same time
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: the nature of the intervention made blinding of participants and personnel not feasible, but the outcome is not likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "An independent surveillance system was implemented" Comment: personnel assessing the outcomes were sufficiently blinded

Soofi 2017 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: The rate of women lost to follow-up was 1% in both the intervention arm and the control arm.
Selective reporting (reporting bias)	Low risk	Comment: the trial was registered with a clinical trials registry and reported the outcomes identified in the study protocols Clinicaltrials.gov registry number: NCT01350765
Other bias	Low risk	Contamination: Quote: "...randomisation through the reporting facilities ensured no contamination between intervention and control clusters"

Zaidi 2012

Methods	This study was a randomised controlled trial conducted from November 2003 to December 2005. The study took place in three low-income communities in and around Karachi, Pakistan. The nearest hospital with neonatal services was located within 45 to 60 minutes driving distance. Community health workers visited newborns at home at regular intervals and referred potentially eligible infants to a nearby primary health care clinic. At the clinic, study physicians determined eligibility and administered injectable antibiotics. Oral antibiotics were administered by the mother at home.	
Participants	Eligible infants were 0 to 59 days of age, met criteria for a PSBI and whose parents refused hospital referral. PSBI was present if infants had any one of the following: apnoea/poor respiratory effort, seizures observed by doctors, bulging fontanelle, temperature > 38.5°C or < 35.5°C, severe lethargy/floppy baby, capillary refill more than two seconds, severe chest indrawing or grunting. PSBI was also present if any three of the following were present: respiratory rate > 60/min, feeding difficulty/poor suck, temperature 37.5°C to 38.5°C or 35.5°C to 36.0°C, lethargy, excessive crying/irritability, weak/abnormal/absent cry, abdominal distension, hypoglycaemia, history of seizures, presence of skin/eye/umbilical infection, any maternal infectious risk factor. Infants were excluded from the trial if the family refused injectable therapy, if signs of severe jaundice or clinically obvious meningitis were present, or if the patient had been previously enrolled in the same trial.	
Interventions	Infants who met the eligibility criteria were randomly assigned to receive one of three treatment regimens at the clinics: procaine penicillin 50,000 units/kg/day once daily and gentamicin 5 mg/kg day once daily, both by intramuscular injections for seven days; ceftriaxone 50 mg/kg/day once daily by intramuscular injection for seven days; or oral TMP-SMX 10 mg/kg divided in twice-daily doses and gentamicin 5 mg/kg day once daily intramuscular injection for seven days	
Outcomes	<p>Primary outcome: treatment failure, defined as: (1) death at any time during the seven-day treatment period, (2) deterioration in clinical condition at any time after the start of therapy, or (3) no improvement after 2 days of therapy, necessitating antibiotic change</p> <p>Secondary outcomes: case fatality rates at 7 and 14 days after enrolment, relapse, withdrawal, therapy completion rates and adverse events</p>	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Block randomization in varying multiples of 3 stratified by site was done with a computer-generated list" Comment: there was appropriate random sequence generation

Zaidi 2012 (Continued)

Allocation concealment (selection bias)	Low risk	Quote: "...treatment group assignment was placed in opaque sealed envelopes that were opened sequentially by study physicians" Comment: there was appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Blinding of therapy was not possible because of the observable differences in delivery of the 3 regimens." Comment: the nature of the intervention made blinding of participants and personnel not feasible, but the outcome is not likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The treating physician was also the assessor of treatment failure outcomes because we thought that he/she was the best judge of whether the baby had improved with therapy" Comment: personnel assessing the outcomes were not sufficiently blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "There was no significant difference among 7-day therapy completion rates in the 3 groups, with 84 of 143 (59%) completing 7 days of penicillin and gentamicin, 80 of 142 (56%) completing 7 days of ceftriaxone and 83 of 137 (61%) completing 7 days of TMP-SMX and gentamicin." "In a modified per-protocol analysis, excluding all withdrawals and the infant with protocol violation, the TMP-SMX plus gentamicin group still had a higher treatment failure rate than the penicillin plus gentamicin group after 7 days of therapy (RR 1.84, 95% CI 0.98 to 3.44), but did not reach statistical significance." Comment: the rates of attrition were similar for the intervention and control groups
Selective reporting (reporting bias)	Low risk	Comment: the trial was registered with a clinical trials registry and reported the outcomes identified in the study protocols Clinicaltrials.gov registry number: 00189384
Other bias	High risk	Response bias Quote: "Another limitation is that use of TMP-SMX was ascertained by mother/family member report when the baby was brought to the clinic, not directly observed."

IMCI: Integrated Management of Childhood Illness

IMNCI: Integrated Management of Neonatal and Childhood Illness

NGO: non-governmental organisation

PSBI: possible serious bacterial infection

TMP-SMX: trimethoprim-sulphamethoxazole

UNICEF: United Nations International Children's Emergency Fund

WHO: World Health Organization

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bang 1990	This was a non-randomised controlled trial.
Bang 1999	This was a non-randomised controlled trial.

Study	Reason for exclusion
Bhandari 1996	This was an observational trial.
Khan 1990	This was a non-randomised controlled trial.
Mtango 1986	This was a randomised trial that included children under the age of 5 with acute respiratory infection. However, the trial did not define the criteria to diagnose an acute respiratory infection. Therefore, it is unknown whether there is any overlap between the trial's diagnosis of an acute respiratory infection and a possible serious bacterial infection, as defined by the review question.
Pandey 1991	This was a non-randomised controlled trial.

DATA AND ANALYSES

Comparison 1. Comparison 1: Full comparison (no subgroup)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal mortality	5	125134	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.68, 0.99]
2 Early neonatal mortality	2	40299	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.65, 0.85]
3 Late neonatal mortality	2	40142	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.55, 0.96]
4 Sepsis specific neonatal mortality	2	40233	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.60, 1.00]

Analysis 1.1. Comparison 1 Comparison 1: Full comparison (no subgroup), Outcome 1 Neonatal mortality.

Analysis 1.2. Comparison 1 Comparison 1: Full comparison (no subgroup), Outcome 2 Early neonatal mortality.

Analysis 1.3. Comparison 1 Comparison 1: Full comparison (no subgroup), Outcome 3 Late neonatal mortality.

Analysis 1.4. Comparison 1 Comparison 1: Full comparison (no subgroup), Outcome 4 Sepsis specific neonatal mortality.

Comparison 2. Comparison 1: Full course versus one dose + referral

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal mortality	5	125134	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.68, 0.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Full course	4	121779	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.04]
1.2 One dose + referral	1	3355	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.38, 0.83]

Analysis 2.1. Comparison 2 Comparison 1: Full course versus one dose + referral, Outcome 1 Neonatal mortality.

Comparison 3. Comparison 1: Route of administration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal mortality	5	125134	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.68, 0.99]
1.1 Injectable	1	5684	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.51, 0.88]
1.2 Oral	2	40223	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.54, 0.90]
1.3 Injectable + oral	2	79227	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.06]

Analysis 3.1. Comparison 3 Comparison 1: Route of administration, Outcome 1 Neonatal mortality.

Comparison 4. Comparison 1: Use of co-interventions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal mortality	5	125134	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.68, 0.99]
1.1 Antibiotics alone	1	18747	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.89, 1.29]
1.2 Antibiotics + cointerventions	4	106387	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.62, 0.94]

Analysis 4.1. Comparison 4 Comparison 1: Use of co-interventions, Outcome 1 Neonatal mortality.

Comparison 5. Comparison 2: Simplified antibiotic regimen compared to standard antibiotic regime

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal mortality	3	3476	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.44, 1.50]
2 Treatment failure	3	3476	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.67, 1.10]
3 Adverse events	3	3476	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.79, 2.41]

Analysis 5.1. Comparison 5 Comparison 2: Simplified antibiotic regimen compared to standard antibiotic regime, Outcome 1 Neonatal mortality.

Analysis 5.2. Comparison 5 Comparison 2: Simplified antibiotic regimen compared to standard antibiotic regime, Outcome 2 Treatment failure.

Analysis 5.3. Comparison 5 Comparison 2: Simplified antibiotic regimen compared to standard antibiotic regime, Outcome 3 Adverse events.

Comparison 6. Comparison 2: 7 days oral amoxicillin + injectable gentamicin compared to 7 days injectable benzylpenicillin + injectable gentamicin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal mortality	3	2001	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.47, 1.51]
2 Treatment failure	3	2001	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.60, 1.11]
3 Adverse events	3	2001	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.72, 2.53]

Analysis 6.1. Comparison 6 Comparison 2: 7 days oral amoxicillin + injectable gentamicin compared to 7 days injectable benzylpenicillin + injectable gentamicin, Outcome 1 Neonatal mortality.

Analysis 6.2. Comparison 6 Comparison 2: 7 days oral amoxicillin + injectable gentamicin compared to 7 days injectable benzylpenicillin + injectable gentamicin, Outcome 2 Treatment failure.

Analysis 6.3. Comparison 6 Comparison 2: 7 days oral amoxicillin + injectable gentamicin compared to 7 days injectable benzylpenicillin + injectable gentamicin, Outcome 3 Adverse events. **Comparison 7. Comparison 2: 2 days injectable benzylpenicillin + injectable gentamicin followed by 5 days oral amoxicillin compared to 7 days injectable benzylpenicillin + injectable gentamicin**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal mortality	3	2036	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.29, 2.65]
2 Treatment failure	3	2036	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.70, 1.25]
3 Adverse events	3	2036	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.67, 2.87]

Analysis 7.1. Comparison 7 Comparison 2: 2 days injectable benzylpenicillin + injectable gentamicin followed by 5 days oral amoxicillin compared to 7 days injectable benzylpenicillin + injectable gentamicin, Outcome 1 Neonatal mortality.

Analysis 7.2. Comparison 7 Comparison 2: 2 days injectable benzylpenicillin + injectable gentamicin followed by 5 days oral amoxicillin compared to 7 days injectable benzylpenicillin + injectable gentamicin, Outcome 2 Treatment failure.

Analysis 7.3. Comparison 7 Comparison 2: 2 days injectable benzylpenicillin + injectable gentamicin followed by 5 days oral amoxicillin compared to 7 days injectable benzylpenicillin + injectable gentamicin, Outcome 3 Adverse events.

Comparison 8. Two days oral amoxicillin + injectable gentamicin followed by 5 days oral amoxicillin compared to 7 days injectable benzylpenicillin + injectable gentamicin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal mortality	1	893	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.24, 1.85]
2 Treatment failure	1	893	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.34, 1.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Adverse events	1	893	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 8.1. Comparison 8 Two days oral amoxicillin + injectable gentamicin followed by 5 days oral amoxicillin compared to 7 days injectable benzylpenicillin + injectable gentamicin, Outcome 1 Neonatal mortality.

Analysis 8.2. Comparison 8 Two days oral amoxicillin + injectable gentamicin followed by 5 days oral amoxicillin compared to 7 days injectable benzylpenicillin + injectable gentamicin, Outcome 2 Treatment failure.

Analysis 8.3. Comparison 8 Two days oral amoxicillin + injectable gentamicin followed by 5 days oral amoxicillin compared to 7 days injectable benzylpenicillin + injectable gentamicin, Outcome 3 Adverse events.

Comparison 9. Seven days oral amoxicillin compared to 7 days injectable benzylpenicillin + injectable gentamicin for fast breathing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal mortality	1	1406	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.20, 4.91]
2 Treatment failure	1	1406	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.68, 1.01]
3 Adverse events	1	1406	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 9.1. Comparison 9 Seven days oral amoxicillin compared to 7 days injectable benzylpenicillin + injectable gentamicin for fast breathing, Outcome 1 Neonatal mortality.

Analysis 9.2. Comparison 9 Seven days oral amoxicillin compared to 7 days injectable benzylpenicillin + injectable gentamicin for fast breathing, Outcome 2 Treatment failure.

Analysis 9.3. Comparison 9 Seven days oral amoxicillin compared to 7 days injectable benzylpenicillin + injectable gentamicin for fast breathing, Outcome 3 Adverse events.

ADDITIONAL TABLES

Table 1. Cointerventions offered in the intervention arm but not the control arm*

	Baqui 2008	Bhandari 2012	Degefie 2017	Gill 2011	Soofi 2017
Community meetings and mobilisation	x	x		x	x
Antenatal home visits	x				
Maternal iron and folic acid supplementation	x				
Distribution of clean delivery kits					x
Basic neonatal resuscitation for home births				x	x
Assessment and management/referral of low birthweight and asphyxiated babies					x
Postnatal home visits	x	x			x
Breastfeeding support	x	x			

Table 1. Cointerventions offered in the intervention arm but not the control arm* (Continued)

Hypothermia assessment and prevention	x	x	
Jaundice assessment	x	x	
Maternal counselling on newborn care/PSBI signs	x	x	x

*Supplementary interventions that are offered in both the intervention and control arm of an individual study are not included in the table.
PSBI: possible serious bacterial infections

APPENDICES

Appendix 1. Cochrane Neonatal standard search strategy

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))

Embase: ((exp infant) OR (infan* OR newborn or neonat* OR premature or very low birth weight or low birth weight or VLBW or LBW).mp AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial).mp

CINAHL: (infan* OR newborn OR neonat* OR premature OR low birth weight OR VLBW OR LBW) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Cochrane Library: (infan* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

We used the following terms for trial registries: (infant OR newborn OR neonatal OR premature OR low birth weight) AND (drug therapy OR infection OR antibiotics)

Appendix 2. 'Risk of bias' tool

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorised the method used to generate the allocation sequence as:

- low risk (any truly random process e.g. random number table; computer random number generator);
- high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorised the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk.

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk, high risk or unclear risk for participants; and
- low risk, high risk or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised the methods as:

- low risk (< 20% missing data);
- high risk ($\geq$ 20% missing data); or
- unclear risk.

6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we compared prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we contacted study authors to gain access to the study protocol. We assessed the methods as:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we described any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk; or
- unclear risk.

If needed, we explored the impact of the level of bias through undertaking sensitivity analyses.

HISTORY

Protocol first published: Issue 1, 2009

Review first published: Issue 4, 2019

Date	Event	Description
29 August 2017	Amended	Protocol has been rewritten. The authors have redefined the scope of this protocol, originally published in 2009 (Zaidi 2009).
13 February 2009	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Jessica Duby and Zohra Lassi completed this review under the supervision of Zulfiqar A. Bhutta.

DECLARATIONS OF INTEREST

JD has no interest to declare.

ZL has no interest to declare.

ZB has no interest to declare.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol for this review was published in 2009 under the title 'Community based management of neonatal sepsis in developing countries' (Zaidi 2009). The original protocol was updated, revised and published in 2018 under the review's current title (Duby 2018). The revised protocol analyses the effects of specific community-based antibiotic regimens which were not considered in the original protocol. The current review follows the methodological plan detailed in the revised protocol. Certain planned subgroup analyses detailed in the protocol were not undertaken due to the nature of the studies.

INDEX TERMS

Medical Subject Headings (MeSH)

*Community Health Services; Anti-Bacterial Agents [*therapeutic use]; Bacterial Infections [*drug therapy]; Developing Countries; Infant Mortality; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant; Infant, Newborn