Supplementary materials

ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia (sCAP).

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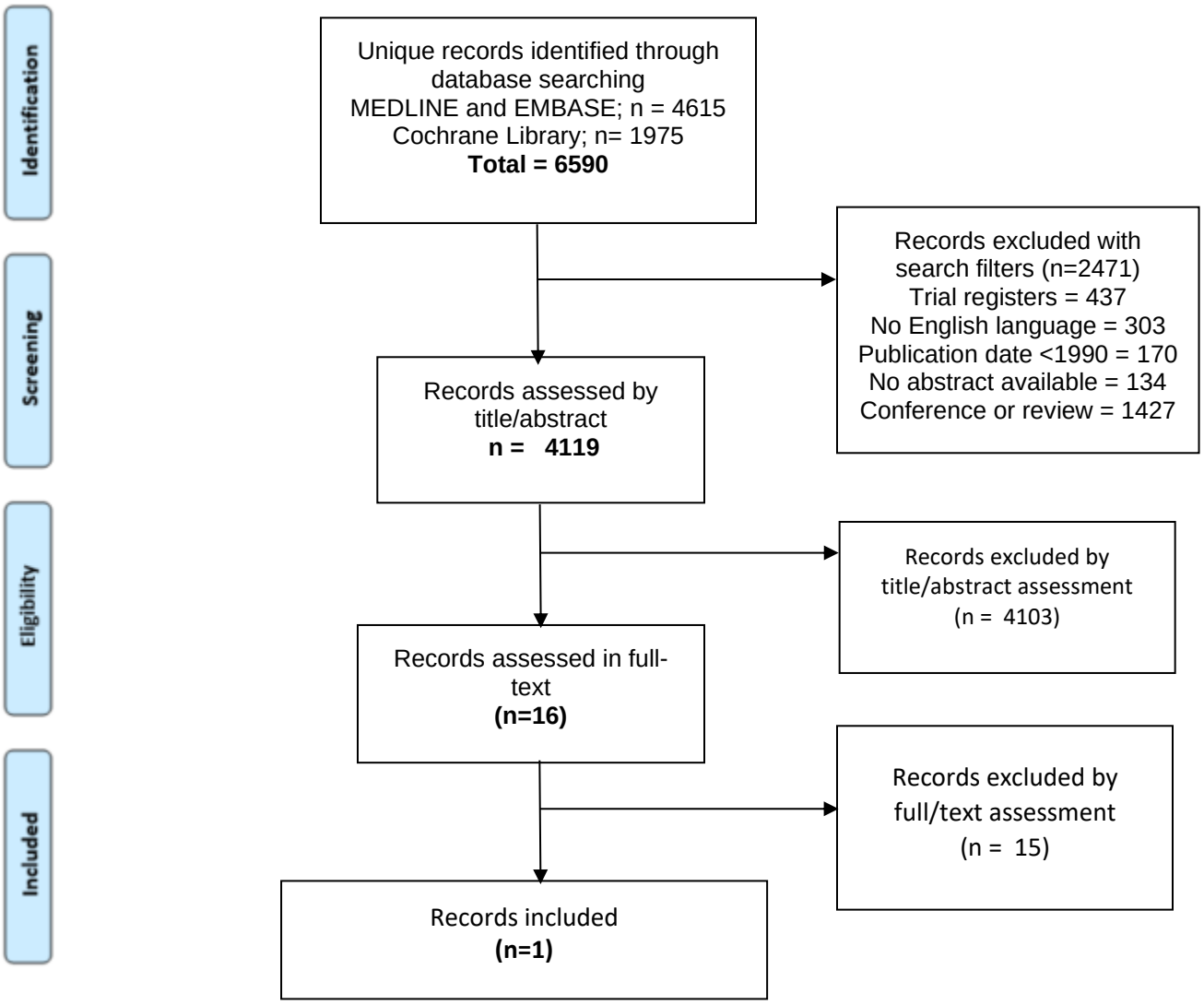

*For this PICO two separate searches were performed, one for RCTs and one for SRs.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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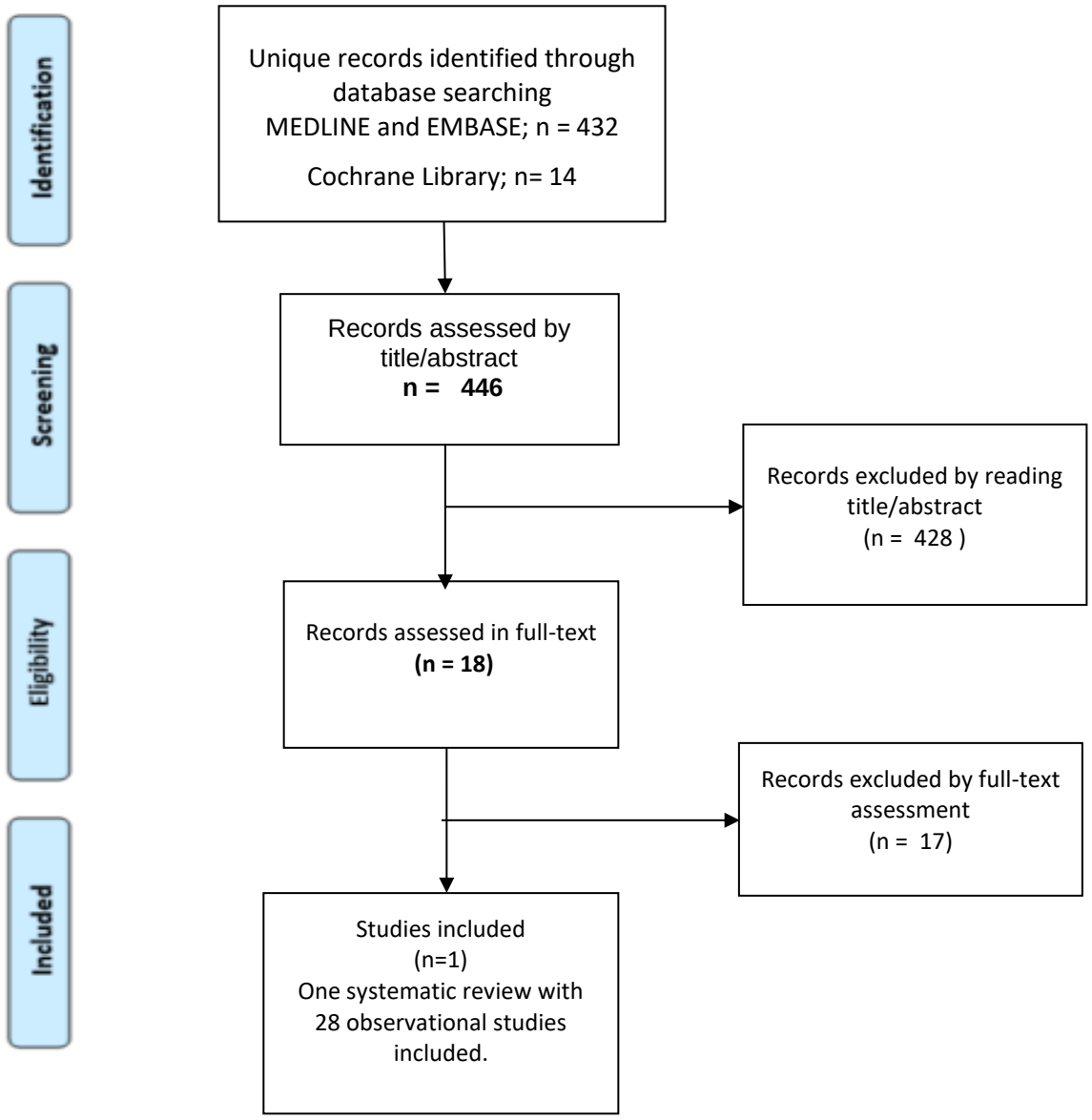
PRISMA Flow Diagram (Searches for Systematic Reviews)*



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Evidence Profiles

Question 1. In patients with sCAP should rapid microbiologic techniques be added to current testing of blood and respiratory tract samples?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rapid diagnostic microbiological methods (PCR)	Non rapid diagnostic microbiological methods (control)	Relative (95% CI)	Absolute (95% CI)		
Incremental detection rate												
23	observational studies [1]	not serious	serious [a]	very serious [b]	not serious	none	2916	4189	-	MD **16 percentual points more** (15 more to 3 more)	⊕◯◯◯ VERY LOW	CRITICAL
PCR detection rate												
12	observational studies [1]	not serious	serious [a]	very serious [c]	not serious	none	2196	0	-	mean **29 percentual points** (17 to 27)	⊕◯◯◯ VERY LOW	CRITICAL
non-PCR detection rate												
9	observational studies [1]	not serious	serious [a]	very serious [c]	not serious	none	0	4189	-	mean **13 percentual points** (9 to 18)	⊕◯◯◯ VERY LOW	CRITICAL
Antibiotic prescription												
1	randomised trials [2]	not serious	not serious [d]	not serious	serious [e]	none	301/360 (83.6%)	294/354 (83.1%)	**OR 0.99** (0.57 to 1.70)	**1 fewer per 1.000** (from 94 fewer to 62 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Intravenous antibiotic prescription												

1	randomised trials [2]	not serious	not serious [d]	not serious	serious [e]	none	196/360 (54.4%)	183/354 (51.7%)	**OR 1.15** (0.83 to 1.50)	**35 more per 1.000** (from 47 fewer to 99 more)	⊕⊕⊕◯ MODERATE	CRITICAL

Single dose of antibiotic

1	randomised trials [2]	not serious	not serious [d]	not serious	serious [f]	none	31/360 (8.6%)	10/354 (2.8%)	**OR 3.26** (1.59 to 6.68)	**58 more per 1.000** (from 16 more to 134 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

Duration of antibiotic prescription

1	randomised trials [2]	not serious	not serious [d]	not serious	serious [e]	none	360	354	-	MD **0.4 days fewer** (1.2 fewer to 0.4 more)	⊕⊕⊕◯ MODERATE	CRITICAL

Length hospital stay

1	randomised trials [2]	not serious	not serious [d]	not serious	serious [f]	none	360	354	-	MD **1.1 days fewer** (2.2 fewer to 0.3 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Large variability between effect estimates

b. Comparison of detection rates come from different studies, not directly compared. there is uncertainty with regards to whether these positive results are false or true. Mixed population of CAP and severe CAP.

c. Detection rate not compared, there is uncertainty with regards to whether these positive results are false or true. Mixed population of CAP and severe CAP.

d. Single study, variability not considered

e. 95%CI range from clinically substantial benefit to harm

f. Low number of events, 95%CI ranges from clinical substantial benefit to futility

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Supplementary evidence (not assessed with GRADE) (n=39)

Pseudomonas Multiplex PCR Studies									
(1)Study	Site(s)	Platform	Sample	Number	SOC Cases	Sensitivity	Specificity	PPV	NPV
Murphy(2)	Multi	BioFire	BAL	846	36 (74)	48.6 (100)	100	100	95.3 (100)
			Sputum	836	106 (161)	97.2 (99.1)	92.2 (100)	64.4 (100)	99.6 (99.8)
Ginocchio (3)	Multi	BioFire	BAL 1226 Sputum 1237	2463	316	96.5	96.3	79.2	99.5
Klein (4)	Multi	Unyvero	BAL	1015	72 (111)	95.8 (99.1)	95.4 (99.8)	61.6 (98.2)	99.7 (99.9)

Gastli (5)	Multi	BioFire	BAL 240, ETA 217, sputum 58	515	45	95.6	96.8	74.1	99.6
Rand (6)	Single	BioFire	BAL, ETA	396	50 (61)	98.0 (98.4)	93.9 (97.0)	70.4 (85.9)	99.7
Foschi (7)	Single	BioFire	ETA 178, BAL52	230	34	91.2	96.9	83.7	98.4
Webber (8)	Single	BioFire	BAL 70, Sputum 130	200	8	100	96.4	53.3	100
Collins (9)	Single	Unyvero	BAL	175	33	100	100	100	100
Monard (10)	Multi	BioFire	BAL 34,ETA 71, sputum 33, BBS 21	159	23	100	96.3	82.1	100
Camelena(11)	Single	BioFire	73 NBBAL, 63 sputu	147	26	100	96.7	86.7	100

			m, 11 PSB						
Maataoui (12)	Single	BioFire	Mini-BAL 77, BAL 28, ETA 3, sputum 4	112	6	100	95.3	54.5	100
Yoo (13)	Single	BioFire	ETA 31, Sputum 69	99	19	100	88.8	67.8	100
Camelena (14)	Single	BioFire	NBBAL	96	14	100	100	100	100
Peiffer-Smadja (15)	Single	Unyvero	BAL 72, PTC 23	95	31	100	97	94	100
Personne (16)	Two	Unyvero	BAL 3, ETA 32, sputum 55	90	13	100	92.2	68.4	100
Ozongwu (17)	Single	Unyvero	BAL 1, ETA 31, sputum 52	85	11 (12)	100	83.8 (84.9)	47.8 (52.2)	100
Sun (18)	Multi	Unyvero	BAL	84	7	71.4	94.8	55.6	97.3

Lee (19)	Single	BioFire	BAL 7 ETA 59	59	7	83.3	98.1	83.3	98.1
Mitton(20)	Single	BioFire	ETA	59	9	100	98	90	100

(n) – after correction of false positive and negative PCRs by additional testing

Excluded: - unable to separate Pseudomonas cases (21-26), <5 Pseudomonas cases (27-34), children only (35)

ESBL Detection = *ctx*M gene detection							
Study	Site(s)	Platform	Sample	Number	ESBL Cases	% Positive Agreement	% Negative agreement
Murphy (2)	Multi	BioFire	BAL	151	7	6/7 (85.7%)	144/144 (100%)
			Sputum	291	10	8/10 (80%)	280/281 (99.6%)
Ginocchio (3)	Multi	BioFire	BAL, Sputum	1537	133	NA	NA
Klein (4)	Multi	Unyvero	BAL	208	9	8/9 (88.9%)	198/199 (99.8%)
Rand (6)	Single	BioFire	BAL, ETA	396	14	NA	NA
Foschi (7)	Single	BioFire	ETA, BAL	NA	6	6/6 (100%)	NA
Webber (8)	Single	BioFire	BAL, Sputum	200	7	4/4 (100%)	NA
Gadsby (24)	Single	Unyvero	BAL	30	8	8/8 (100%)	22/22 (100%)
Monard (10)	Multi	BioFire	BAL,ETA, sputum, BBS	159	11	NA	NA
Camelena(11)	Single	BioFire	NBBAL,sputum,PSB	NA	3	1/3 (33.3%)	NA
Maataoui (12)	Single	BioFire	Mini-BAL,BAL,ETA,sputum	NA	9	8/9 (88.9%)	NA

Yoo (13)	Single	BioFire	ETA, Sputum	100	16	14/16 (87.5%)	NA
Camelena (14)	Single	BioFire	NBBAL	NA	2	1 / 2 (50%)	NA
Peiffer-Smadja (15)	Single	Unyvero	BAL, PTC	48	5	5/5 (100%)	45/48 (93.7%)
Ozongwu (17)	Single	Unyvero	BAL, ETA, sputum	39	2	1 / 2 (50%)	36/37 (97.3%)
Zacharioudakis (32)	Single	Biofire	Sputum	NA	3	3/3 (100%)	NA
Lee (19)	Single	BioFire	BAL, ETA	32	4	1 / 4 (25%)	NA
Mitton(20)	Single	BioFire	ETA	59	7	5/7 (71.4%)	NA
Unable to assess presence of ESBL in pathogen if culture did not grow. In mixed culture, unable to assess which Gram-negative pathogen harbors ESBL gene							

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S. aureus									
Study	Site(s)	Platform	Sample	Number	SOC Cases	Sensitivity	Specificity	PPV	NPV
Murphy(2)	Multi	BioFire	BAL	846	47 (115)	97.9(99.1)	91.2(99.9)	39.7(99.1)	99.9
			Sputum	836	112 (205)	99.1(99.5)	91.2(100)	54.4(100)	99.8
Ginocchio (3)	Multi	BioFire	BAL 1226 Sputum 1237	2463	531	97.1	82.2	58.1	99.1
Klein (4)	Multi	Unyvero	BAL	1015	71 (99)	88.7(94.9)	95.7(98.9)	60.0(90.4)	99.1(99.5)
Gastli (5)	Multi	BioFire	BAL 240, ETA 217, sputum 58	515	98	98.0	88.5	66.7	99.5
Rand (6)	Single	BioFire	BAL, ETA	396	45 (55)	100	85.2(87.7)	46.4(56.7)	100
Foschi (7)	Single	BioFire	ETA 178, BAL52	230	15	100	95.3	60	100
Webber (8)	Single	BioFire	BAL 70,Sputum 130	200	22	100	87.6	50	100
Collins (9)	Single	Unyvero	BAL	175	37	91.9(92.3)	98.5(99.3)	94.4(97.3)	97.8
Camelena(11)	Single	BioFire	73 NBBAL, 63 sputum, 11 PSB	147	16	94.1	98.5	88.9	99.2

Yoo (13)	Single	BioFire	ETA 31, Sputum 69	99	16	100	83.3	53.3	100
Kolenda (30)	Three	BioFire	36 NBBAL,13 BAL, 50 ETA	99	7	100	93.5	53.8	100
Camelena (14)	Single	BioFire	NBBAL	96	11	91	98.8	91	98.8
Peiffer-Smadja (15)	Single	Unyvero	BAL 72, PTC 23	95	11	72.7	100	100	96.6
Tellapragada (33)	Single	Unyvero	ETA 61,BAL 11,PSB 8, ETA/sputum 2	83	23	100	86.7	74.2	100
Zacharioudakis (32)	Single	BioFire	Sputum	70	7	100	95.2	70	100
Mitton(20)	Single	BioFire	ETA	59	6	100	88.7	50	100
Sparks (34)	Single	BioFire	Sputum 27, BAL 12	39	7	100	87.5	63.6	100
Limited S. aureus/MRSA Assay									
Cercenado (36)	Single	Cepheid	ETA	135*	105	99.0	72.2	90.7	96.3
Trevino (37)	Single	Cepheid	BAL, ETA	100	21	88.9	86.8	40	98.8
Coppens (1)	Single	Cepheid	ETA	79	39	100	95(100)	95.1(100)	100
Paonessa (38)	Single	Cepheid	BAL, NBBAL	247	48	95.8	89.9	69.7	98.9

* Enriched specimens; (n) – after correction of false positive and negative PCRs by additional testing

Excluded: - unable to separate S. aureus cases (10, 24, 26, 39), $\leq$ 5 cases of S. aureus (12, 16-19, 27, 28)

***mec*A detection (in studies with at least 5 cases)**							
Study	Site(s)	Platform	Sample	Number	MRSA Cases	% Positive Agreement	% Negative agreement
Murphy (2)	Multi	BioFire	BAL	151	45	40/45 (88.9%)	64/70 (91.4%)
			Sputum	291	98	94/98 (95.9%)	91/104 (87.5%)
Ginocchio (3)	Multi	BioFire	BAL, Sputum	531	84	82/84 (97.6%)	423/447 (94.6%)
Klein (4)	Multi	Unyvero	BAL	208	9	8/9 (88.9%)	198/199 (99.8%)
Yoo (13)	Single	BioFire	ETA, Sputum	100	16	14/16 (87.5%)	NA
Rand (6)	Single	BioFire	BAL, ETA	45*	25	20/25 (80%)	20/20 (100%)*
Foschi (7)	Single	BioFire	ETA, BAL	NA	8	6/8 (80%)	14/17 (82.4%)
Webber (8)	Single	BioFire	BAL, Sputum	200	8	8/8 (100%)	10/14 (71.4%)*
Collins (9)	Single	Unyvero	BAL	175	6	6/6 (100%)	NA
Cercenado (36)	Single	Cepheid	ETA	135	43	43/43 (100%)	55/56 (98.2%)

Trevino (37)	Single	Cepheid	BAL, ETA	100	6	5/6 (83.3%)	89/90 (98.9%)
Paonessa (38)	Single	Cepheid	BAL, NBBAL	247	23	22/23 (95.7%)	220/224 (98.2%)
* in *S. aureus* cases only							

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Evidence to Decisions (EtD) framework

Question 1. In patients with sCAP should rapid microbiologic techniques be added to current testing of blood and respiratory tract samples?	
POPULATION:	Adult patients with severe CAP
INTERVENTION:	Use of mono- or multiplex-polymerase chain reaction (PCR) assays to determine etiology of SCAP

Test accuracy

How accurate are PCRs for diagnosis of etiology in SCAP?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ Inaccurate ○ Accurate ○ **Very accurate** ○ Varies ○ Don't know	PCR has high sensitivity (0.71 to 1.0) and high specificity (0.72 to 1.00) for the diagnosis of CAP etiology. Negative predictive value >95% in all studies	No true gold standard against which results of PCR can be compared. Sensitivity and specificity only assessed for pathogens on panel. Majority of evidence for false positive PCR compared with culture suggests false negative culture rather than false positive PCR (1-4).

Desirable Effects

How substantial are the desirable anticipated effects of PCR testing for SCAP etiology?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ **Moderate** ○ Large ○ Varies ○ Don't know	Multiplex PCRs will detect many pathogens routinely covered by usual CAP antibiotics. However, high negative predictive value potentially allows discontinuation of broad spectrum antibiotics when resistant pathogens are suspected	Lack of susceptibility markers for many pathogens/resistance mechanisms can limit narrowing of antibiotic therapy. However, detection of resistance genes highly reliable.

Undesirable Effects

How substantial are the undesirable anticipated effects of PCR testing for SCAP etiology?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ **Small** ○ Trivial ○ Varies ○ Don't know	Inappropriate narrowing of antibiotics for pathogens or resistance mechanisms not on multiplex panel risks adverse outcomes. Significantly less likely for SCAP than for HAP/VAP	

Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of accuracy for PCR testing for SCAP etiology?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High but variable ○ No included studies	Not formally rated with GRADE. The certainty of the evidence of test accuracy varies by pathogen and type of specimen.	Timing of sample acquisition likely to have an effect although less than for cultures. Multiplex technology may result in less than optimal PCR conditions for each pathogen

Certainty of the evidence of for PCR testing for SCAP etiology test result/management

How certain is the link between test results and management decisions?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ **Very low** ○ Low ○ Moderate ○ High ○ No included studies	One true RCT of limited PCR (MRSA only) demonstrates safety of withholding antibiotic based on result.	Multiple studies implying changes in therapy but not mandated and not algorithmic

Balance of effects

Does the balance between desirable and undesirable effects favor for PCR testing for SCAP etiology or conventional culture-based testing only?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ **Favors the intervention** ○ Varies ○ Don't know	Detection of unsuspected pathogens and ability to de-escalate specific antibiotics favour PCR testing. Adverse effects of stopping antibiotics based on negative multiplex PCR unknown	Limited number of pathogens on any multiplex PCR platform still raises uncertainty for rare pathogens that might respond to prescribed antibiotics Cost implications may limit widespread implementation.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No clear cost benefit analysis available	Moderate cost for diagnostic platform but many institutions may have purchased previously for other multiplex PCR panels Per test cost moderate but clearly greater than for culture based diagnosis. Cost of avoiding antibiotics, antibiotic side effects, and appropriate escalation of therapy make this financial assessment difficult.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ **Probably increased** ○ Increased ○ Varies ○ Don't know	No data	Because of additional costs of equipment and per test, less likely to be available in resource constrained settings, potentially leading to increased health disparity

Acceptability

Is PCR testing for SCAP etiology acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ **Varies** ○ Don't know	No data	Lay people likely to favour more accurate diagnosis and fewer antibiotics. Strong endorsement by antibiotic stewardship teams and clinicians. Hospital administrators and laboratory managers may be challenged by additional costs, especially if clinical decisions are not based on results. Acceptance may vary depending on resources and healthcare settings.

Feasibility

Is PCR testing for SCAP etiology feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ○ Yes ○ **Varies** ○ Don't know	Multiple studies of rapid PCR for blood cultures and antibiotic stewardship efforts	Very feasible, especially if platform already available in institution. Turnaround time and notifications may be a challenge

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

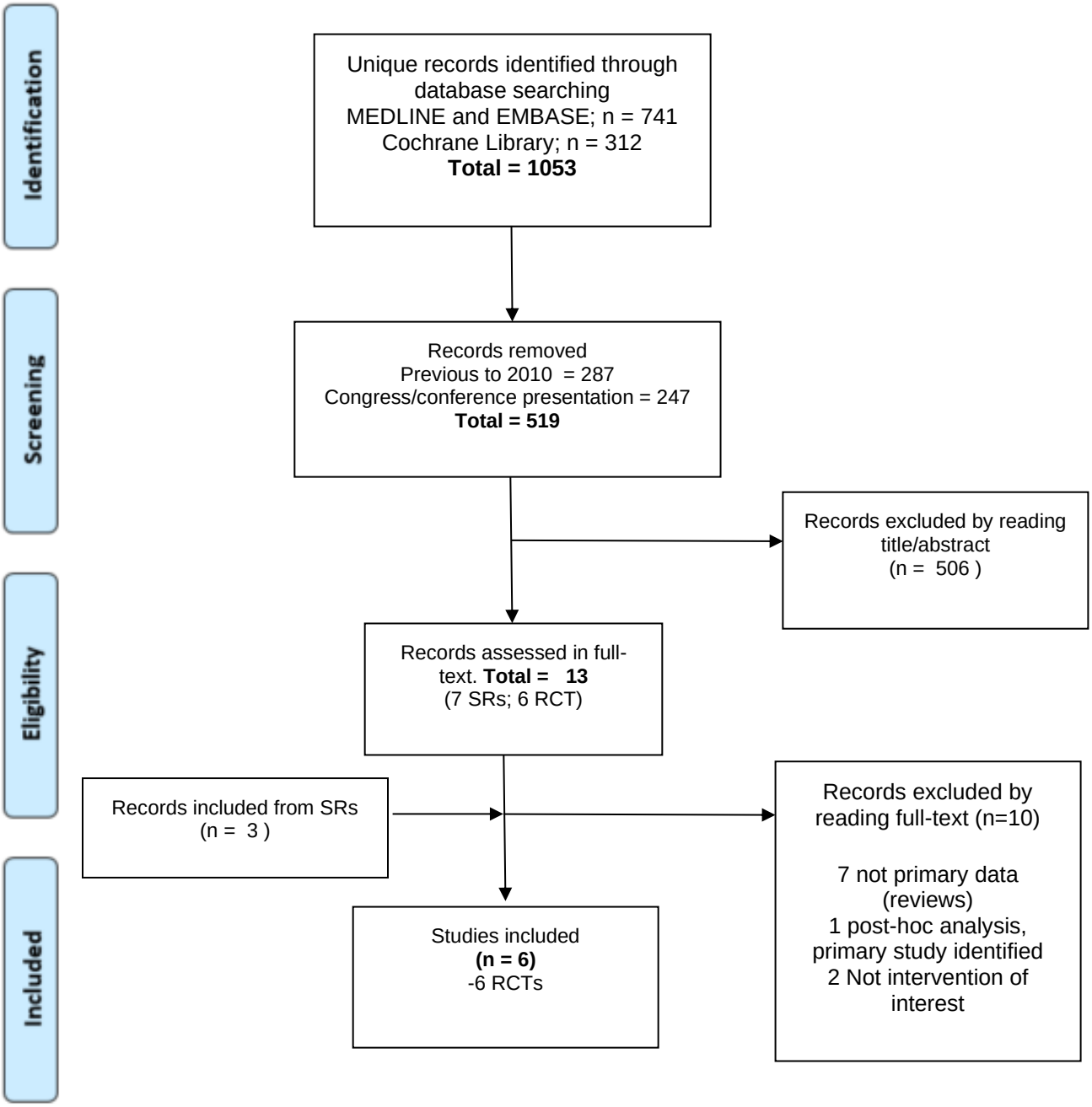
CONCLUSIONS

Recommendation

If the technology is available, we suggest sending a lower respiratory tract (LRT) sample (either sputum or endotracheal aspirates) for multiplex PCR testing (virus and/or bacterial detection) whenever non-standard sCAP antibiotics are prescribed or considered (conditional recommendation, very low quality of evidence).

Question 2. In hypoxemic patients with sCAP, can either non-invasive mechanical ventilation (NIV) or high-flow nasal oxygen (HFNC) be used initially—rather than supplemental standard oxygen administration—to avoid intubation and reduce mortality?

PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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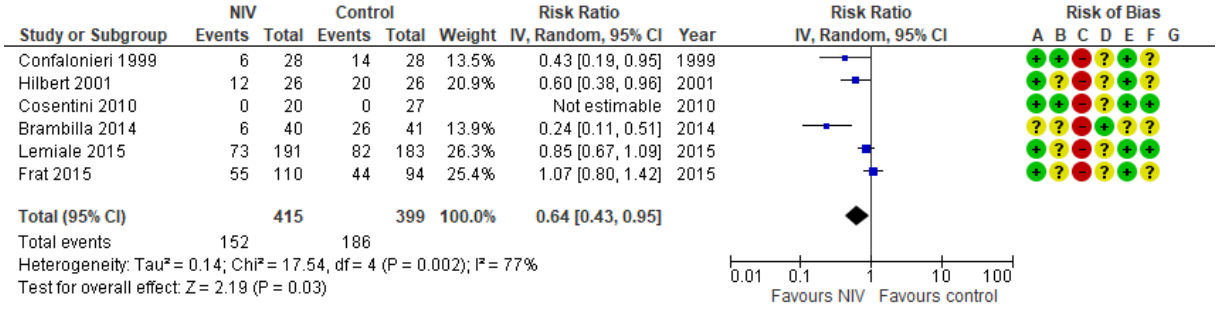
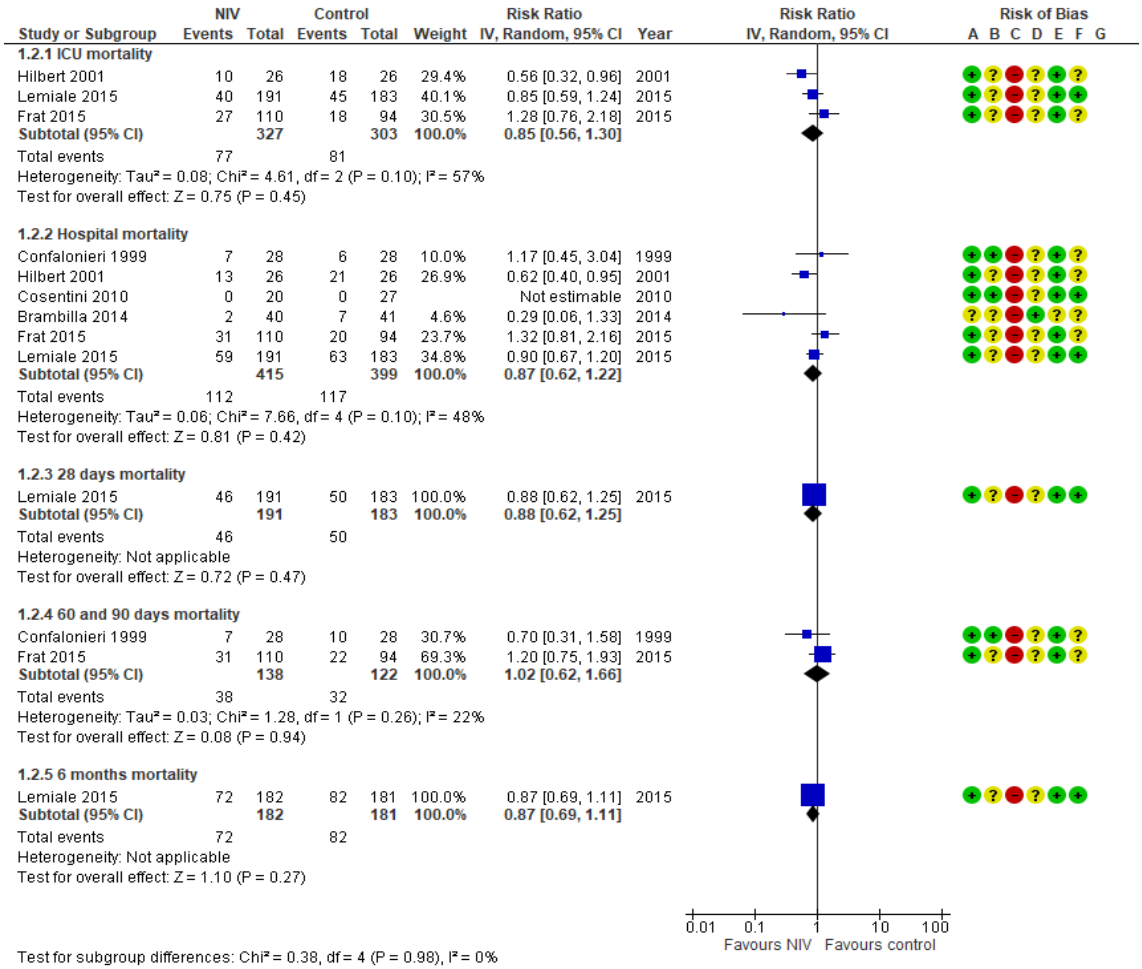
Forest Plots

Intubation



Mortality (ICU mortality, hospital mortality, 28 days mortality, 90 days, 6 months mortality)



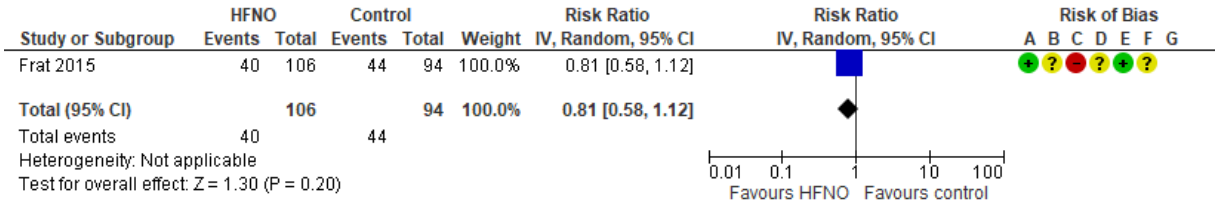
Test for subgroup differences: Chi² = 0.38, df = 4 (P = 0.98), I² = 0%

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

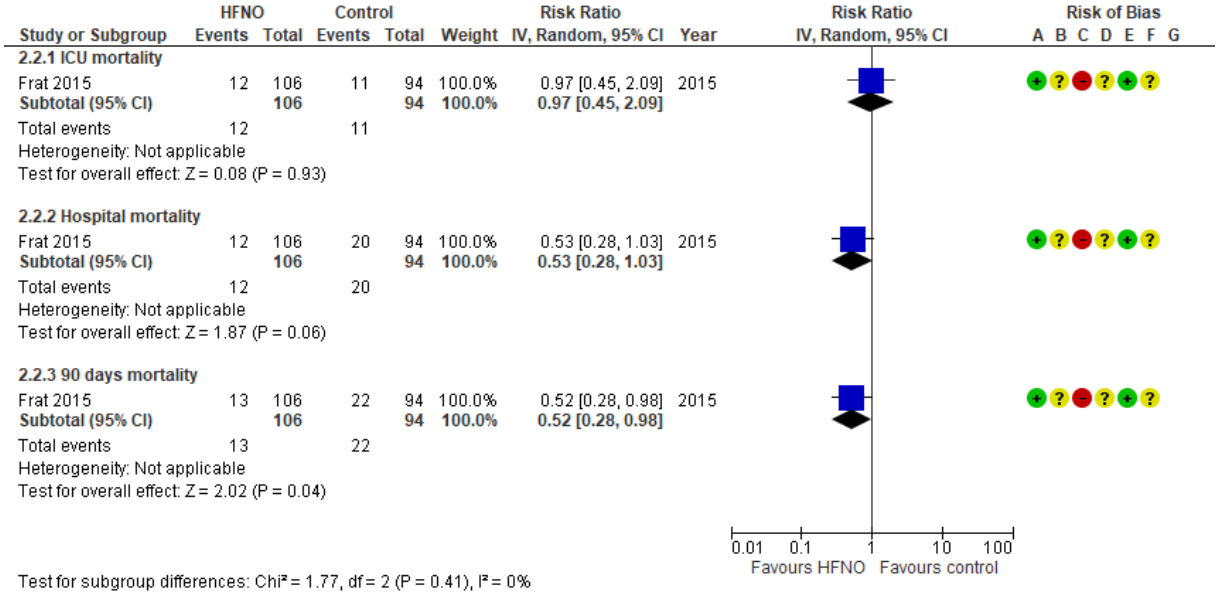
Forest plots: HFNO vs standard therapy

Intubation



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Mortality (ICU mortalilty, hospital mortality, 90 days mortality)



Test for subgroup differences: Chi² = 1.77, df = 2 (P = 0.41), I² = 0%

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Evidence profile: NIV vs conventional oxygen.

Study setting: Adults with sCAP admitted for inpatient treatment in different countries (Italy, France, Belgium).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NIV	conventional oxygen	Relative (95% CI)	Absolute (95% CI)		
Intubation at 28 days												
6	randomised trials[1,2,3,4,5,6]	very serious[a,b]	not serious	not serious	not serious	none	152/415 (36.6%)	186/399 (46.6%)	**RR 0.64** (0.43 to 0.95)	**168 fewer per 1,000** (from 266 fewer to 23 fewer)	⨁⨁◯◯ Low	CRITICAL
Mortality - ICU mortality												
3	randomised trials[2,5,6]	not serious	not serious	not serious	serious[c]	none	77/327 (23.5%)	81/303 (26.7%)	**RR 0.85** (0.56 to 1.30)	**40 fewer per 1,000** (from 118 fewer to 80 more)	⨁⨁⨁◯ Moderate	CRITICAL
Mortality - Hospital mortality												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NIV	conventional oxygen	Relative (95% CI)	Absolute (95% CI)		
6	randomised trials[1,2,3,4,5,6]	not serious	not serious	not serious	serious[c]	none	112/415 (27.0%)	117/399 (29.3%)	**RR 0.87** (0.62 to 1.22)	**38 fewer per 1,000** (from 111 fewer to 65 more)	⨁⨁⨁◯ Moderate	CRITICAL

Mortality - 28 days mortality

1	randomised trials[6]	not serious	not serious	not serious	serious[c]	none	46/191 (24.1%)	50/183 (27.3%)	**RR 0.88** (0.62 to 1.25)	**33 fewer per 1,000** (from 104 fewer to 68 more)	⨁⨁⨁◯ Moderate	CRITICAL

Mortality - 60 and 90 days mortality

2	randomised trials[1,5]	not serious	not serious	not serious	serious[c]	none	38/138 (27.5%)	32/122 (26.2%)	**RR 1.02** (0.62 to 1.66)	**5 more per 1,000** (from 100 fewer to 173 more)	⨁⨁⨁◯ Moderate	CRITICAL

Mortality - 6 months mortality

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NIV	conventional oxygen	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials[6]	not serious	not serious	not serious	serious[c]	none	72/182 (39.6%)	82/181 (45.3%)	**RR 0.87** (0.69 to 1.11)	**59 fewer per 1,000** (from 140 fewer to 50 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Due to the nature of the intervention, blinding was not feasible (i.e. all information is from studies at high risk of bias). Additionally, decision to intubate is inherently subjective, even though predefined intubation criteria may alleviate this subjectivity to some extent. Therefore, there is high risk of performance bias.

b. 26 patients (6.5%) in the control group received NIV as rescue therapy, of whom 19 were intubated, thus jeopardising the validity of intention to treat analysis

c. The confidence interval for the pooled effect doesn't exclude harm caused by the intervention.

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d'Onco-Hematologie. Effect of Noninvasive Ventilation vs Oxygen Therapy on Mortality Among Immunocompromised Patients With Acute Respiratory Failure: A Randomized Clinical Trial. JAMA; 2015.

Evidence profile: HFNO vs conventional oxygen.

Study setting: Adults with sCAP admitted for inpatient treatment in different countries (France).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HFNO	conventional oxygen	Relative (95% CI)	Absolute (95% CI)		
Intubation 28 days												
1	randomised trials[1]	very serious[a,b]	not serious	not serious	serious[c]	none	40/106 (37.7%)	44/94 (46.8%)	**RR 0.81** (0.58 to 1.12)	**89 fewer per 1,000** (from 197 fewer to 56 more)	⊕◯◯◯ Very low	CRITICAL
Mortality - ICU mortality												
1	randomised trials[1]	not serious	not serious	not serious	serious[c]	none	12/106 (11.3%)	11/94 (11.7%)	**RR 0.97** (0.45 to 2.09)	**4 fewer per 1,000** (from 64 fewer to 128 more)	⊕⊕⊕◯ Moderate	CRITICAL
Mortality - Hospital mortality												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HFNO	conventional oxygen	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials[1]	not serious	not serious	not serious	serious[c]	none	12/106 (11.3%)	20/94 (21.3%)	**RR 0.53** (0.28 to 1.03)	**100 fewer per 1,000** (from 153 fewer to 6 more)	⨁⨁⨁◯ Moderate	CRITICAL

Mortality - 90 mortality

1	randomised trials[1]	not serious	not serious	serious[d]	not serious	none	13/106 (12.3%)	22/94 (23.4%)	**RR 0.52** (0.28 to 0.98)	**112 fewer per 1,000** (from 169 fewer to 5 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Due to the nature of the intervention, blinding was not feasible

b. 14 patients in the HFNO group received NIV as a rescue therapy, 9 (64%) of whom the were intubated, thus jeopardising validity of the intention-to-treat analysis

c. The confidence interval for the effect just includes an appreciable benefit or harm

d. It is likely that the effect of HFNO would be most pronounced during hospitalisation; hence, it is not unlikely that the observed difference in survival at later stages is due to factors other than the intervention

References

1. Frat, J. P., Thille, A. W., Mercat, A., Girault, C., Ragot, S., Perbet, S., Prat, G., Boulain, T., Morawiec, E., Cottereau, A., Devaquet, J., Nseir, S., Razazi, K., Mira, J. P., Argaud, L., Chakarian, J. C., Ricard, J. D., Wittebole, X., Chevalier, S., Herbland, A., Fartoukh, M., Constantin, J. M., Tonnelier, J. M., Pierrot, M., Mathonnet, A., Beduneau, G., Deletage-Metreau, C., Richard, J. C., Brochard, L., Robert, R., Group, Florali Study, Network, Reva. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med; 2015.

Evidence to Decision (EtD) Frameworks

Question 2. In hypoxemic patients with sCAP, can either non-invasive mechanical ventilation (NIV) or high-flow nasal oxygen (HFNC) be used initially—rather than supplemental standard oxygen administration—to avoid intubation and reduce mortality?	
POPULATION:	Patients with severe community acquired pneumonia (as defined in the study)
INTERVENTION:	NIV or HFNO
COMPARISON:	Conventional oxygen therapy

ASSESSMENT

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial **X** Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Summary of Findings **Desirable** Intubation decreased with NIV (0.64 [0.43, 0.95]). Combining data from 6 studies Hospital and 90 day mortality less with HFNO (0.52 [0.28, 0.980]). Data are extracted only from one study. **Neutral/Little effect** ICU mortality similar with NIV Hospital mortality similar with NIV 28d mortality similar with NIV 60d and 90d similar with NIV 6 month mortality similar with NIV Lower Intubation Rate with NIV vs HFNO demonstrated only for Covid 19 ICU mortality similar with HFNO Hospital mortality similar with HFNO	Consider NIV and HFNO separately (only from Frat) Overall no effect for NIV only (Bambrilla changes the effect depend on numbers considered) Small, moderate at best, effect from HFNO (Table 2 Frat 2015) Brambilla: 81 patients: sCAP 51 CAP / 24 HCAP / 6 others

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small **X Trivial** ○ Varies ○ Don't know	**Neutral/little effect** The potential for undesirable effects with prolonged use of NIV or HFNO No significant effect of hospital or ICU mortality Inconsistent effects of intubation between NIV and HFNO Heterogeneity amongst the various study populations.	Observational data: 24-48 hours as a threshold to decide on intubation. After that patient's outcomes with intubation criteria are worse as more severe Prolonged use of HFNC may have some adverse consequences (caution) In patients allocated to NIV or HFNO, there were 1 case of gastric distention and 2 cases of VAP. In controls, 7 cases of VAP, 4 cases of sinusitis and 1 pneumothorax occurred.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Very low **X Low** ○ Moderate ○ High ○ No included studies	Low for NIV, and very low for HFNC.	Due to Risk of bias and imprecision.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability **X Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Not systematically reviewed as a part of this TF. However, intubation and mortality are judged to be among the most important outcomes in patients with sCAP.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison Does not favor either the intervention or the comparison **X Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	There was no observed negative effects with the use of NIV or HFNO in patients with sCAP; Most outcomes were neutral with intubation and 90d mortality being favorable for NIV and HFNO respectively.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs **X Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Not systematically reviewed as a part of this TF. The estimated costs of providing NIV or HFNO in lieu of standard nasal cannula oxygen therapy was not reported in the studies.	HFNC may have relevant resource implications. Low certainty as the cost and availability of resources for NIV and HFNO may vary greatly across settings .

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison **X Probably favors the comparison** ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies	Not systematically reviewed as a part of this TF	The group was consistent in selecting "Probably favours the intervention." All agreed towards the side of cost effectiveness of NIV anf HFNO vs comparison.

○ No included studies		

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact **X Probably increased** ○ Increased ○ Varies ○ Don't know	Not systematically reviewed as a part of this TF	sCAP patients disproportionately come from disadvantaged populations, so treating sCAP may improve equity. In low or middle income countries /populations, hospital based NIV or HFNO may not be feasible and a recommendation for NIV or HFNO may exacerbate health equity vs. more financially advantageous regions .

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes **X Yes** ○ Varies ○ Don't know	Not systematically reviewed as a part of this TF	HFNC more acceptable intervention vs NIV (Frat 2015). Many clinicians would find NIV or HFNO acceptable due to their use in other acute respiratory conditions -- it is a familiar therapy to those who treat COVID. Patients may vary with regard to acceptability of NIV or HFNO, however if it improves clinical outcomes it may be acceptable.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes **X Varies** ○ Don't know	Not systematically reviewed as a part of this TF	HFNC more feasible to implement NIV may have some implementation issues. Some regions may not have infrastructure to support NIV or HFNO is sCAP; however there is widespread use of NIV and HFNO in other countries which can provide practice

		models to guide practice. This will vary depending on the health care system, resources, and patient location.

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	**X**	○

CONCLUSIONS

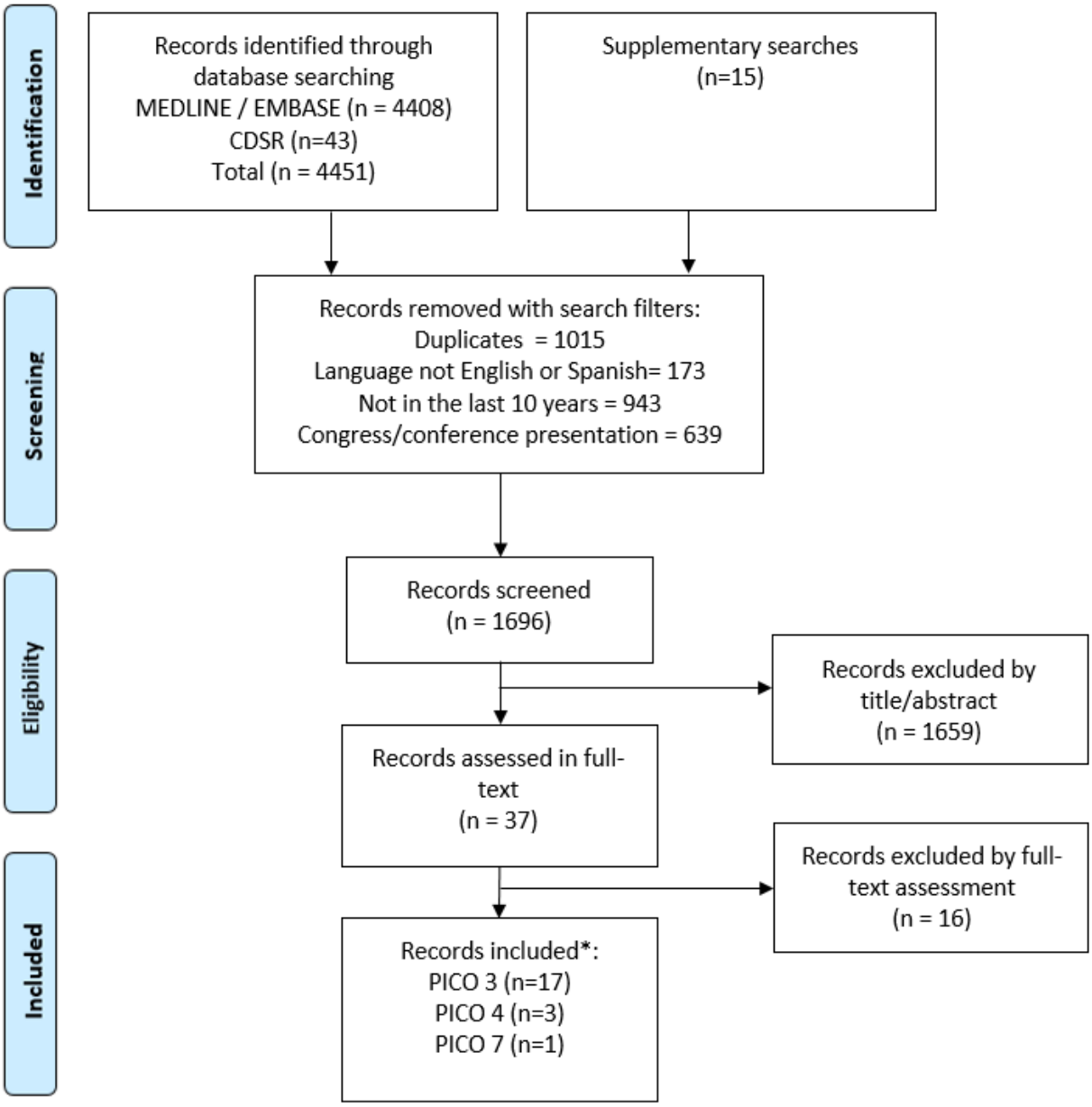
Recommendation

In patients with sCAP and acute hypoxemic respiratory failure not needing immediate intubation, we suggest using HFNC instead of standard oxygen (conditional recommendation, very low quality of evidence).

NIV might be an option in certain patients with persistent hypoxemic respiratory failure not needing immediate intubation, irrespective of HFNC (conditional recommendation, low quality of evidence).

Question 3. When using initial empiric therapy for sCAP, should a macrolide or fluoroquinolone be used as part of combination therapy, to reduce mortality and adverse clinical outcomes?

PRISMA Flow Diagram



***For PICOs 3,4,7 (concerning antibiotics) one search strategy was used, results of which are presented in one PRISMA Flow Diagram**

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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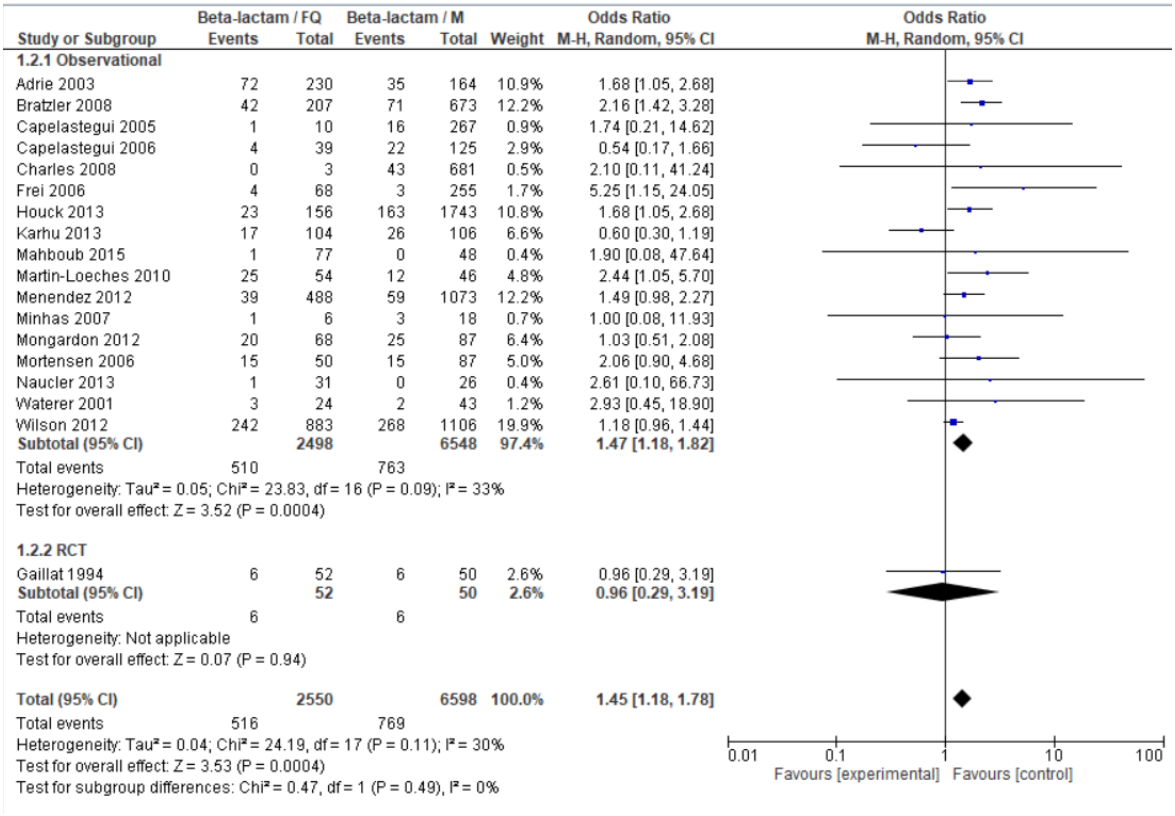
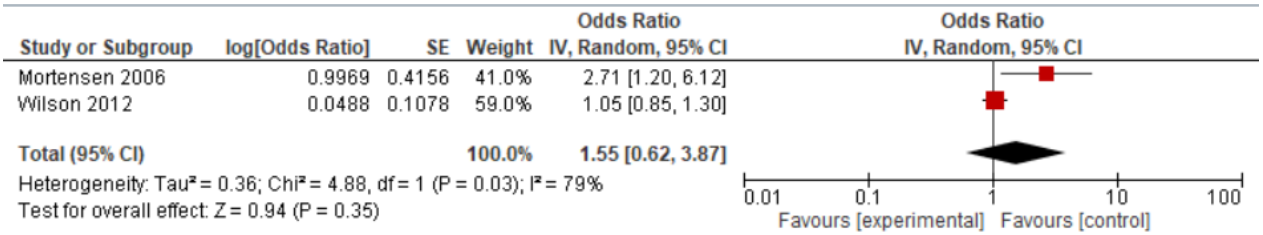
Forest Plots

Mortality – all studies

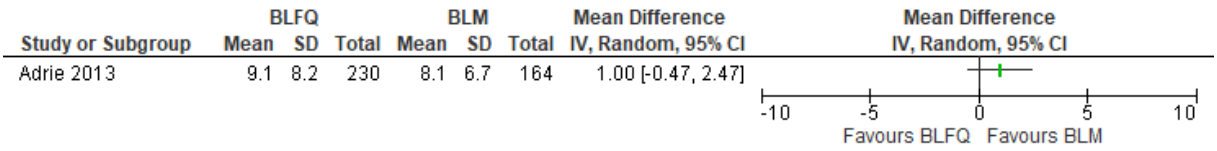


30 days mortality (adjusted)

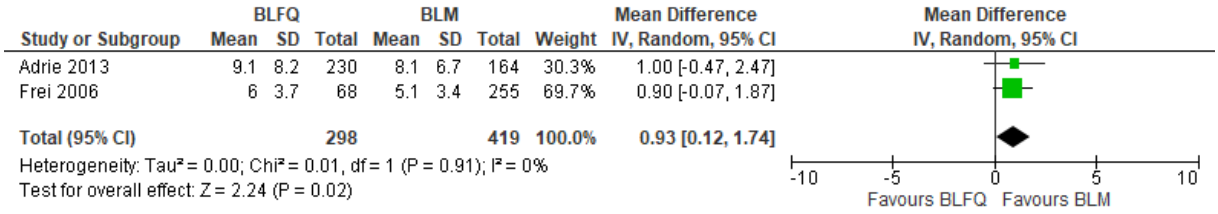


Duration of antibiotic treatment in days

Severe CAP (in GRADE Evidence Profile)

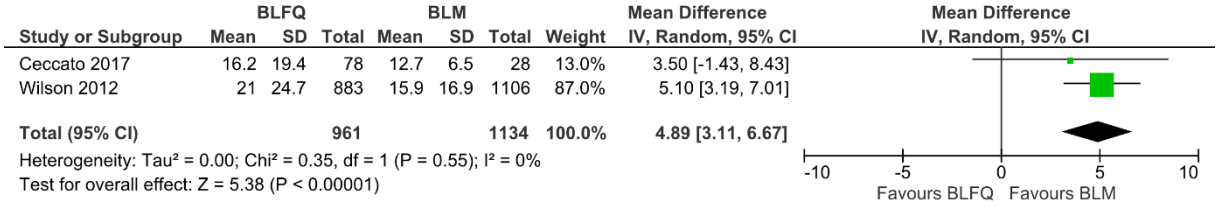


Mixed population (severe and nonsevere cases included)



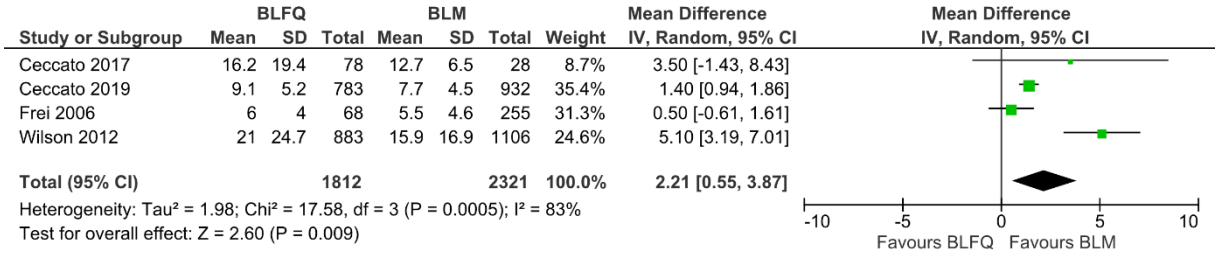
Length of hospital stay in days

Severe CAP (in GRADE Evidence Profile)



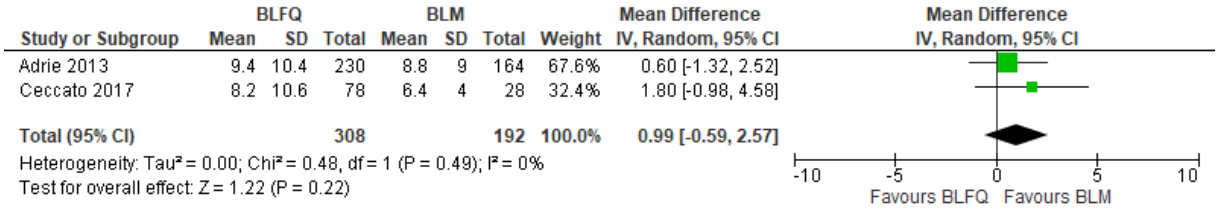
Of note: when comparing medians between BLFQ and BLM (as reported in the original publication), BLFQ shows a slightly longer hospital stay in days: *median [IQR]:* BLFQ (18 [9; 30]) vs BLM (17.5 [10.5; 35]); when comparing mean values (for better interpretation), BLFQ shows a slightly reduced length: *mean [SD]:* BLFQ 19.1 [15.7] vs BLM 21.2 [18.3].

Mixed population (severe and nonsevere cases included)



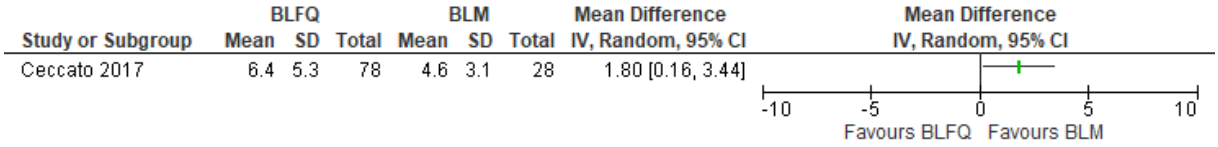
Length of ICU stay in days

Severe CAP (in GRADE Evidence Profile)

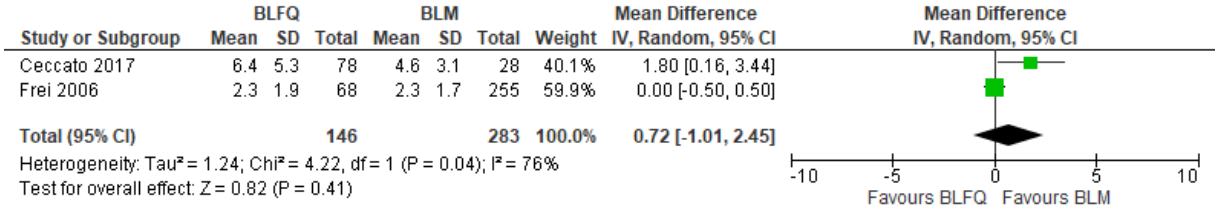


Time to clinical stability in days

Severe CAP (in GRADE Evidence Profile)

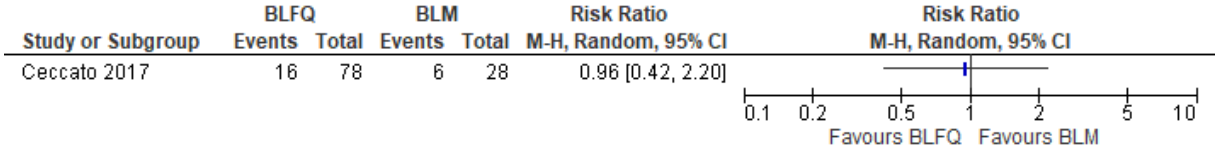


Mixed population (severe and nonsevere cases included)



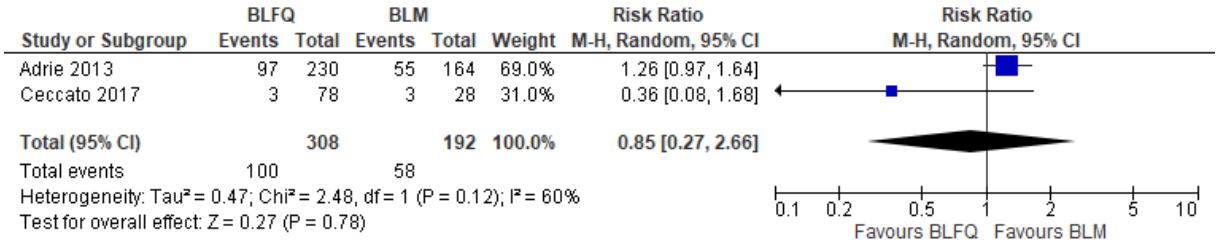
Treatment failure (composite outcome including incidence of septic shock and invasive mechanical ventilation)

Severe CAP (in GRADE Evidence Profile)

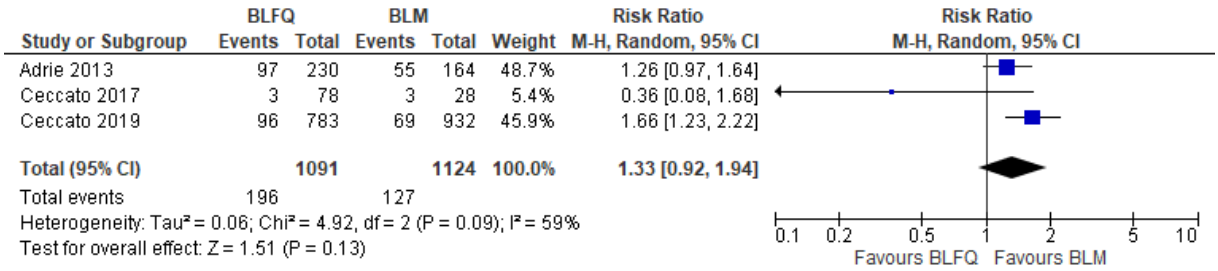


Incidence of septic shock

Severe CAP (in GRADE Evidence Profile)

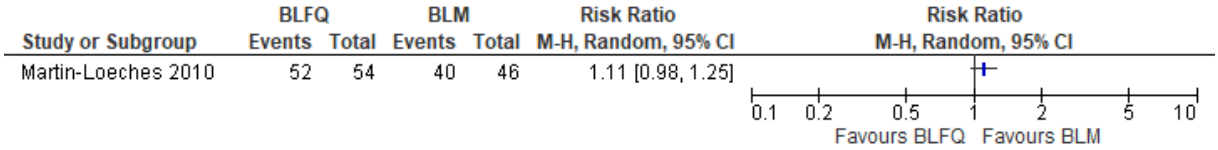


Mixed population (severe and nonsevere cases included)



Incidence of severe sepsis and septic shock

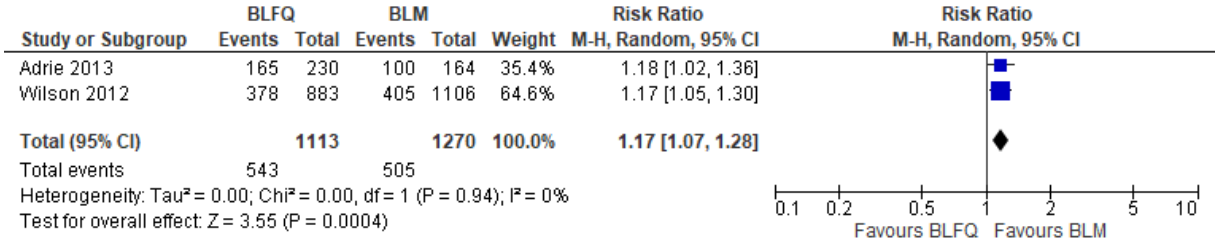
Severe CAP (in GRADE Evidence Profile)



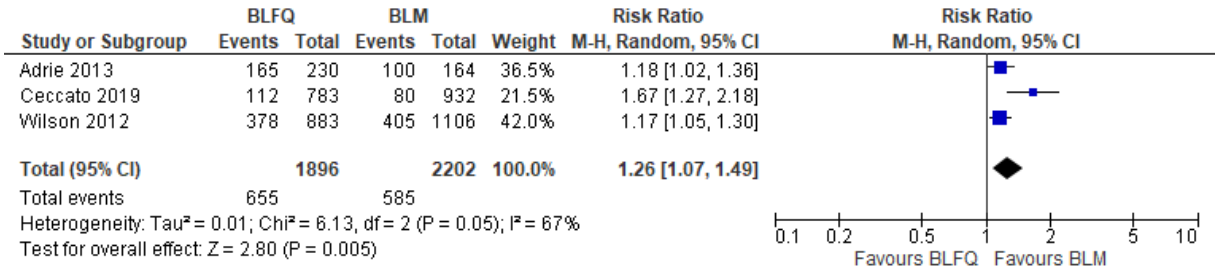
Mechanical Ventilation

Mechanical ventilation (invasive and noninvasive)

Severe CAP (in GRADE Evidence Profile)



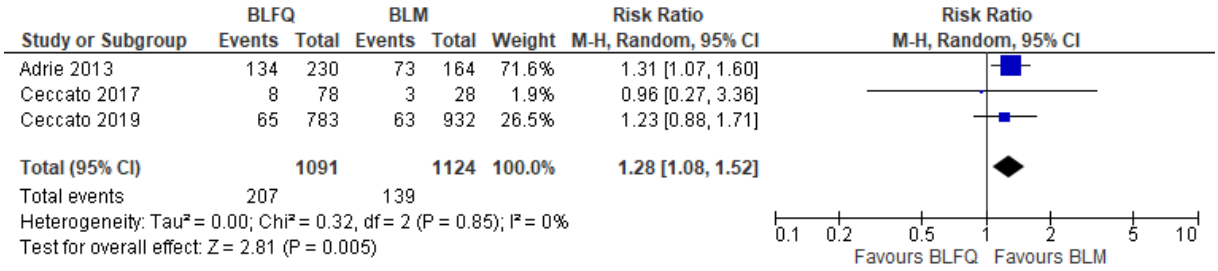
Mixed population (severe and nonsevere cases included)



Mechanical Ventilation (invasive)

Severe CAP

Mixed population (severe and nonsevere cases included)



Question 3. When using initial empiric therapy for sCAP, should a macrolide or fluoroquinolone be used as part of combination therapy, to reduce mortality and adverse clinical outcomes?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	beta-lactam/FQ	beta-lactam/M	Relative (95% CI)	Absolute (95% CI)		
Mortality all studies												
18	observational studies [1-18]	serious [a]	serious [g]	not serious [c]	not serious	none	516/2550 (20.2%)	769/6598 (11.7%)	**OR 1.45** (1.18 to 1.78)	**44 more per 1000** (from 18 more to 74 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality all studies - Observational												
17	observational studies [1-10, 12-18]	serious [a]	serious [g]	not serious [c]	not serious	none	510/2498 (20.4%)	763/6548 (11.7%)	**OR 1.47** (1.18 to 1.82)	**46 more per 1000** (from 18 more to 77 more)	⨁◯◯◯ VERY LOW	CRITICAL
30 days mortality (adjusted)												
2	observational studies [8,10]	not serious	serious [b]	not serious	serious [h]	none	257/933 (27.5%)	283/1193 (23.7%)	**OR 1.55** (0.62 to 3.87)	**88 more per 1000** (from 76 fewer to 309 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	beta-lactam/FQ	beta-lactam/M	Relative (95% CI)	Absolute (95% CI)		
ICU survival (adjusted)												
1	observational studies [6]	not serious	not serious [d]	not serious	not serious	none	52	40	**HR 0.44** (0.20 to 0.95)		⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Pooled non-adjusted (crude) values not accounting for risk factors

b. Large variability among effect estimates, significant heterogeneity

c. Although a certain number of the patients accounted would not be classified as severe CAP according to this guideline / clinical question

d. Single study

e. Antibiotic regimes not currently used

f. Very low number of events; 95%CI includes the possibility of a large benefit or a harm

g. Large variability among effect estimates, borderline statistical heterogeneity

h. 95%CI includes the possibility of a large benefit or a harm

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1. Adrie C, Schwebel C, Garrouste-Orgeas M, Vignoud L, Planquette B, Azoulay E, et al. Initial use of one or two antibiotics for critically ill patients with community- acquired pneumonia: impact on survival and bacterial resistance. Crit Care 2013;17:R265.
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Evidence profile for participants with sCAP

Study setting: Participants with sCAP hospitalized or in ICU;

Certainty assessment							Events (if applicable)/ N participants		Effect		Certainty	Importance
N studies (max follow-up)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	beta-lactam/FQ	beta-lactam/M	Relative (95% CI)	Absolute (95% CI)		
Duration of antibiotic treatment in days												
1 (60 days)	observational	very serious [a]	not serious	not serious	serious [b]	none	230	164	-	MD 1 more (0.47 fewer to 2.47 more)	⨁◯◯◯ VERY LOW	CRITICAL
Length of hospital stay in days												
2 (30 days)	observational	very serious [a]	not serious	not serious	not serious	none	961	1134	-	MD 4.89 higher (3.11 higher to 6.67 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Length of ICU stay in days												

Certainty assessment							Events (if applicable)/ N participants		Effect		Certainty	Importance
N studies (max follow-up)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	beta-lactam/FQ	beta-lactam/M	Relative (95% CI)	Absolute (95% CI)		
2 (60 days)	observational	very serious [a]	not serious	not serious	serious [b]	none	308	192	-	MD 0.99 more (0.59 fewer to 2.57 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Time to clinical stability in days												
1 (NR)*	observational	very serious [a]	not serious	not serious	serious [d]	none	78	28	-	MD 1.8 more 0.16 more to 3.44 more	⊕◯◯◯ VERY LOW	IMPORTANT
Treatment failure (composite outcome including incidence of septic shock and invasive mechanical ventilation)												
1 (NR)*	observational	very serious [a]	not serious	not serious	very serious [b d]	none	16/78 (20.5%)	6/28 (21.4%)	RR 0.96 (0.42-2.20)	9 fewer per 1000 (from 124 fewer to 257 more)	⊕◯◯◯ VERY LOW	CRITICAL
Incidence of septic shock												

Certainty assessment							Events (if applicable)/ N participants		Effect		Certainty	Importance
N studies (max follow-up)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	beta-lactam/FQ	beta-lactam/M	Relative (95% CI)	Absolute (95% CI)		
2 (60 days)	observational	very serious [a]	serious [c]	not serious	serious [b]	none	100/308 (32.5%)	58/192 (30.2%)	RR 0.85 (0.27-2.66)	45 fewer per 1000 (from 221 fewer to 501 more)	⊕◯◯◯ VERY LOW	CRITICAL
Incidence of severe sepsis and septic shock												
1 (30 days)	observational	very serious [a]	not serious	not serious	serious [b]	none	52/54 (96.3%)	40/46 (87.0%)	RR 1.11 (0.98-1.25)	96 more per 1000 (from 17 fewer to 217 more)	⊕◯◯◯ VERY LOW	CRITICAL
Mechanical ventilation (invasive and noninvasive)												
2 (60 days)	observational	very serious [a]	not serious	not serious	not serious	none	543/1113 (48.8%)	505/1270 (39.8%)	RR 1.17 (1.07-1.28)	68 more per 1000 (from 28 more to 111 more)	⊕◯◯◯ VERY LOW	CRITICAL

BLM=ß-Lactam plus Macrolide; BLFQ=ß-Lactam plus Fluoroquinolone CI: confidence interval; ICU: intensive care unit; RR: risk ratio; MD: mean difference.

* Until discharge from hospital.

Explanations

a. Risk of bias downgraded by two levels: major concerns for confounding / selection bias and lack of blinding; Furthermore selective reporting cannot be excluded.

b. Imprecision downgraded by one level: 95%-CI is consistent with the possibility of benefit and harm / with the possibility of fewer and the possibility of more events.

c. Inconsistency downgraded by one level: high I^2; i.e., the proportion of the variation in point estimates due to "between-study differences" is large, I^2>50%.

d. Imprecision downgraded by one level: due to the low number of participants resulting from a single clinical study.

Literature

1. Adrie C, Schwebel C, Garrouste-Orgeas M, et al. Initial use of one or two antibiotics for critically ill patients with community-acquired pneumonia: impact on survival and bacterial resistance. Crit Care. 2013;17(6):R265.
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Evidence to Decision (EtD) Frameworks

Question 3. When using initial empiric therapy for sCAP, should a macrolide or fluoroquinolone be used as part of combination therapy, to reduce mortality and adverse clinical outcomes?	
POPULATION:	Patients with severe community acquired pneumonia (as defined in the study)
INTERVENTION:	Fluoroquinolones combined with beta-lactam
COMPARISON:	Macrolides combined with beta-lactam
MAIN OUTCOMES:	Overall mortality, Mortality at 30 days
SETTING:	Hospital
PERSPECTIVE:	

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate x **Large** ○ Varies ○ Don't know	The large majority of data on mortality of patients with severe CAP receiving FQ *versus* macrolide in addition to beta-lactam as empiric antibiotic therapy are based on 17 observational studies with very low certainty, serious risk of bias and inconsistency.). Although the majority of the evidence is based on observational study, thousands of patients have been evaluated showing a large desirable effect in favour of the comparator (macrolide) rather than the intervention (FQ) given in addition to beta-lactams as empiric antibiotic therapy. The only RCT available so far, enrolled 117 patients and shows low generalizability in light of the long time that has elapsed since the study was carried out as testified by some of the antibiotics considered in the trial that are rarely used nowadays in clinical practice.	Macrolide has a relevant and well-known immunomodulatory/anti-inflammatory effect which might have an impact on clinical outcomes besides its antimicrobial properties. The task force also considered the duration of treatment of macrolides being between 3 and 5 days. This would be a reasonable timing especially in the context of de-escalation therapy.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Large ○ Moderate	Safety profiles of both FQ and macrolide are well-known. Adverse events for FQ and macrolide were not considered a	Both macrolides and FQs are among antibiotic classes associated with QT prolongation and

○ Small ○ Trivial ○ Varies ○ Don't know	critical outcome by the task force and the small studies evaluated by the systematic review were not powered enough to test differences in safety between FQ and macrolides. Azithromycin and clarithromycin, like erythromycin have been associated with gastrointestinal side effects, hepatoxicity, QT prolongation, and other cardiovascular events.	cardiotoxicity. Macrolides, including azithromycin may induce QTc interval prolongation setting the stage for *torsade de pointes*. Clinicians should consider this adverse effect when selecting among antibiotics with the understanding that macrolide and non-macrolide antibiotics, especially fluoroquinolones, also may induce QTc interval prolongation and *torsade de pointes.*

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Very low ○ Low ○ Moderate ○ High ○ No included studies	Certainty of evidence has been judged very low for all outcomes, due to their design, risk of bias or imprecision.	RCT specific in sCAP population would be desiderable to be conducted.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability **x Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Not systematically reviewed as a part of this TF	There has been small variability on how the panel rated critical outcomes. The guideline panel agreed by consensus that there is possibly important uncertainty or variability.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

X Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Although sustained mainly by observational studies, data on both mortality and the need for either invasive or non-invasive mechanical ventilation are in favors of macrolide in comparison to FQ when given in addition to betalactams as empiric antibiotic therapy in patients with severe CAP. Considering the fact that adverse events of both FQ and macrolide are well-known since several years, the balance between desirable and undesirable effects favor macrolides (comparison)	None

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies **x Don't know**	Not systematically reviewed as a part of this TF	Cost of fluorquinolones might be an issue in some countries whilst macrolides would be not expensive and more available

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ **No included studies**	Not systematically reviewed as a part of this TF	The panel considered that the intervention probably would be accepted

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ **Don't know**	Not systematically reviewed as a part of this TF	The panel agreed that there is probably no impact on equity

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no x Probably yes ○ Yes ○ Varies ○ Don't know	Not systematically reviewed as a part of this TF	The panel considered that the intervention probably would be accepted

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no x Probably yes ○ Yes ○ Varies ○ Don't know	Not systematically reviewed as a part of this TF	The panel considered that the intervention probably would be accepted

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

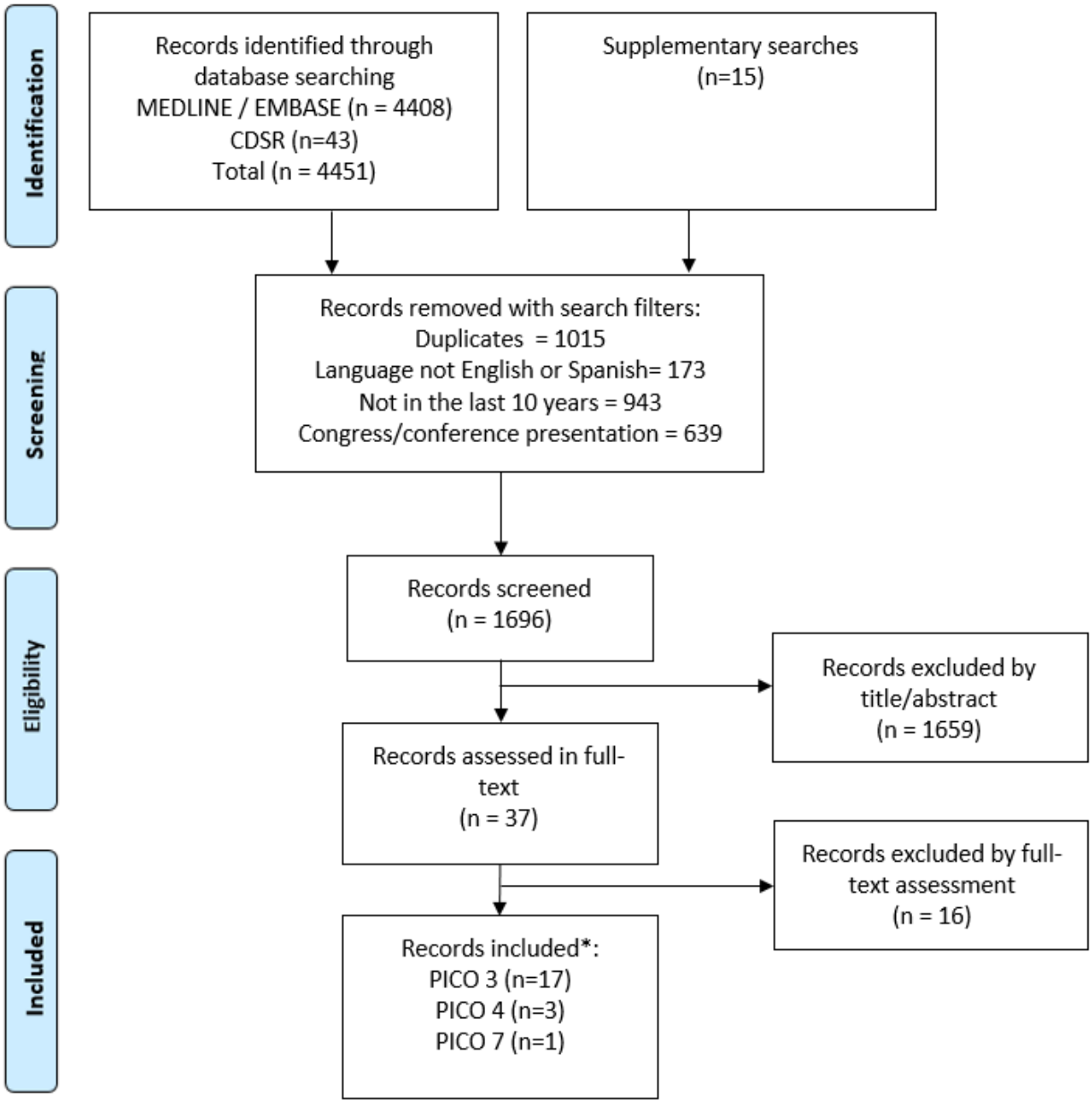
CONCLUSIONS

Recommendation

We suggest the addition of macrolides, not fluoroquinolones, to beta-lactams as empiric antibiotic therapy in hospitalized patients with sCAP (conditional recommendation, very low quality of evidence).

Question 4. In patients with sCAP, can serum procalcitonin (PCT) be used to reduce the duration of antibiotic therapy and improve other outcomes in comparison to standard of care not guided by serial biomarker measurements?

PRISMA Flow Diagram

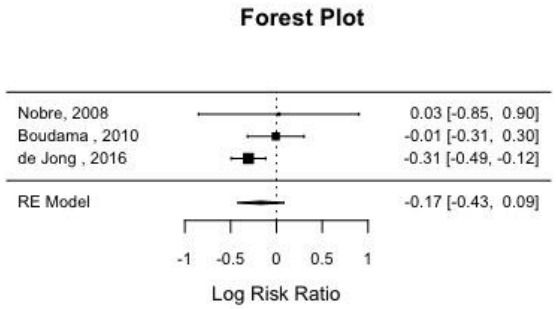


***For PICOs 3,4,7 (concerning antibiotics) one search strategy was used, results of which are presented in one PRISMA Flow Diagram**

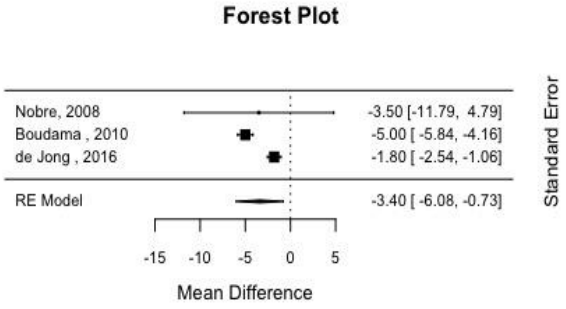
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org**.**

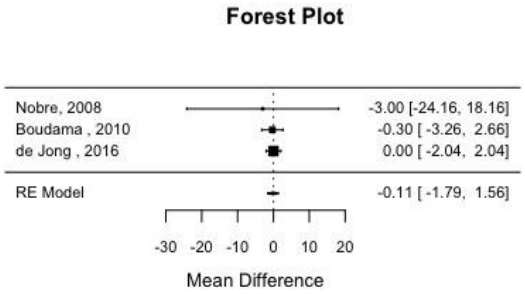
Mortality between the groups.



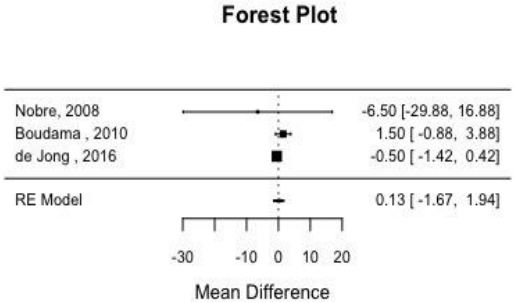
Duration of antibiotic treatment.



Hospital length of stay (LOS).



ICU length of stay (LOS).



Evidence Profiles

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	procalcitonin guided AB treatment	control / no PCT guided AB treatment	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3	randomised trials	not serious	not serious	serious [a]	serious [b]	none	222/1107	268/1139	Log RR -0.17 (-0.43 to 0.09)		⨁⨁◯◯ LOW	CRITICAL
Antibiotic treatment duration												
3	randomised trials	not serious	not serious	serious [a]	not serious	none	879	926	-	MD **3.4 days fewer** (6.08 fewer to 0.73 fewer)	⨁⨁◯◯ LOW	CRITICAL
Hospital length of stay												
3	randomised trials	not serious	not serious	serious [a]	serious [b]	none	1107	1139	-	MD **0.11 days fewer** (1.79 fewer to 1.56 more)	⨁⨁◯◯ LOW	IMPORTANT
Intensive care unit (CU) length of stay												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	procalcitonin guided AB treatment	control / no PCT guided AB treatment	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	not serious	not serious	serious [a]	serious [b]	none	1107	1139	-	MD **0.13 days more** (1.67 fewer to 1.94 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

a. None of the studies specifically included patients with sCAP. Included studies were performed in the ICU at at least 50% of the patients had a suspected lower respiratory tract infection.

b. Wide 95%CI that includes a potential benefit or harm

Literature

1. Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: A randomized trial. *Am J Respir Crit Care Med* 2008;177:498–505.

2. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, Schortgen F, Lasocki S, Veber B, Dehoux M, Bernard M, Pasquet B, Regnier B, Brun-Buisson C, Chastre J, Wolff M. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* 2010;375:463–474.

3. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, Loef BG, Dormans T, van Melsen GC, Kluiters YC, Kemperman H, van den Elsen MJ, Schouten JA, Streefkerk JO, Krabbe HG, Kieft H, Kluge GH, van Dam VC, van Pelt J, Bormans L, Otten MB, Reidinga AC, Endeman H, Twisk JW, van de Garde EMW, de Smet AMGA, Kesecioglu J, Girbes AR, Nijsten MW, *et al.* Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: A randomised, controlled, open-label trial. *Lancet Infect Dis* 2016;16:819–827.

Evidence to Decision (EtD) Frameworks

Question 4. In patients with sCAP, can serum procalcitonin (PCT) be used to reduce the duration of antibiotic therapy and improve other outcomes in comparison to standard of care not guided by serial biomarker measurements?	
POPULATION:	Patients with severe community acquired pneumonia (as defined in the study)
INTERVENTION:	Procalcitonin (PCT) guided antibiotic treatment
COMPARISON:	Control or no PCT guided treatment

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ **Moderate** ○ Large ○ Varies ○ Don't know	In 3 RCTs including >50% CAP (Nobre, Bouadma L, de Jong): -Mean difference in antibiotic duration in PCT arm: -3.4 (-6.08, -0.73) significant -No difference in hospital LOS: -0.11 (-1.79, 1.56) -No difference in ICU length of stay: 0.13 (-1.67, 1.94) -less infection-associated adverse events (7.2% vs. 15%) -lower number of antibiotic days (5 vs. 10 days) -lower mortality at 28-days (15.2% vs28.2%).	The guideline panel agreed that the overall clinical benefit in reducing number of days on antibiotic treatment was large/ moderate. Although no studies specifically studied severe CAP, the panel selected studies in sepsis including >40% of CAP. Considering the current recommendation of 7 days of antibiotic duration, the absolute benefit might be even less apparent With regard days of length of hospital stay the benefit is no apparent
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ **Moderate** ○ Small ○ Trivial ○ Varies ○ Don't know	No difference in mortality: Log RR -0.17 (-0.43, 0.09) (Nobre, Bouadma L and de Jong) Less infection-associated adverse events (Kyriazopoulu): (7.2% vs. 15%)	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ **Low** ○ Moderate ○ High ○ No included studies	A review of literature revealed no studies that specifically studied the role of procalcitonin in limiting antibiotic use in severe CAP patient. Studies performed in the ICU included critically ill populations with sepsis from different organs In 3 RCTs including >50% CAP with two arms comparing PCT with standard care. (Nobre, Bouadma L and de Jong)	Imprecision: studies with a limited sample size, wide 95CI of the effect estimates. Indirectness: None of the studies specifically included patients with sCAP. Included studies were performed in the ICU at least 40% of the patients had a suspected lower respiratory tract infection. Only one study reported outcomes for the subgroup of CAP patients. A potential limitation of benefits of using PCT levels to guide antibiotic duration are also related by the fact that PCT may be not elevated in mixed infections (bacterial plus viral) or intracellular microorganisms such as *Legionella or Mycoplasma*

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ **Probably no important uncertainty or variability** ○ No important uncertainty or variability	Not systematically reviewed as a part of this TF	There has been small variability on how the panel rated critical outcomes. The guideline panel agreed by consensus that there is possibly important uncertainty or variability in how much people value duration of treatment but less or no uncertainty or variability for mortality outcome.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	The benefits and undesirable effects of PCT guided antibiotic therapy in adult patients with sCAP are presented from severely ill patients with sepsis or septic shock. Benefits for the individual are potentially moderate and for larger society are moderate-to-large, although the evidence relies on sepsis or ICU patients and there is a lack of specific well-conducted investigations for severe CAP. Antibiotic treatment for adults with sCAP, including both the initiation of antibacterial therapy and the duration of therapy, must be weighed against the well-established risks of antibiotics, both to the individual and to wider society.	PCT reduces antibiotic duration without a negative effect on mortality (in Kyriazopoulu study reducing 28-days mortality): although with no impact on hospital or ICU days of stay. The panel considered it likely that most physicians with specific expertise in the care of adult patients with sCAP would undertake antibiotic treatment only when suspicious that the underlying etiology is bacterial and trying to limit the duration of therapy based on local and national guidelines.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Not systematically reviewed as a part of this TF	Cost of SERIAL measurements might be an issue in some countries

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ **No included studies**	Not systematically reviewed as a part of this TF	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ **Probably no impact**	Not systematically reviewed as a part of this TF	The panel agreed by consensus that there is probably no impact on equity

○ Probably increased ○ Increased ○ Varies ○ Don't know		
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ **Probably yes** ○ Yes ○ Varies ○ Don't know	Not systematically reviewed as a part of this TF	The panel considered that the intervention probably would be accepted
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ **Probably yes** ○ Yes ○ Varies ○ Don't know	Not systematically reviewed as a part of this TF	Although PCT might not be available in all centers the panel agree that PCT is a biomarker well known and widely used in sepsis / other infections

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

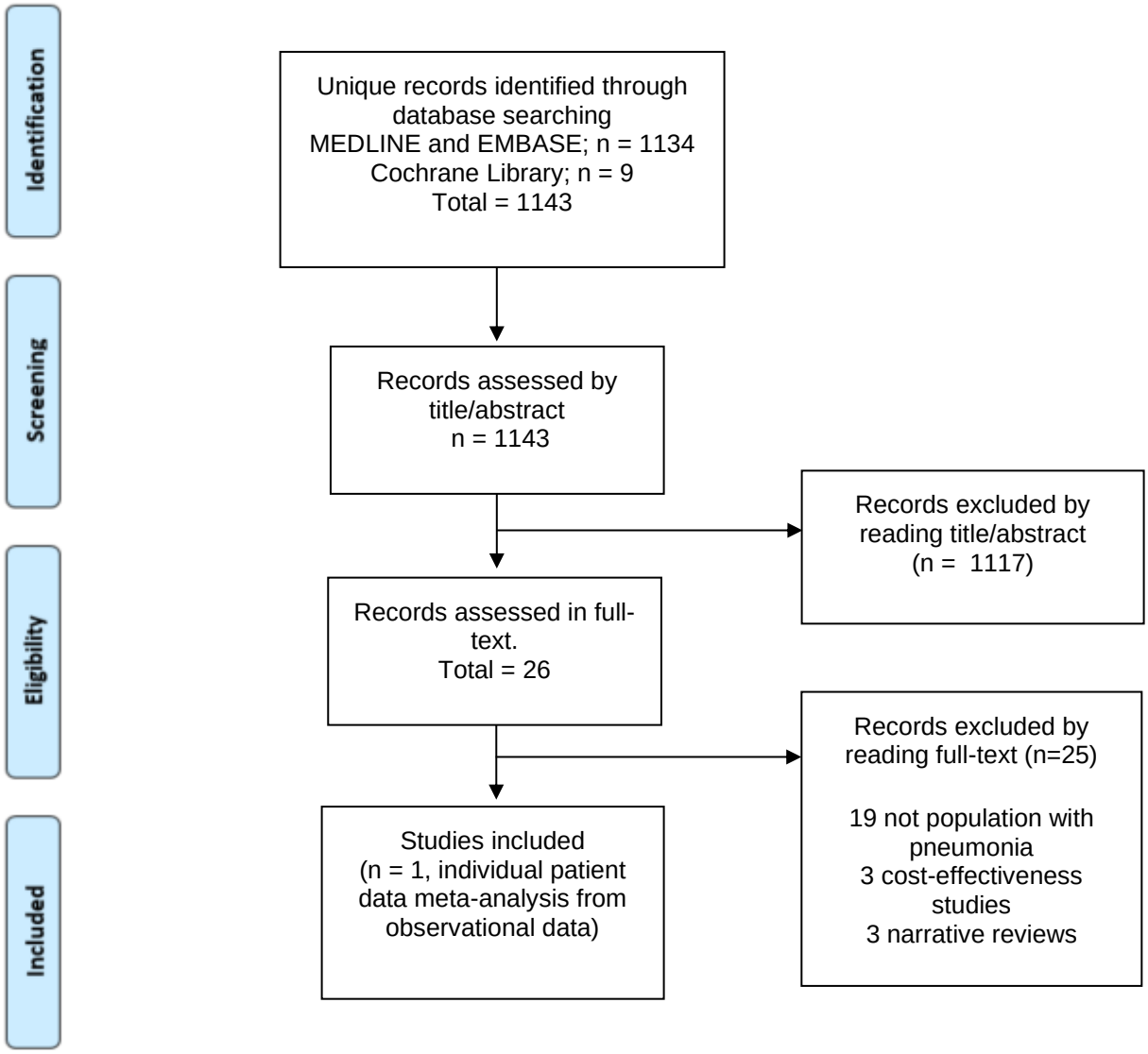
CONCLUSIONS

Recommendation

We suggest the use of PCT to reduce the duration of antibiotic days in patients with sCAP (conditional recommendation, low quality of evidence)

Question 5. Should oseltamivir be added to standard therapy in patients with sCAP and confirmed influenza?

PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Evidence profiles

Setting defined by the ERS: Not defined. **Study setting:** Mixed population (76% adults, 8% immunocompromised) with CAP admitted for inpatient treatment in 38 countries.

Empiric neuraminidase inhibitors (NI) compared to control for sCAP and suspected influenza

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	empiric neuraminidase inhibitors	control	Relative (95% CI)	Absolute (95% CI)		
Intubation												
1[1]	observational studies	very serious[a]	not serious	serious[b]	not serious	none	-/5396	-/582	**RR 1.67** (1.22 to 2.29)	**266 more per 1,000** (from 87 more to 512 more)[c]	⊕◯◯◯ Very low	CRITICAL
ARDS												
1[1]	observational studies	very serious[a]	not serious	serious[b]	serious[d]	none	-/5396	-/582	**RR 2.13** (0.87 to 5.21)	**50 more per 1,000** (from 6 fewer to 188 more)[e]	⊕◯◯◯ Very low	CRITICAL
Hospital mortality												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	empiric neuraminidase inhibitors	control	Relative (95% CI)	Absolute (95% CI)		
1[1]	observational studies	serious[a,f]	not serious	serious[b]	serious[d]	none	-/5396	-/582	**RR 0.90** (0.67 to 1.21)	**15 fewer per 1,000** (from 50 fewer to 32 more)[g]	⊕◯◯◯ Very low	CRITICAL

Mortality (early vs late NIs treatment)

1[1]	observational studies	serious[h]	not serious	serious[i]	not serious	none	-/1067	-/2843	**RR 0.70** (0.55 to 0.88)	**45 fewer per 1,000** (from 68 fewer to 18 fewer)[g]	⊕◯◯◯ Very low	CRITICAL

ICU admission

1[1]	observational studies	very serious[a]	not serious	serious[b]	not serious	none	-/5396	-/582	**RR 1.59** (1.21 to 2.09)	**329 more per 1,000** (from 117 more to 609 more)[j]	⊕◯◯◯ Very low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

a. Serious limitation due to retrospective design and inherent unmeasured confounding. Confounding by indication is relevant because those more severe cases (managed in ICU, intubated or with ARDS) were more likely to be managed with NIs. Large number of patients loss of follow-up (16% for unknown intervention exposure; 17,5% unknown pneumonia status)

b. The population does not include sCAP patients receiving empiric NIs but patients with radiologically confirmed influenza related pneumonia who received NIs or not. Population includes adult (76%) and children (24%) and severity of pneumonia is not known.

c. Numbers of events distribution among intervention and control groups are not known however the overall incidence of intubation (mechanical ventilation) in IRP patients was 39.7%

d. Wide 95%CI that includes large benefits or harm

e. Numbers of events distribution among intervention and control groups are not known however the overall incidence of ARDS in IRP patients was 4.4%

f. Serious limitation due to retrospective design and inherent unmeasured confounding, small risk of confounding by indication. Large number of patients lost of follow-up (16% for unknown intervention exposure; 17,5% unknown pneumonia status)

g. Numbers of events distribution among intervention and control groups are not known however the overall death rate in IRP patients was 15.1%

h. Serious limitation due to retrospective design and inherent unmeasured confounding, no risk of confounding by indication since all received NIs. Large number of patients lost of follow-up (16% for unknown intervention exposure; 17,5% unknown pneumonia status)

i. The population does not include sCAP patients receiving empiric NIs but patients with radiologically confirmed influenza related pneumonia who received NIs. Population includes adult (76%) and children (24%) and severity of pneumonia is not known.

j. Numbers of events distribution among intervention and control groups are not known however the overall incidence of ICU admission in IRP patients was 55.8%

References

1.Muthuri, S. G., Venkatesan, S., Myles, P. R., Leonardi-Bee, J., Lim, W. S., Al Mamun, A., Anovadiya, A. P., Araujo, W. N., Azziz-Baumgartner, E., Baez, C., Bantar, C., Barhoush, M. M., Bassetti, M., Beovic, B., Bingisser, R., Bonmarin, I., Borja-Aburto, V. H., Cao, B., Carratala, J., Cuezzo, M. R., Denholm, J. T., Dominguez, S. R., Duarte, P. A., Dubnov-Raz, G., Echavarria, M., Fanella, S., Fraser, J., Gao, Z., Gerardin, P., Giannella, M., Gubbels, S., Herberg, J., Higuera Iglesias, A. L., Hoeger, P. H., Hoffmann, M., Hu, X., Islam, Q. T., Jimenez, M. F., Kandeel, A., Keijzers, G., Khalili, H., Khandaker, G., Knight, M., Kusznierz, G., Kuzman, I., Kwan, A. M., Lahlou Amine, I., Langenegger, E., Lankarani, K. B., Leo, Y. S., Linko, R., Liu, P., Madanat, F., Manabe, T., Mayo-Montero, E., McGeer, A., Memish, Z. A., Metan, G., Mikic, D., Mohn, K. G., Moradi, A., Nymadawa, P., Ozbay, B., Ozkan, M., Parekh, D., Paul, M., Poeppl, W., Polack, F. P., Rath, B. A., Rodriguez, A. H., Siqueira, M. M., Skret-Magierlo, J., Talarek, E., Tang, J. W., Torres, A., Torun, S. H., Tran, D., Uyeki, T. M., van Zwol, A., Vaudry, W., Velyvyte, D., Vidmar, T., Zarogoulidis, P., Investigators, Pride Consortium, Nguyen-Van-Tam, J. S.. Impact of neuraminidase inhibitors on influenza A(H1N1)pdm09-related pneumonia: an individual participant data meta-analysis. Influenza Other Respir Viruses; 2016.

Evidence to Decision (EtD) Frameworks

Question 5: Should oseltamivir be added to standard therapy in patients with sCAP and confirmed influenza?	
POPULATION:	Patients with severe community acquired pneumonia (as defined in the study)
INTERVENTION:	empiric neuraminidase inhibitors
COMPARISON:	control / placebo / no treatment
MAIN OUTCOMES:	Intubation at 28 days, ICU mortality, Hospital mortality, Mortality at 28 days, Mortality at 90 days
SETTING:	Hospital
PERSPECTIVE:	

ASSESSMENT

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial **x Small** ○ Moderate ○ Large ○ Varies ○ Don't know	Patients with severe community acquired pneumonia (as defined in the study) with empiric neuraminidase inhibitors control / placebo / no treatment. No RCTs were found	individual patient data meta-analysis from 2014 including only observational data found that oseltamivir or zanamivir in comparison to non-treated patients oseltamivir reduced mortality High prevalence of viral (influenza) CAP during season, both bacterial and viral infections are common. Mortality of Influenza pneumonia in ICU is high.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small **x Trivial** ○ Varies ○ Don't know	Patients with severe community acquired pneumonia (as defined in the study) with empiric neuraminidase inhibitors control / placebo / no treatment. No RCTs were found	Not an important issue. Risks are anticipated to be trivial. Reported side effects are nausea.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
x Very low ○ Low ○ Moderate ○ High ○ No included studies	Patients with severe community acquired pneumonia (as defined in the study) with empiric neuraminidase inhibitors control / placebo / no treatment. No RCTs were found	Very low quality, data from observational evidence, serious Risk of bias due to confounding by indication. No real direct data answering the question. Only individual patient data meta-analysis from including only observational data

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ **Probably no important uncertainty or variability** ○ No important uncertainty or variability	Not systematically reviewed as a part of this TF	In general, it would be likely that severely ill patients value potential benefit from a therapy without significant risks and doctors would also value potential benefit at acceptable cost and without significant risks. However, if the drug is ineffective any side effect is likely to be unacceptable to patients.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

x Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	For patients with severe CAP due to Influenza confirmed by PCR, we suggest oseltamivir as part of the treatment. (Conditional recommendation, very low quality of evidence) When PCR is not available to confirm influenza, oseltamivir should be considered during the Influenza season. (Conditional recommendation, very low quality of evidence). Due to the lack of convincing evidence, future studies are needed to evaluate duration and the effectiveness of oseltamivir regarding the empiric use of oseltamivir in suspected influenza sCAP.	Importantly that this recommendation is to confirmed influenza

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ **Don't know**	Not systematically reviewed as a part of this TF	Depending on the perspective of health care costs (LMIC versus HIC) the cost of the intervention is low, it is simple, does not require monitoring for the intervention and does not take much time. However, especially in patient-surges, saving the drug for populations where it has been shown to work seems logical. Even though treatment might seem defensible in the absence of evidence given the good safety profile and acceptable costs, it comes with non-marginal costs to the scientific community and may halt progress in development of new antiviral drugs.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ **No included studies**	Not systematically reviewed as a part of this TF	Even though a recommendation in favour of oseltamivir might seem defensible in the absence of evidence given the good safety profile and acceptable costs, it comes with non-marginal costs for the scientific community and may halt progress in developing new antiviral drugs. As a result of the current recommendations, conducting high-quality randomised clinical trials on the effectivity of oseltamivir in the ICU is challenging as the control group would be withheld a drug that is recommended in guidelines. Furthermore, new drugs must be found

		superior to oseltamivir to be registered for treatment of the disease as per FDA and EMA regulations.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ **Probably reduced** ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Not systematically reviewed as a part of this TF	If the intervention is unaffordable for countries, despite the relatively low cost, it could reduce equity

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	Not systematically reviewed as a part of this TF	Oral drug with few side effects

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	Not systematically reviewed as a part of this TF	Oral drug with few side effects

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

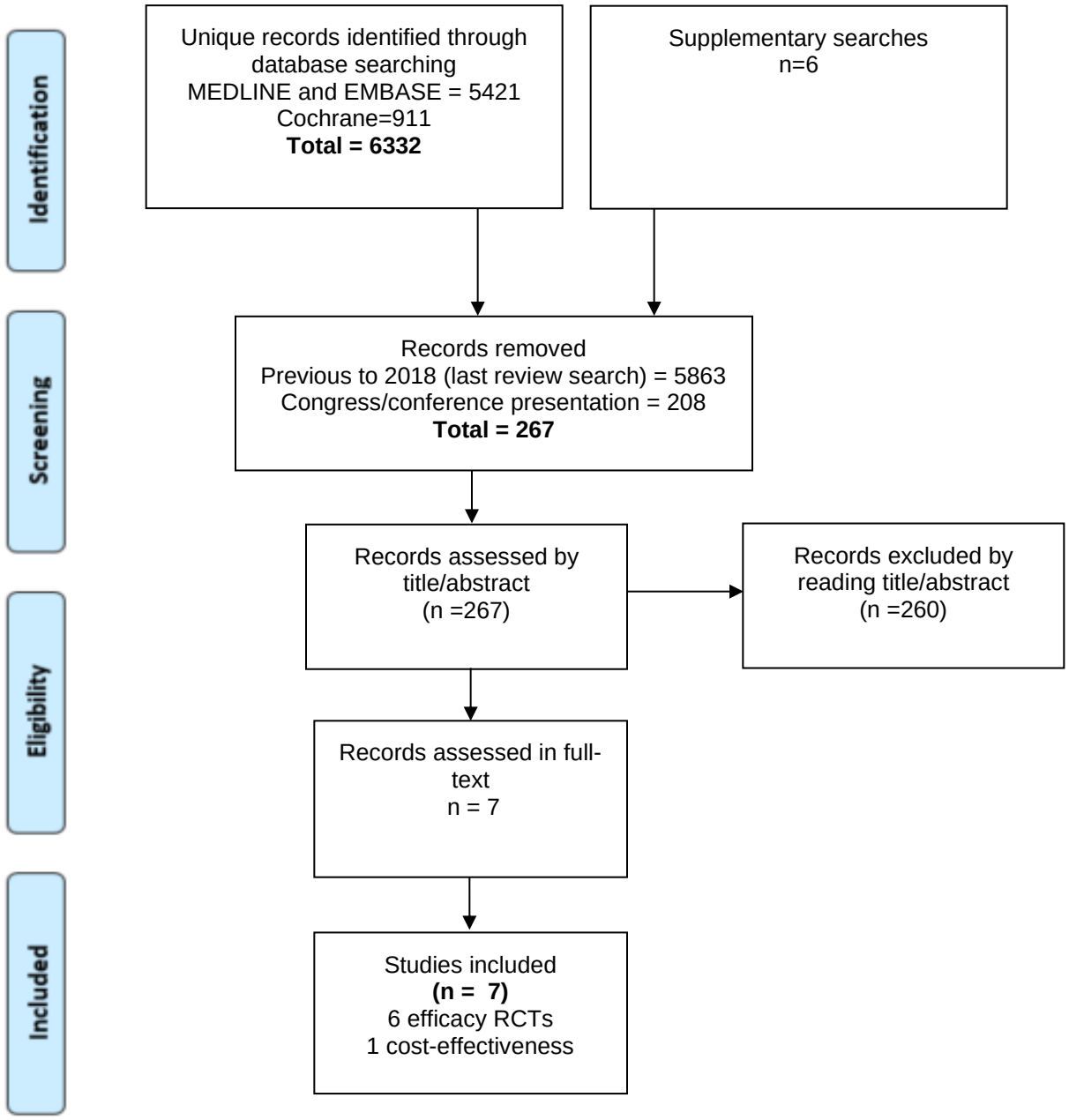
Recommendation

We suggest the use of oseltamivir for patients with sCAP due to influenza confirmed by PCR (conditional recommendation, very low quality of evidence)

When PCR is not available to confirm influenza, we suggest the use of empirical oseltamivir during the influenza season (conditional recommendation, very low quality of evidence).

Question 6. Does the addition of steroids to antibiotic therapy in specific sCAP populations lead to better outcomes in comparison to when steroid therapy is not used?

PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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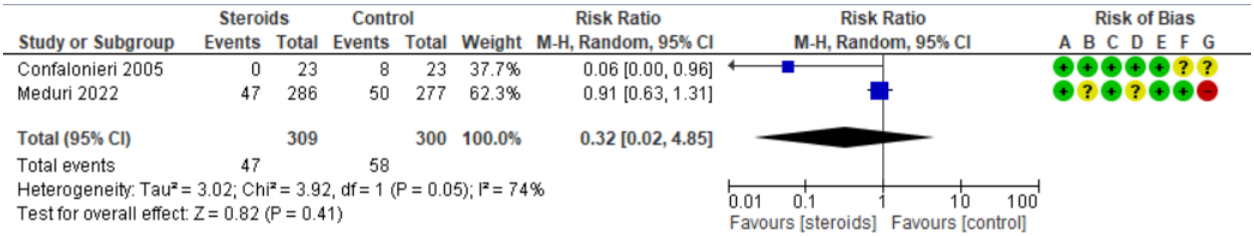
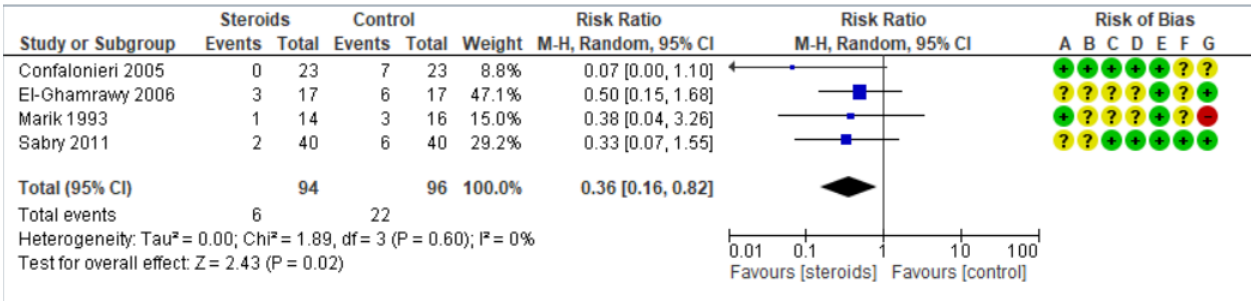
Forest plots.

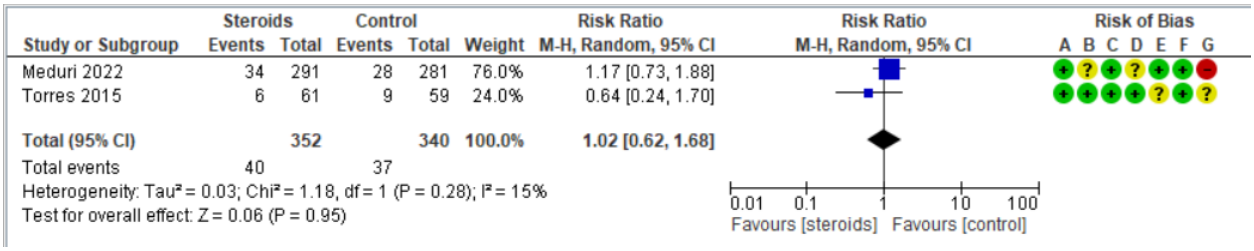
60-day mortality



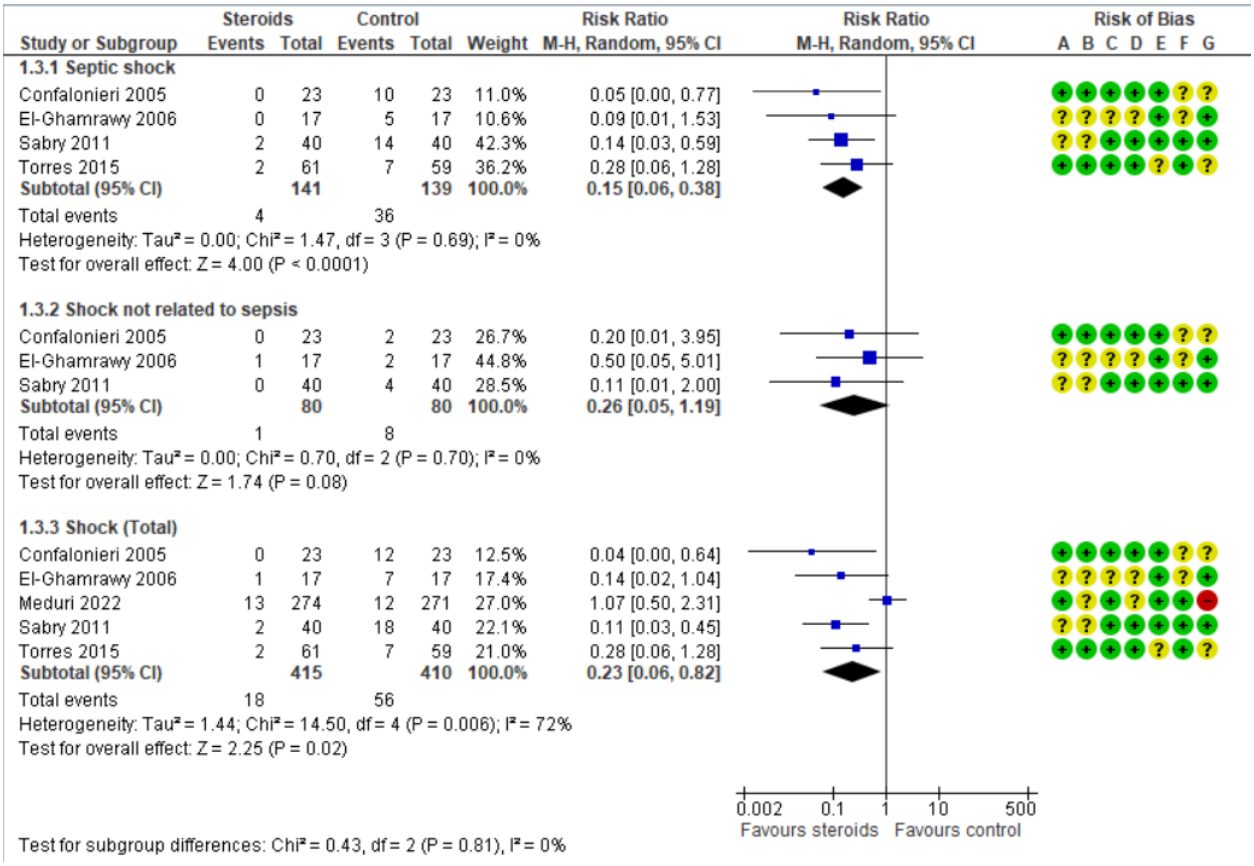
Mortality (ICU mortality)



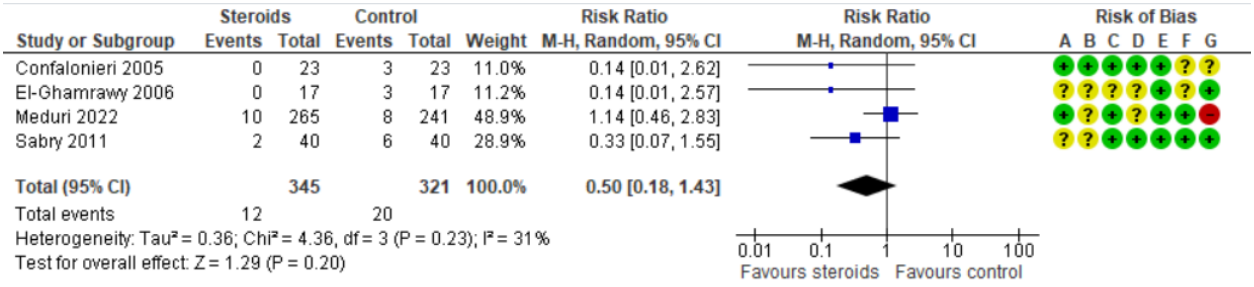
Hospital Mortality



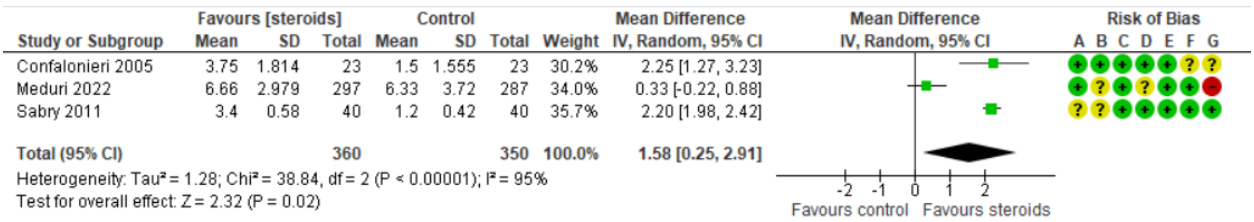
Shock



Acute Respiratory Distress Syndrome



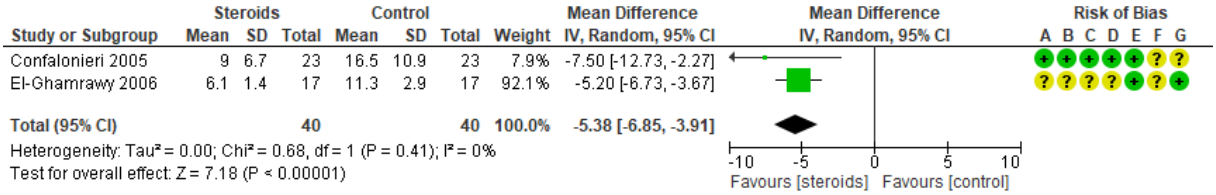
Mechanical ventilation free days (by day 8)



Confalonieri 2005: results reported in medians (range), estimation of means was calculated as proposed by Wan et al. 2014 (scenario 1).

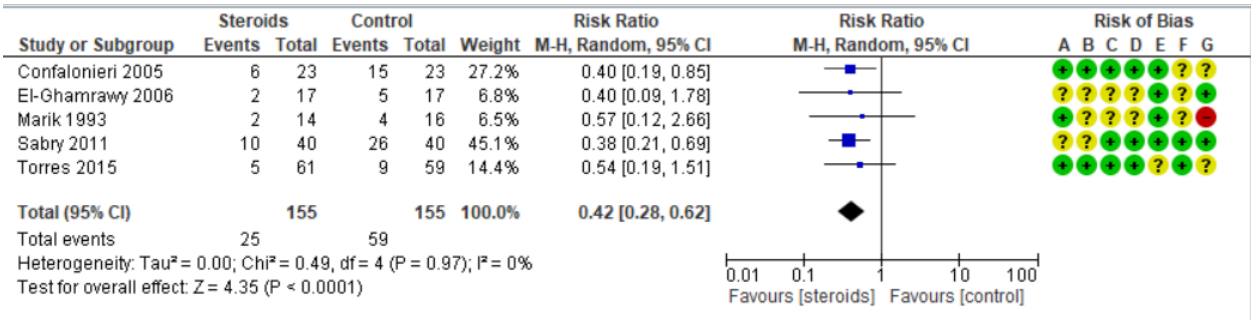
Meduri 2022: Days on MV reported by Median (range). Estimation of means was calculated as proposed by Wan et al. 2014 (scenario 1)

Duration of mechanical ventilation (days)

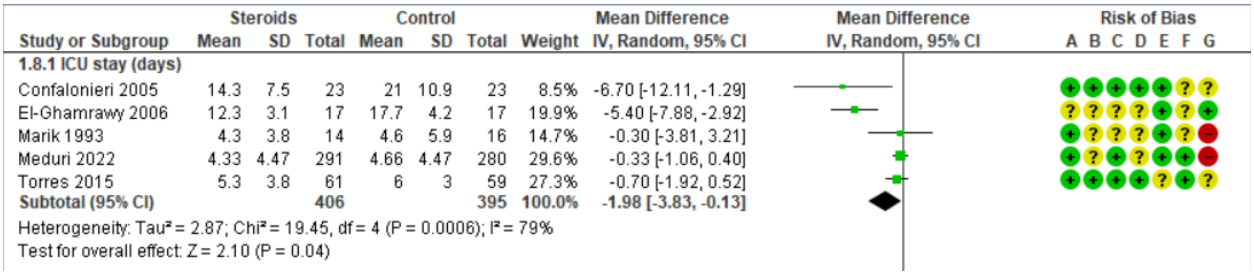


Confalonieri 2005: results reported in medians (range), estimation of means was calculated as proposed by Wan et al. 2014 (scenario 1)

Number of patients on mechanical ventilation



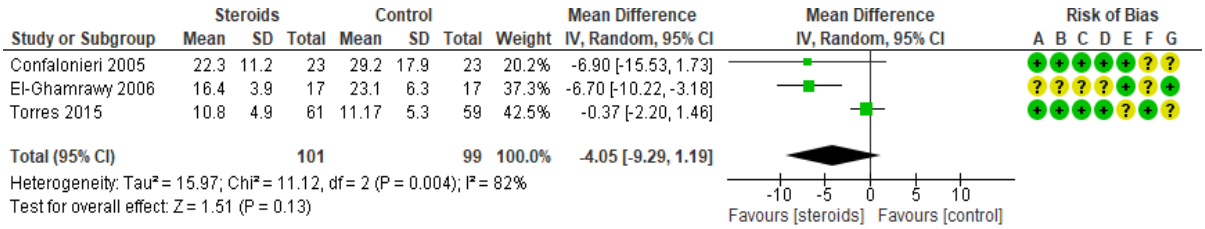
ICU stay (days)



Confalonieri 2005: results reported in medians (range), estimation of means was calculated as proposed by Wan et al. 2014 (scenario 1).

Torres 2015: results reported in medians (IQR), estimation of means was calculated as proposed by Wan et al. 2014 (scenario 3).

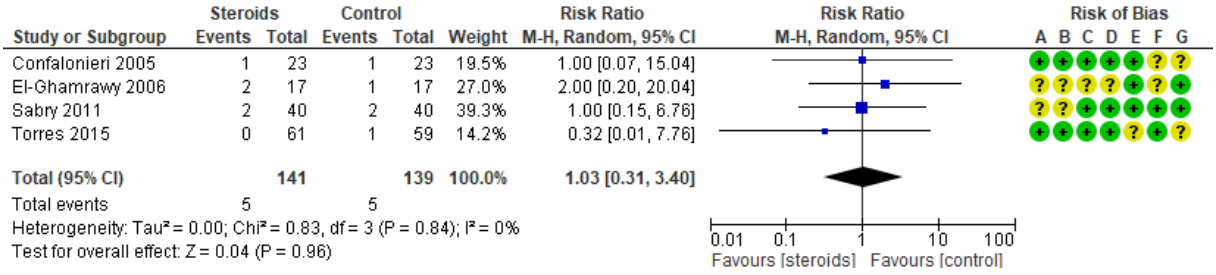
Hospital stay (days)



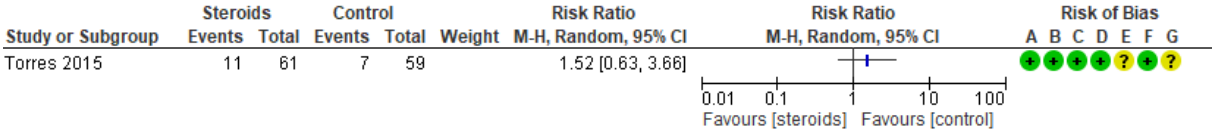
Confalonieri 2005: results reported in medians (range), estimation of means was calculated as proposed by Wan et al. 2014 (scenario 1).

Torres 2015: results reported in medians (IQR), estimation of means was calculated as proposed by Wan et al. 2014 (scenario 3).

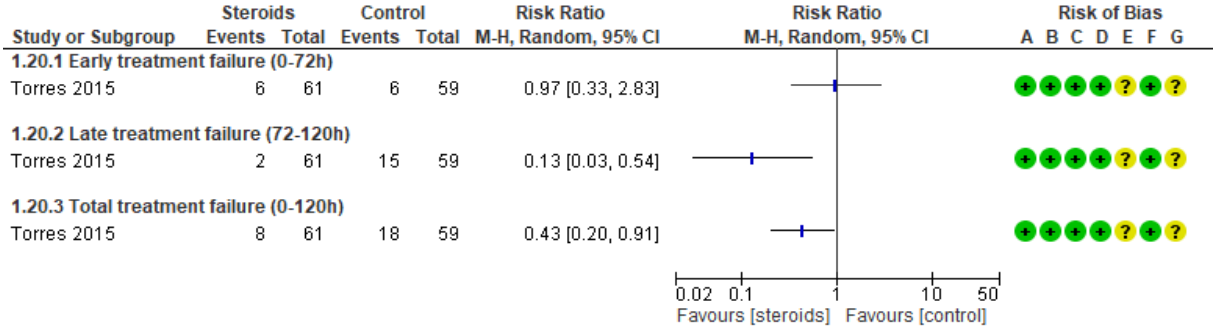
Gastrointestinal bleeding



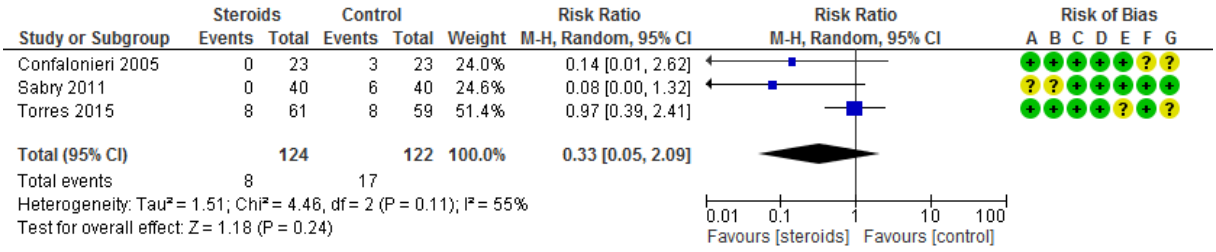
Hyperglicemia



Treatment failure



Acute kidney failure/injury



Evidence profiles

Study setting: Adults with sCAP admitted for inpatient treatment in different countries (Spain, Egypt, S.Arabia, Italy, South Africa).

Certainty assessment						Study event rate (%)		Effect estimate		Overall certainty of evidence	Importance
№ of participants (studies), follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Steroids	No steroids	Relative (95% CI)	Absolute (95% CI)		
Mortality - ICU mortality – dichotomous outcome											
190 (4 RCTs), in ICU	serious[a]	not serious	not serious	serious[f]	none	6/94 (6.4%)	22/96 (22.9%)	**RR 0.36** (0.16 to 0.82)	**147 fewer per 1.000** (from 192 fewer to 41 fewer)	⨁⨁◯◯ LOW	CRITICAL
Mortality - Hospital mortality – dichotomous outcome											
692 (2 RCT), in hospital	not serious	not serious	not serious	serious[c]	none	40/352 11.4%)	37/340 (10.9%)	**RR 1.02** (0.62 to 1.68)	**2 more per 1.000** (from 41 fewer to 74 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Shock (total) – dichotomous outcome											
825 (5 RCTs), in hospital	serious[a]	serious[d]	not serious	not serious	none	18/415 (4.3%)	56/410 (13.7%)	**RR 0.23** (0.06 to 0.82)	**105 fewer per 1.000** (from 128 fewer to 25 fewer)	⨁⨁◯◯ LOW	CRITICAL
Septic Shock – dichotomous outcome											
280 (4 RCTs), in hospital	serious[a]	not serious	not serious	serious[f]	none	4/141 (2.8%)	36/139 (25.9%)	**RR 0.15** (0.06 to 0.38)	**220 fewer per 1.000** (from 243	⨁⨁◯◯ LOW	CRITICAL

									fewer to 161 fewer)		
Acute respiratory distress syndrome – dichotomous outcome											
666 (4 RCTS), in hospital	serious[a]	not serious	not serious	serious[c]	none	12/345 (3.5%)	20/321 (6.2%)	**RR 0.50** (0.18 to 1.43)	**31 fewer per 1.000** (from 51 fewer to 27 more)	⊕⊕◯◯ LOW	CRITICAL
Mechanical ventilation (free days by day 8) – continuous outcome											
710 (3 RCTs), up to day 8	Not serious	serious[d]	not serious	serious[c]	none	360	350	-	MD **1.58 higher** (0.25 lower to 2.91 higher)	⊕⊕◯◯ LOW	CRITICAL
Duration of mechanical ventilation (days) – continuous outcome											
80 (2 RCTs), in ICU	serious[a]	not serious	not serious	serious[f]	none	40	40	-	MD **5.38 lower** (6.85 lower to 3.91 lower)	⊕⊕◯◯ LOW	CRITICAL
Number of patients on mechanical ventilation – dichotomous outcome											
310 (5 RCTs), in ICU	serious[a]	not serious	not serious	serious[f]	none	25/155 (16.1%)	59/155 (38.1%)	**RR 0.42** (0.28 to 0.62)	**221 fewer per 1.000** (from 274 fewer to 145 fewer)	⊕⊕◯◯ LOW	CRITICAL
ICU stay (days) – continuous outcome											
801 (5 RCTs), in ICU	serious[a]	serious[d]	not serious	not serious	none	406	395	-	MD **1.98 lower** (3.83 lower to 0.13 lower)	⊕⊕◯◯ LOW	CRITICAL

Hospital stay (days) – continuous outcome											
200 (3 RCTs), in hospital	serious[a]	serious[d]	not serious	serious[c]	none	101	99	-	MD **4.05 lower** (9.29 lower to 1.19 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Gastrointestinal bleeding – dichotomous outcome											
280 (4 RCTs), in hospital	serious[a]	not serious	not serious	very serious[e]	none	5/141 (3.5%)	5/139 (3.6%)	**RR 1.03** (0.31 to 3.40)	**1 more per 1.000** (from 25 fewer to 86 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Hyperglicemia – dichotomous outcome											
120 (1 RCT), in hospital	not serious	not serious	not serious	very serious[e]	none	11/61 (18.0%)	7/59 (11.9%)	**RR 1.52** (0.63 to 3.66)	**62 more per 1.000** (from 44 fewer to 316 more)	⊕⊕◯◯ LOW	IMPORTANT
Early treatment failure – dichotomous outcome											
120 (1 RCT), 0-72h	not serious	not serious	not serious	very serious[e]	none	6/61 (9.8%)	6/59 (10.2%)	**RR 0.97** (0.33 to 2.83)	**3 fewer per 1.000** (from 68 fewer to 186 more)	⊕⊕◯◯ LOW	IMPORTANT
Late treatment failure – dichotomous outcome											
120 (1 RCT), 72-120h	not serious	not serious	not serious	serious[f]	none	2/61 (3.3%)	15/59 (25.4%)	**RR 0.13** (0.03 to 0.54)	**221 fewer per 1.000** (from 247 fewer to 117 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Total treatment failure – dichotomous outcome											

120 (1 RCT), 0-120h	not serious	not serious	not serious	serious[f]	none	8/61 (13.1%)	18/59 (30.5%)	**RR 0.43** (0.20 to 0.91)	**174 fewer per 1.000** (from 244 fewer to 27 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Acute kidney failure/injury											
246 (3 RCT), in hospital	not serious	serious[d]	not serious	very serious[e]	none	8/124 (6.5%)	17/122 (13.9%)	**RR 0.33** (0.05 to 2.09)	**93 fewer per 1.000** (from 132 fewer to 152 more)	⊕◯◯◯ VERY LOW	IMPORTANT

CI: confidence interval; ICU: intensive care unit; RCT: Randomised controlled trial; RR: risk ratio; MD: mean difference; h:hour

Explanations for the certainty of evidence:

a. **Concerns about risk of bias: downgraded by 1 level** due to an unclear risk of bias of selection bias and/or uncertainties regarding blinding in all or most of the included studies

c. Concerns about imprecision: downgraded by 1 level due to the 95% CI being consistent with the possibility for benefit or harm.

d. Concerns about unexplained inconsistency: downgraded by 1 level due to high I^2 and variances of point estimates and their Cis across some studies.

e. **Concerns about imprecision: downgraded by 2 levels** due to the low number of participants and due to the 95% CI being consistent with the possibility for benefit and the possibility of harm (dichotomous outcome) or the possibility of improving and the possibility of worsening symptoms (continuous outcome).[17]

f. Concerns about imprecision: downgraded by 1 level due to the low number of participants.

Literature

1. Torres A, Sibila O, Ferrer M, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *Jama.* 2015;313(7):677-686.

2. Sabry NA, Omar EE-D. Corticosteroids and ICU course of community acquired pneumonia in Egyptian settings. *Pharmacology & Pharmacy.* 2011;2(02):73.

3. El-Ghamrawy A, Shokeir M, Esmat A. Effects of low-dose hydrocortisone in ICU patients with severe community-acquired pneumonia. *Egyptian Journal of Chest.* 2006;55:91-99.

4. Confalonieri M, Urbino R, Potena A, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *American journal of respiratory and critical care medicine.* 2005;171(3):242-248.

5. Marik P, Kraus P, Sribante J, Havlik I, Lipman J, Johnson DW. Hydrocortisone and tumor necrosis factor in severe community-acquired pneumonia: a randomized controlled study. *Chest.* 1993;104(2):389-392.

6. Meduri GU, Shih MC, Bridges L, Martin TJ, El-Solh A, Seam N, Davis-Karim A, Umberger R, Anzueto A, Sriram P, Lan C, Restrepo MI, Guardiola JJ, Buck T, Johnson DP, Suffredini A, Bell WA, Lin J, Zhao L, Uyeda L, Nielsen L, Huang GD; ESCAPe Study Group. Low-dose methylprednisolone treatment in critically ill patients with severe community-acquired pneumonia. Intensive Care Med. 2022 May 13:1–15.

Evidence to Decision (EtD) Frameworks

Question 6. Does the addition of steroids to antibiotic therapy in specific sCAP populations lead to better outcomes in comparison to when steroid therapy is not used?	
POPULATION:	Patients with severe community acquired pneumonia (as defined in the study)
INTERVENTION:	Corticosteroids as adjunct treatment (any type, dose or route)
COMPARISON:	Placebo or control (no adjunctive steroids)

ASSESSMENT

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ **Large** ○ Varies ○ Don't know	Pooling together all the RCT´s performed in severe community-acquired pneumonia corticosteroids decreased ICU mortality	One large RCT (NCT01283009) on 586 patients with Severe CAP (IDSA/ATS criteria) has been completed but results are not yet available. It is a double-blind placebo-controlled study with methylprednisolone for 20 days. Primary outcome is all cause mortality at 60 days. Large positive effect : ICU mortality, shock, septic shock Based on common exclusion criteria from clinical trials, remarks should include that this recommendation does not apply to patients with viral pneumonia (Influenza, MeRS), uncontrolled diabetes and receiving corticosteroids for other reasons

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ **Trivial** ○ Varies ○ Don't know	Short term adverse events / toxicity of steroids is trivial. Transient and clinically insignificant hyperglycaemia as the only evidence side-effect in short term.	

Certainty of evidence

What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ **Low** ○ Moderate ○ High ○ No included studies	Low quality of evidence due to imprecision in most outcomes. Although the effect is large is not robust and removing studies with no-events the effect estimate becomes non-significant. Low to very low quality of evidence for adverse events however adverse events of steroids are well known from other populations.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ **Probably no important uncertainty or variability** ○ No important uncertainty or variability	Not systematically reviewed as a part of this TF	There has been small variability on how the panel rated critical outcomes. The guideline panel agreed by consensus that there is probably no important uncertainty or variability in how much people value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	Corticosteroids led to a significant reduction in mortality, shock, septic shock, duration of mechanical ventilation, number of patients on mechanical ventilation, and frequency of late treatment failure. However, the certainty of evidence is low.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ **Moderate savings** ○ Large savings ○ Varies ○ Don't know	Not systematically reviewed as a part of this TF	Steroids are not expensive intervention. According to the cost-effectiveness study (Pilakos 2019), the intervention would be associated to some savings according to deaths averted.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ No included studies	Not systematically reviewed as a part of this TF A recent cost-effectiveness study (Pliakos, Chest 2019) constructed a decision-analytic model comparing the use of corticosteroids (plus antibiotics) with that of placebo (plus antibiotics) for the treatment of community-acquired pneumonia. Costs and outcomes were calculated for a time horizon of 2 months and taking the societal perspective. Costs are reported in USD 2018. The study found that the **corticosteroid strategy resulted in savings of $70,587 per death averted in severe CAP**, whereas it resulted in additional costs of $483,016 per death averted in non-severe CAP.	Guideline panel agreed on the low costs of steroids. Cost effectiveness study was based on a large reduction of mortality associated to steroid treatment however the quality of this evidence is low (and would probably change after the publication of a new large clinical trial).

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ **Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know	Not systematically reviewed as a part of this TF	The guideline panel agreed by consensus that there is probably no impact on equity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ **Probably yes** ○ Yes ○ Varies ○ Don't know	Not systematically reviewed as a part of this TF	Uncertainties around how to identify those patients likely to benefit most from steroids, treatment duration and doses and uncertainties around steroids true effect (low quality of evidence) may limit the acceptability.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	Not systematically reviewed as a part of this TF	Steroids are broadly accessible.

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

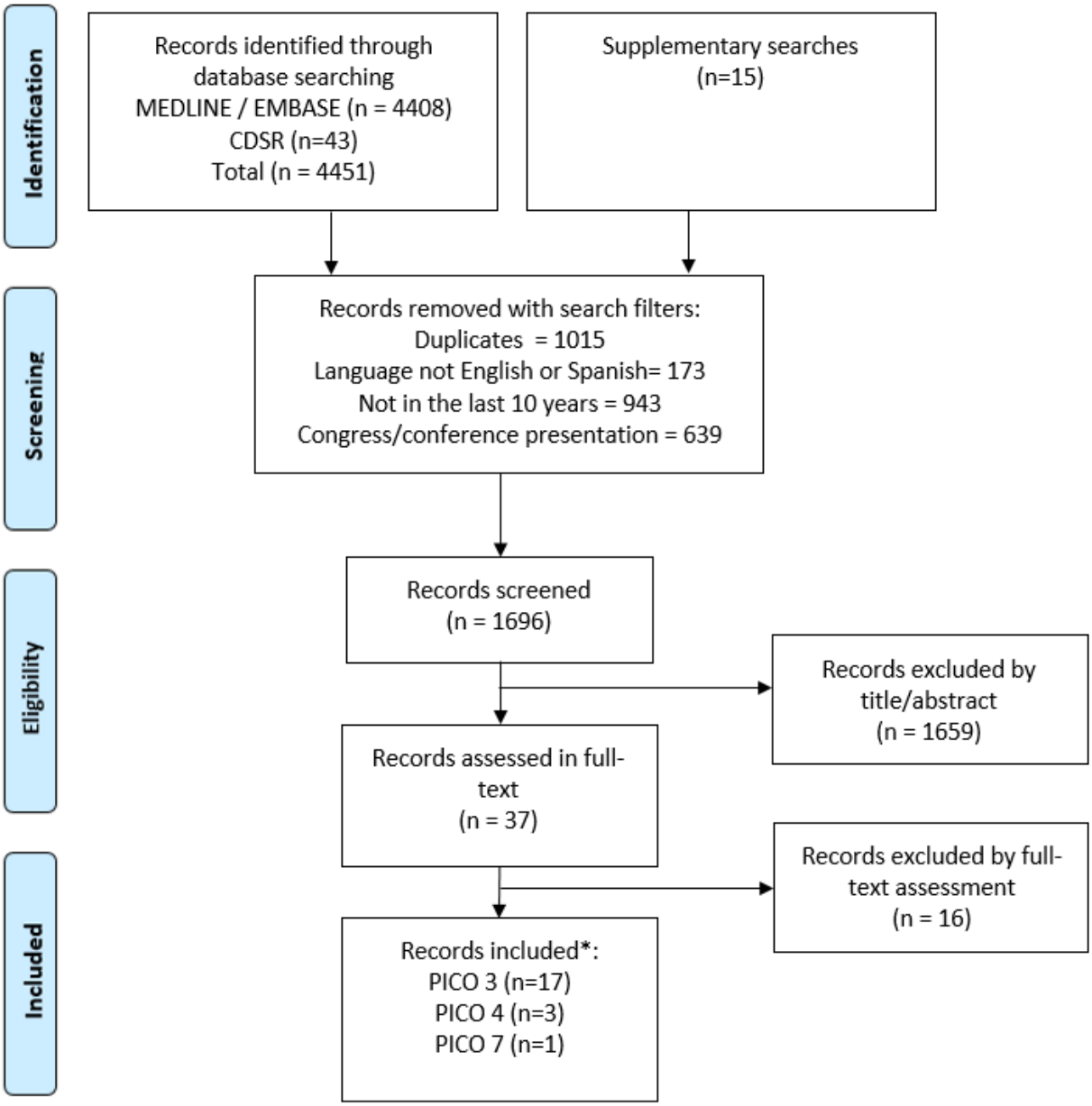
CONCLUSIONS

Recommendation

In patients with sCAP, we suggest the use of corticosteroids if shock is present (conditional recommendation, low quality of evidence).

Question 7. Does the use of a prediction score for drug-resistant pathogens lead to more appropriate therapy and improved outcomes (mortality, treatment failure, duration of antibiotic therapy, prolonged ICU stay)?

PRISMA Flow Diagram



***For PICOs 3,4,7 (concerning antibiotics) one search strategy was used, results of which are presented in one PRISMA Flow Diagram**

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Summary of finding table (GRADE evidence profile) for implementation cohorts for drug-resistant pathogens in community-acquired pneumonia.

From Brito and Niedermann MDR Risk factors: Nursing Home, Hemodialysis, Recent hospitalization ≤90 days, Immunosuppression, Poor functional status, antibiotic use in ≤180 days

Certainty assessment						Study event rate (%)		Effect estimate		Overall certainty of evidence	Importance
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	0-1 MDR factors	≥2 MDR factors	Relative (95% CI)	Absolute (95% CI)		
30 days- Mortality											
1089 (1 prospective cohort)	serious[a]	not serious	not serious	not serious	none	34/752 (4.5%)	42/337 (12.5%)	**OR 0.33** (0.21 to 0.53)	**80 fewer per 1.000** (from 96 fewer to 54 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Need for ICU admission or mechanical ventilation											
1089 (1 prospective cohort)	serious[a]	not serious	not serious	not serious	none	32/752 (4.3%)	103/337 (30.6%)	**OR 0.10** (0.07 to 0.15)	**263 fewer per 1.000** (from 276 fewer to 244 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Initial treatment failure											
1089 (1 prospective cohort)	serious[a]	not serious	not serious	not serious	none	77/752 (10.2%)	57/337 (16.9%)	**OR 0.56** (0.39 to 0.81)	**67 fewer per 1.000** (from 96 fewer to 28 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

Explanations

Non adjusted crude results for event rates and Odds Ratios

References: [Implementation cohort] Maruyama T, Fujisawa T, Ishida T, Ito A, Oyamada Y, Fujimoto K, Yoshida M, Maeda H, Miyashita N, Nagai H, Imamura Y, Shime N, Suzuki S, Amishima M, Higa F, Kobayashi H, Suga S, Tsutsui K, Kohno S, Brito V, Niederman MS. A Therapeutic Strategy for All Pneumonia Patients: A 3-Year Prospective Multicenter Cohort Study Using Risk Factors for Multidrug-resistant Pathogens to Select Initial Empiric Therapy. Clin Infect Dis. 2019 Mar 19;68(7):1080-1088.

Summary of finding table (GRADE evidence profile) for implementation cohorts for drug-resistant pathogens in community-acquired pneumonia.

From Webb DRIP score: Major factors: Antibiotic use ≤60 days, Nursing home, Enteral feeding, Prior DRP infection ≤1 year; Minor factors: Hospitalization ≤60 days, chronic lung disease, poor functional status, gastric acid suppression, wound care, MRSA colonization ≤1 year

Certainty assessment						Study event rate (%)		Effect estimate	Overall certainty of evidence	Importance
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Use of ePNa-DRIP score	Use of ePNa-HCAP score	Relative (95% CI)		
Use of broad-spectrum antibiotic										
2169 (prospective cohort)	not serious	not serious	not serious	serious[a]	none	NA	NA	**OR 0.62** (0.39 to 0.98)	⊕⊕⊕◯ MODERATE	CRITICAL
Mortality										
2169 (prospective cohort)	not serious	not serious	not serious	Serious[b]	none	NA	NA	**OR 0.84** (0.43 to 1.6)	⊕⊕⊕◯ MODERATE	CRITICAL
Length of stay										
2169 (prospective cohort)	not serious	not serious	not serious	Serious[b]	none	NA	NA	**OR 0.98** (0.82 to 1.2)	⊕⊕⊕◯ MODERATE	IMPORTANT

Explanations

Wide 95%CI that includes large effect and a potential irrelevant effect

Wide 95%CI that includes large beneficial effect and a potential harm

References

[Implementation cohort] Webb BJ, Sorensen J, Mecham I, et al. Antibiotic use and outcomes after implementation of the drug resistance in pneumonia score in ED patients with community-onset pneumonia. Chest 2019; 156:843–851.

Summary of finding table (GRADE evidence profile) for prediction scores for drug-resistant pathogens in community-acquired pneumonia

Certainty assessment						Effect estimate			Overall certainty of evidence
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (range)	Specificity (range)	PPV and NPV (range)	
Risk factors: Recent Hospitalization, Nursing home resident, Hemodialysis , Critical illness						**Definition of drug-resistant pathogens in community-acquired pneumonia:** MRSA, P. aeruginosa, ESBL Klebsiella species, nonfermenting gram			
5671 (6 cohort studies)[1]	serious[a]	not serious	not serious	serious[b]	none	0.72 to 0.886	0.40 to 0.69	PPV: 0.36 to 0.63 NPV: 0.85 to 0.91	⊕⊕⊕◯ VERY LOW
Risk factors: Nursing Home, Hemodialysis, Recent hospitalization ≤90 days, Immunosuppression, Poor functional status, antibiotic use in ≤180 days						**Definition of drug-resistant pathogens in community-acquired pneumonia:** Per ATS/IDSA 2005 Pneumonia guidelines			
1857 (4 cohort studies)[2]	serious[a]	not serious	not serious	serious[b]	none	0.45 to 0.939	0.53 to 0.86	PPV: 0.43 to 0.49 NPV: 0.87 to 0.92	⊕⊕⊕◯ VERY LOW
Risk factors: CVA, DM, COPD, Antibiotics ≤90 days, immunosuppression, wound care, infusion therapy, Nursing home, Recent hospitalization ≤90 days, Chronic renal failure						**Definition of drug-resistant pathogens in community-acquired pneumonia:** MRSA; P. aeruginosa; S. maltophilia; Vanc-resistant Enterococcus; Acinetobacter Baumanii; ESBL Enterobacter; other nonfermentating gran-bacilli			

Certainty assessment						Effect estimate			Overall certainty of evidence
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (range)	Specificity (range)	PPV and NPV (range)	
5387 (6 cohort studies)[3]	serious[a]	not serious	not serious	serious[b]	none	0.71 to 0.88	0.47 to 0.71	PPV: 0.33 to 0.49 NPV: 0.9 to 0.92	⊕⊕⊕◯ VERY LOW
Risk factors: Recent hospitalization, Immunosuppression, Antibiotics ≤90 days, Gastric acid suppression, Enteral feed, Nonambulatory status. **MRSA Risk Factors**: Hemodialysis CHF + MRSA						**Definition of drug-resistant pathogens in community-acquired pneumonia:** MDR: nonsusceptible to at least one agent in ≥3 microbial categories XDR (extensively drug-resistant): nonsusceptible to ≥1 agent in all but ≤2 antimicrobial categories PDR (pandrug-resistant): resistant to all antimicrobial agents			
2949 (4 cohort studies)[4]	serious[a]	not serious	not serious	serious[b]	none	0.45 to 0.84	0.60 to 0.909	PPV: 0.26 to 0.5 NPV: 0.87 to 0.91	⊕⊕⊕◯ VERY LOW
Risk factors: Age <30 or >79, Recent hospitalization, Nursing home ≤90 days, Prior IV Antibiotics ≤30 days, ICU admission, CVA, Dementia, Female, Diabetes						**Definition of drug-resistant pathogens in community-acquired pneumonia:** MRSA			
6897 (4 cohort studies)[5]	serious[a]	not serious	not serious	serious[b]	none	0.495 to 0.97	0.30 to 0.641	PPV: 0.19 to 0.23 NPV: 0.9 to 0.98	⊕⊕⊕◯ VERY LOW

Risk factors: Age, gender (male), Antibiotics, Chronic respiratory disorder, CKD, Confusion, Fever						**Definition of drug-resistant pathogens in community-acquired pneumonia:** P. aeruginosa, MRSA, ESBL			
2519 (5 cohort studies)[6]	serious[a]	not serious	not serious	not serious	none	0.61 to 1	0.71 to 0.90	PPV: 0.13 to 0.5 NPV: 0.82 to 0.97	⊕⊕◯◯ LOW
Risk factors: Major factors: Antibiotic use ≤60 days, Nursing home, Enteral feeding, Prior DRP infection ≤1 year Minor factors: Hospitalization ≤60 days, chronic lung disease, poor functional status, gastric acid suppression, wound care, MRSA colonization ≤1 year						**Definition of drug-resistant pathogens in community-acquired pneumonia:** Any organism resistant to treatment with ceftriaxone + azithromycin or levofloxacin			
1633 (4 cohort studies)[7]	serious[a]	not serious	not serious	not serious	none	0.70 to 0.82	0.71 to 0.82	PPV: 0.08 to 0.68 NPV: 0.9 to 0.99	⊕⊕◯◯ LOW

Explanations

Observational data includes derivation cohort and external retrospective validation cohorts

It was not possible to pool diagnostic data which is represented as a range. Relatively large range of accuracy values.

References

1. [Derivation cohort] Shorr AF, Zilberberg MD, Micek ST, Kollef MH. Prediction of infection due to antibiotic-resistant bacteria by select risk factors for health care-associated pneumonia. Arch Intern Med. 2008 Nov 10;168(20):2205-10.
2. [Derivation cohort] Brito V, Niederman MS. Healthcare-associated pneumonia is a heterogeneous disease, and all patients do not need the same broad-spectrum antibiotic therapy as complex nosocomial pneumonia. Curr Opin Infect Dis. 2009 Jun;22(3):316-25.
3. [Derivation cohort] Aliberti S, Di Pasquale M, Zanaboni AM, Cosentini R, Brambilla AM, Seghezzi S, Tarsia P, Mantero M, Blasi F. Stratifying risk factors for multidrug-resistant pathogens in hospitalized patients coming from the community with pneumonia. Clin Infect Dis. 2012 Feb 15;54(4):470-8.
4. [Derivation cohort] Shindo Y, Ito R, Kobayashi D, Ando M, Ichikawa M, Shiraki A, Goto Y, Fukui Y, Iwaki M, Okumura J, Yamaguchi I, Yagi T, Tanikawa Y, Sugino Y, Shindoh J, Ogasawara T, Nomura F, Saka H, Yamamoto M, Taniguchi H, Suzuki R, Saito H, Kawamura T, Hasegawa Y. Risk factors for drug-resistant pathogens in community-acquired and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2013 Oct 15;188(8):985-95.

5. [Derivation cohort] Shorr AF, Myers DE, Huang DB, Nathanson BH, Emons MF, Kollef MH. A risk score for identifying methicillin-resistant Staphylococcus aureus in patients presenting to the hospital with pneumonia. BMC Infect Dis. 2013 Jun 6;13:268.
6. [Derivation cohort] Prina E, Ranzani OT, Polverino E, Cillóniz C, Ferrer M, Fernandez L, Puig de la Bellacasa J, Menéndez R, Mensa J, Torres A. Risk factors associated with potentially antibiotic-resistant pathogens in community-acquired pneumonia. Ann Am Thorac Soc. 2015 Feb;12(2):153-60.
7. [Derivation cohort] Webb BJ, Dascomb K, Stenehjem E, Vikram HR, Agrwal N, Sakata K, Williams K, Bockorny B, Bagavathy K, Mirza S, Metersky M, Dean NC. Derivation and Multicenter Validation of the Drug Resistance in Pneumonia Clinical Prediction Score. Antimicrob Agents Chemother. 2016 Apr 22;60(5):2652-63.

Supplementary Table, question 7. Evidence for prediction of drug resistant pathogens in sCAP.

Prediction score	Derivation cohort (number of patients)	Drug resistant pathogens covered by the score	Risk factors (number of points)	Prevalence in low and high risk scores	Performance of the score	Implementation study
Niederman and Brito (2007), HCAP criteria	Japan (n=321)	Defined according to ATS/IDSA 2005 guidelines	Any of: Nursing Home, Hemodialysis, Recent hospitalization ≤90 days (1) Any of: Immunosuppression, Poor functional status, antibiotic use in <180 days (1)	NA	Se=0.94 Sp=0.55 AUROC=NA Se=0.91 (0.81-0.76) Sp=0.53 (0.44-0.62) PPV=0.49 (0.40-0.58) NPV=0.92 (0.83-0.97) AUROC=0.80 (0.74-0.87) Se=0.45 (0.33-0.57) Sp=0.86 (0.81-0.90) PPV=0.43 (0.32-0.55) NPV=0.87 (0.82-0.90) AUROC=0.78 (0.74-0.82)	
Shorr (2008)	USA (n=639)	MDR pathogens : MRSA Pseudomonas aeruginosa Acinetobacter spp ESBL producing enterobacterales	Sum 4 variables (10 points): Recent hospitalization (4) Long term care facility (3) Chronic hemodilaysis (2) Admission to the ICU within 24 hours of evaluation in the ED (1)	Low risk= 17% High risk= 77%	Cutoff≥1 Se=88.6% Sp=54.5% PPV=0.63 NPV=0.85 AUROC=0.71 (0.66-0.73) Cutoff≥1 Se=0.88 (0.77-0.94) Sp=0.4 (0.31-0.48) PPV= 0.42 (0.34-0.50) NPV= 0.87 (0.75-0.94) AUROC=0.77 (0.70-0.85) Cutoff≥1 Se=0.72 (0.60-0.82) Sp=0.69 (0.63-0.74) PPV= 0.36 (0.28-0.45) NPV= 0.91 (0.87-0.95) AUROC=0.73 (0.66-0.80) AUROC=0.77 (0.58-0.96)	No
Schreiber	USA (n=190)	MDR pathogens : MRSA Pseudomonas aeruginosa ESBL producing enterobacterales	Sum 3 variables (6 points): Immunosuppression (3) Admission from long-term care (2) Prior antibiotics (1)	Low risk= 60% High risk= 40%	Cutoff≥2 Se=0.80 Sp=0.63 AUROC=0.71 Cutoff≥2 Se=0.71 (0.55-0.79) Sp=0.66 (0.58-0.74) PPV= 0.53 (0.42-0.63) NPV=0.86 (0.77-0.92) AUROC=0.72 (0.64-0.79)	

					Cutoff≥2 Se=0.51 (0.39-0.63) Sp=0.77 (0.72-0.82) PPV= 0.36 (0.26-0.46) NPV=0.87 (0.82-0.91) AUROC=0.67 (0.60-0.74)	
Aliberti (2012)	Italy (n=935)	MDR pathogens : MRSA Pseudomonas aeruginosa resistant to quinolones, antipseudomonal penicillins, cephalosporins, carbapenems Acinetobacter spp. ESBL producing enterobacterales Stenotrophomonas maltophilia Vancomycin-resistant Enterococcus	Sum 6 variables (12.5 points): Chronic renal failure (5) Hospitalization for greater than or equal to 2 days or more in the preceding 90 days (4) Residence in a nursing home (3); Cerebrovascular disease (0.5) Diabetes (0.5) Chronic lung disease (0.5) Antimicrobial therapy in preceding 90 days (0.5) Immunosuppression (0.5) Home wound care (0.5) Home infusion therapy (0.5)	Low risk= 8% High risk= 38%	Cutoff≥3 Se=0.75 Sp=0.71 AUROC=0.79 (0.71-0.87) Cutoff≥0.5 Se=0.88 (0.77-0.94) Sp=0.55 (0.46-0.64) PPV= 0.49 (0.40-0.58) NPV= 0.90 (0.81-0.95) AUROC=0.73 (0.66-0.8) Cutoff≥3 Se=NA Sp=NA AUROC=0.85 (0.75-0.96) Cutoff≥3 Se=0.79 (0.68-0.88) Sp=0.61 (0.56-0.67) PPV= 0.33 (0.26-0.41) NPV= 0.92 (0.88-0.96) AUROC=0.71 (0.65-0.77)	No
Schindo (2013), CAP-DRP rule	Japan (n=1413)	DRP defined by resistance to β-lactams (ceftriaxone or ampicilin-sulbactam), macrolides and fluoroquinolones MRSA (47%) Pseudomonas aeruginosa (24%) ESBL-producing enterobacterales (12%)	Sum of 6 variables (10 points) : Prior hospitalization Immunosuppression Previous antibiotic use Use of gastric acid-suppressive agents Tube feeding Non ambulatory status	Low risk= 6.5% High risk= 63%	CAP-DRP≥3 Se=0.47 Sp=0.91 PPV=0.26 NPV=0.91 AUROC= 0.79 (0.74-0.84) CAP-DRP≥3 Se=0.83 (0.72-0.91) Sp=0.60 (0.51-0.68) PPV= 0.5 (0.41-0.60) NPV=0.88 (0.79-0.94) AUROC=0.79 (0.73-0.86) CAP-DRP≥3 Se=0.45 (0.34-0.57), Sp=0.87 (0.83-0.91) PPV=0.47 (0.35-0.59) NPV=0.87 (0.82-0.9) AUROC=0.73 (0.66-0.79)	No
Shorr (2013), MRSA risk score	USA (n=5975)	MRSA	Sum of 8 variables (10 points):	Low risk <10%	Cutoff<2 Se=0.59 Sp=0.60 PPV=0.19	No

			age < 30 or > 79 years (1) Recent hospitalization or ICU admission (2) Prior nursing home/long term acute care exposure (1) Prior IV antibiotic therapy (1) ICU admission (2) Dementia (1) Cerebrovascular disease (1), Female with diabetes (1)	High risk> 30%	NPV=0.90 AUROC= 0.64 (0.6-0.67) Cutoff≥2 Se=0.97 (0.81-1), Sp=0.3 (0.23-0.37, PPV=0.21 (0.15-0.28), NPV=0.98 (0.88-1) AUROC=NA Cutoff≥2 Se=0.84 (0.71-0.93) Sp=0.55 (0.49-0.61) PPV=0.23 (0.17-0.30) NPV=0.96 (0.92-0.98) PPV=NA NPV=NA AUROC=NA	
Prina (2014)	Spain (n=1597)	PES pathogens : Pseudomonas aeruginosa ESBL producing enterobacterales MRSA	Sum of 6 variables (12 points): age < 40 (0) or 40-65 (1) or <65 years (2) Male (1) Antibiotics (2) Chronic respiratory disorder (2) Chronic kidney disease (3) Confusion (2) Fever (-1)	Low risk= 1% High risk= 70%	Cutoff≥5 Se=0.7, Sp=0.71, PPV=NA NPV=NA AUROC=0.75 (0.71-0.80) Cutoff≥5 Se=0.71 (0.59-0.81), Sp=0.65 (0.56-0.73), PPV= 0.5 (0.4-0.6) NPV= 0.82 (0.73-0.89) AUROC=0.74 (0.67-0.81) Cutoff≥2 Se=0.96 (0.89-0.99) Sp=0.09 (0.06-0.13) PPV= 0.21 (0.17-0.25) NPV= 0.90 (0.74-0.98) AUROC=0.70 (0.63-0.77) Cutoff >4 points: Se=0.61 (0.44-0.78) Sp=0.77 (0.73-0.8) PPV=0.13 (0.08-0.19) NPV=0.97 (0.95-0.99) AUROC=0.78 (0.72-0.85)	No
Webb (2016), DRIP (Drug Resistance in Pneumonia) score	USA (n=201)	DRP defined by resistance to either ceftriaxone plus azithromycin or levofloxacin.	Sum 10 variables (14 points): Antibiotic use within previous 60 days (2) Residence in long-term care facility (2) Tube feeding (2) Prior infection with a drug resistant-pathogens (1 yr) (2) Hospitalization within previous 60 days (1)	-	Cutoff≥4 Se=0.82 (0.67-0.88) Sp=0.81 (0.73-0.87) PPV=0.68 (0.56-0.78) NPV=0.90 (0.81-0.93) AUROC=0.88 (0.82-0.93) Cutoff≥4 Se=0.71 (0.44-0.89), Sp=0.82 (0.79-0.85), PPV=0.08 (0.05-0.14) NPV=0.99 (0.98-1) AUROC=0.79 (0.65-0.93)	

			Chronic pulmonary disease (1) Poor functional status (1) Gastric acid suppression (1) Wound care (1) MRSA colonization (1)			

Evidence to Decision (EtD) Frameworks

Question 7: Does the use of a prediction score for drug-resistant pathogens lead to more appropriate therapy and improved outcomes (mortality, treatment failure, duration of antibiotic therapy, prolonged ICU stay)?	
POPULATION:	Patients with severe community acquired pneumonia (as defined in the study)
INTERVENTION:	Use of prediction scores for drug-resistant pathogens in community-acquired pneumonia
COMPARISON:	Standard treatment

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate **X Large** ○ Varies ○ Don't know	Relatively low accuracy data for most of the risk scores of MDR pathogens. Brito / Niedermann 2009, Prina 2015 and Webb 2016 performed better than others. But high negative predictive value for the vast majority of the scores Only two (Brito / Niedermann 2009 and Webb 2016) have been implemented. Brito / Niedermann 2009 shows that lower scores are associated with significant lower mortality, need for ICU admission / MV and initial treatment failure. Webb 2016 showed that in comparison to HCAP score DRIP score reduced the need of broad-spectrum antibiotic therapy but not mortality and length of stay	Use of any of these risk scores should be considered according to the local epidemiology and in addition to other clinical and diagnostic data. Outcome reductions observed in Brito / Niedermann 2009 for low-high scores are similar to those observed when comparing CAP vs HAP pneumonias.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large ○ Moderate **X Small** ○ Trivial ○ Varies ○ Don't know	Low risk of misclassification given the high negative predictive values of the scores	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low **X Low** **X Moderate** ○ High ○ No included studies	Low to very low for accuracy data (derivation and validation cohorts) Moderate for implementation data	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability **X Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Not systematically reviewed as a part of this TF	There has been small variability on how the panel rated critical outcomes. The guideline panel agreed by consensus that there is possibly important uncertainty or variability in how much people value the need of intubation but less or no uncertainty or variability for mortality outcome.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention **X Favors the intervention** ○ Varies ○ Don't know	In a recent systematic review, fourteen published risk prediction methods for DRP were identified, of which eight were externally validated. They are characterised by high sensitivity and generally low specificity that may favour overtreatment. However, most of these scores have high negative predictive values (mostly more than 90%) suggesting that their use may allow broad-spectrum regimens and spare a proportion of patients with low-risk scores	

Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ **Don't know**	Not systematically reviewed as a part of this TF.	

Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention	Not systematically reviewed as a part of this TF.	

○ Favors the intervention ○ Varies ○ **No included studies**		
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ **Don't know**	Not systematically reviewed as a part of this TF.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ **Don't know**	Not systematically reviewed as a part of this TF.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes	Not systematically reviewed as a part of this TF.	

○ Varies ○ **Don't know**		

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

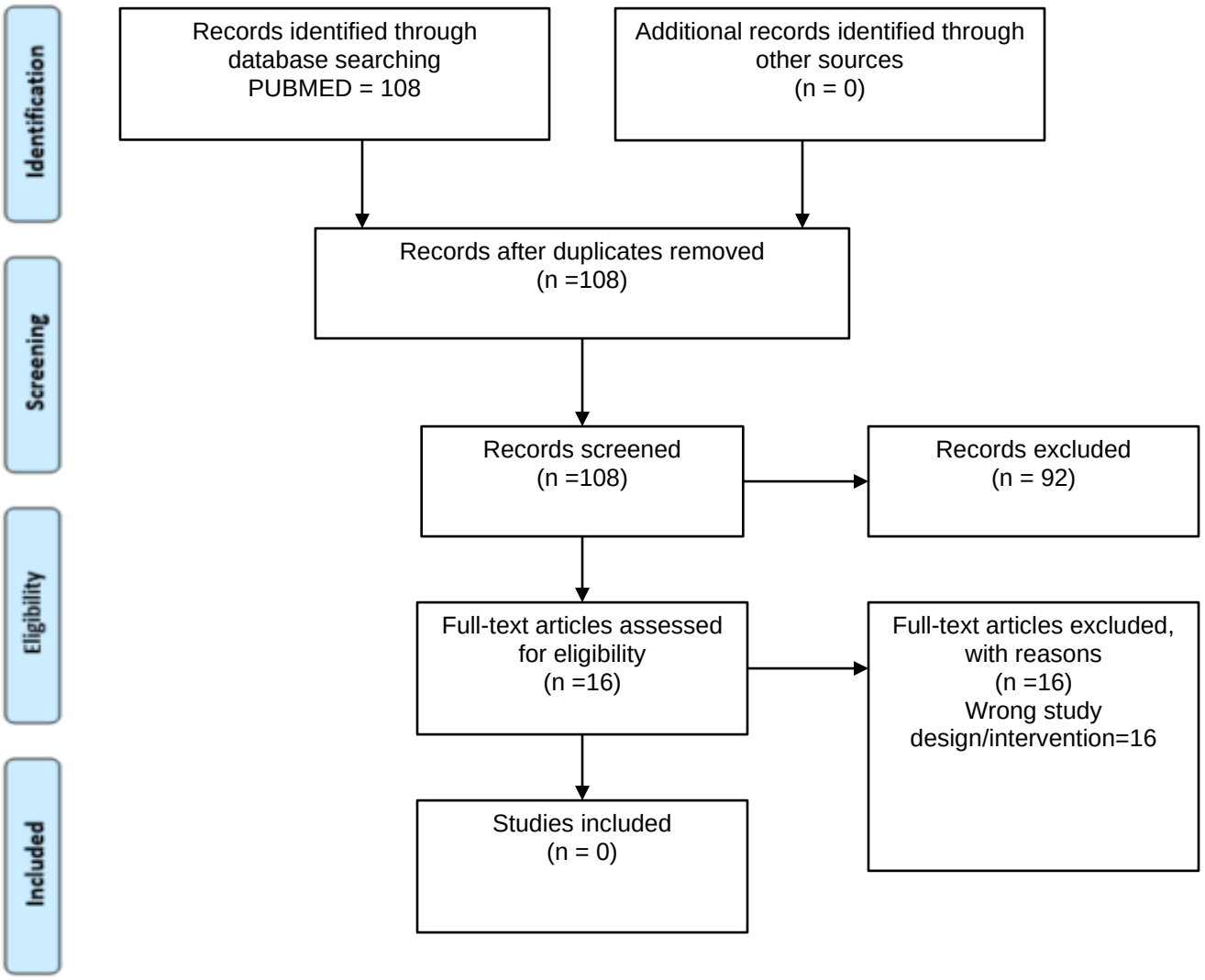
CONCLUSIONS

Recommendation

We suggest integrating specific risk factors (eventually computed into clinical scores) based on local epidemiology and previous colonisation to guide decisions regarding drug-resistant pathogen (excluding those immunocompromised) for the empiric antibiotic prescription of sCAP patients (conditional recommendation, moderate quality of evidence).

Question 8. Do patients with sCAP and aspiration risk factors have better outcomes (mortality, LOS, treatment failure) if treated with a risk-based therapy regimen instead of standard sCAP antibiotics?

PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Evidence to Decision (EtD) Frameworks

Question 8. Do patients with sCAP and aspiration risk factors have better outcomes (mortality, LOS, treatment failure) if treated with a risk-based therapy regimen instead of standard sCAP antibiotics?	
POPULATION:	sCAP patients with aspiration risk factors
INTERVENTION:	use of a risk-based therapy regimen providing therapy for anaerobic bacteria
COMPARISON:	standard sCAP therapy, based on risk factors for MDR pathogens

Assessment

Problem **Is the problem a priority?**		
Judgement	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ **Varies** ○ Don't know	No prospective RCTs to address this question, but the use of specific anti-anaerobic antibiotic therapy is not standardized and benefits are not known. Some need to get data to standardize the approach to therapy. Among the studies done, there is no proven benefit of specific anti-anaerobic therapy, no real data in sCAP patients.	Routine use of anti-anaerobic therapy could create harm, and benefits are not clear.
Desirable Effects **How substantial are the desirable anticipated effects?**		
Judgement	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ **Don't know**	No evidence that coverage of anaerobic bacteria improves outcome No evidence that coverage of anaerobic bacteria can prevent progression to lung abscess in high risk patients	Anaerobic bacteria are not very common in aspiration pneumonia, with gram-negatives being identified more often Use of high oxygen concentrations may eradicate anaerobic bacteria, independent of antibiotic choice Most standard sCAP therapies can eradicate anaerobic bacteria either directly, or by

		eradicating other pathogens, on which anaerobes depend.
Undesirable Effects **How substantial are the undesirable anticipated effects?**		
Judgement	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ **Moderate** ○ Small ○ Trivial ○ Varies ○ Don't know	Use of anti-anaerobic therapy may lead to *C. difficile* infection Use of anti-anaerobic therapy can add to the emergence of resistant gram—positive and gram-negative organisms, potentially without providing any benefit.	
Certainty of evidence **What is the overall certainty of the evidence of effects?**		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ **Very low** ○ Low ○ Moderate ○ High ○ No included studies	Not formally assessed as no studies were included. No prospective RCTs of this question in sCAP patients Few sCAP patients studied in trials already done	Presumed benefits and harms are extrapolated from theoretical considerations and bacteriologic data, but no direct information in sCAP patients with aspiration risks
Values **Is there important uncertainty about or variability in how much people value the main outcomes?**		
Judgement	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ **Possibly important uncertainty or variability** ○ Probably no important	Not assessed.	Panel values an improved clinical outcome, but no data to indicate that choosing anti-anaerobic therapy can achieve this outcome.

uncertainty or variability ○ No important uncertainty or variability		Panel also values avoiding the undesirable effects above, but also no data to show that therapy choice can have this impact.
Balance of effects **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**		
Judgement	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ **Probably favors the comparison** ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Based on available indirect evidence , no improved outcome with anti-anaerobic therapy, and thus no need to modify empiric antibiotic choice, based on aspiration risk factors	No data to identify if there are specific populations with aspiration risks who might benefit from anti-anaerobic therapy No data focused on sCAP patients.
Resources required **How large are the resource requirements (costs)?**		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○Varies ○ **Don't know**	Not assessed.	but could be considerable if no clinical benefit, but the undesirable effects cited above do occur
Certainty of evidence of required resources **What is the certainty of the evidence of resource requirements (costs)?**		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ○ **No included studies**	Not assessed.	Would be dependent on the frequency of benefit and the incidence of harm/complications, which is not known in this population

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ **Probably favors the comparison** ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Not assessed	No direct data, but if there is harm, without benefit, then the comparator would be more cost effective.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ **Don't know**	Not assessed	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ **Don't know**	Not assessed	Presumed that key stakeholders will determine acceptability based on the balance between desired and undesired effects, which are not directly known for this population

Feasibility **Is the intervention feasible to implement?**		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	Not assessed	Choice of different empiric antibiotics will be easy to implement if supported by data and guidelines.

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

Conclusions

Recommendation

In patients with sCAP and aspiration risk factors we suggest standard CAP therapy regimen and not specific therapy targeting anaerobic bacteria (ungraded, good practice statement).

Good Practise Statement Checklist

(From: Guyatt, Gordon H., et al. "Guideline panels should not GRADE good practice statements." Journal of clinical epidemiology 68.5 (2015): 597.)

	Questions	**Response**
1	Is the statement clear and actionable?	Yes, it is not necessary to use specific anti-anaerobic therapy for severe aspiration pneumonia and standard therapy is effective. Clinicians can act on this recommendation.
2	Is the message really necessary?	Yes, so that unnecessary anti-anaerobic therapy and its attendant risk for clostridium difficile colitis can be avoided.
3	Is the net benefit large and unequivocal?	Avoiding collateral damage from unnecessary anti-anaerobic therapy has direct patient care benefits.
4	Is the evidence difficult to collect and summarize?	No, it has been summarized in the statement. There are no direct studies of the specific question and this is also stated in the summary.
5	If a public health guideline, are there specific issues that should be considered (eg, equity)	Not applicable
6	Have you made the rationale explicit?	Yes
7	Is this better to be formally GRADEd?	No, not enough relevant direct evidence.

Search strategies

Question 1: In patients with sCAP should rapid microbiologic techniques be added to current testing of blood and respiratory tract samples?

Note: Population modified from other searches in this guideline to include Pneumococcal Infections and Streptococcus pneumoniae due to nature of the intervention

Search 1 – SRs/MAs/HTAs

Search date: August 27, 2019

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present, Embase Classic+Embase 1947 to 2019 August 26; Wiley Cochrane

Limits: Humans

Excluded: Letters, notes, comments, editorials, case reports

Study design filter: Systematic Review/Meta-Analyses, Health Technology Assessments

Ovid MEDLINE(R), Embase

#	Searches	Results
1	exp Pneumonia/	392105
2	exp Pneumococcal Infections/ use ppez or pneumococcal infection/ use emczd or exp Streptococcus pneumoniae/ use ppez	39521
3	(pneumoni* or peripneumoni* or pleuropneumoni* pneumococc* or lobitis or ((pulmon* or lung*) adj inflammation*)).ti,ab,kf,kw.	451975
4	or/1-3	629397
5	exp Polymerase Chain Reaction/	1301486
6	*C-Reactive Protein/ use ppez	16974
7	*C Reactive Protein/ use emczd	23166

8	*Procalcitonin/	4560
9	*Spectrometry, Mass, Matrix-Assisted Laser Desorption-Ionization/ use ppez	8561
10	*matrix-assisted laser desorption-ionization mass spectrometry/ use emczd	729
11	exp Molecular Diagnostic Techniques/ use ppez	16600
12	*In Situ Hybridization, Fluorescence/ use ppez	6384
13	exp molecular diagnosis/ use emczd or *fluorescence in situ hybridization/ use emczd	24103
14	exp Rapid Test/ use emczd	10856
15	exp Point-of-Care Systems/ use ppez	13065
16	exp "point of care testing"/ use emczd	12073
17	*Biological Markers/	82823
18	exp *Immunoassay/	107103
19	((rapid* or real?time or point of care or poc or bedside) adj2 (test* or detect* or identification or diagnos* or assay* or immunoassay* or immunofluores* or microimmunofluores*)).ti,ab,kf,kw.	156152
20	((nucleic acid amplification or crp or c reactive protein or procalcitonin) adj2 (test* or assay*)).ti,ab,kf,kw.	9744
21	((Enzyme adj2 immunoassay) or (urinary adj antigen*) or (urine adj antigen*) or lateral flow assay*).ti,ab,kf,kw.	55179
22	or/5-21	1754327

23	4 and 22	37094
24	animals/ not (humans/ and animals/)	5954601
25	23 not 24	35366
26	limit 24 to (case reports or comment or congress or editorial or letter or conference abstract or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher,Embase; records were retained]	125057
27	Case Report/	4535252
28	25 not (26 or 27)	30705
29	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/	559008
30	Meta Analysis.pt.	104127
31	(meta analy* or metaanaly* or health technolog* assess*).ti,ab,kf,kw.	372309
32	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	715776
33	(((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pub med or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab,kf,kw.	738258
34	(cochrane or (health adj2 technology assessment) or evidence report).jw.	44099
35	or/29-34	998524

36	28 and 35	511
37	remove duplicates from 36	432

Wiley Cochrane

#1 MeSH descriptor: [Pneumonia] explode all trees 3179

#2 MeSH descriptor: [Pneumococcal Infections] explode all trees 678

#3 MeSH descriptor: [Streptococcus pneumoniae] explode all trees 550

#4 (pneumoni* or peripneumoni* or pleuropneumoni* pneumococc* or lobitis or ((pulmon* or lung*) next/1 inflammation*)):ti4387

#5 #1 or #2 or #3 or #4 6562

#6 MeSH descriptor: [Polymerase Chain Reaction] explode all trees 2196

#7 MeSH descriptor: [C-Reactive Protein] explode all trees 4407

#8 MeSH descriptor: [Procalcitonin] explode all trees 10

#9 MeSH descriptor: [Spectrometry, Mass, Matrix-Assisted Laser Desorption-Ionization] explode all trees 64

#10 MeSH descriptor: [Molecular Diagnostic Techniques] explode all trees 54

#11 MeSH descriptor: [In Situ Hybridization, Fluorescence] explode all trees 219

#12 MeSH descriptor: [Point-of-Care Systems] explode all trees 450

#13 MeSH descriptor: [Biomarkers] explode all trees 19321

#14 MeSH descriptor: [Immunoassay] explode all trees 4679

#15 ((rapid* or real-time or real time or point of care or poc or bedside) near/2 (test* or detect* or identification or diagnos* or assay* or immunoassay* or immunofluores* or microimmunofluores*)):ti,ab 121559

#16 ((nucleic acid amplification or crp or c reactive protein or procalcitonin) near/2 (test* or assay*)):ti,ab 2470

#17 ((Enzyme near/2 immunoassay) or (urinary near/1 antigen*) or (urine near/1 antigen*) or lateral flow assay*):ti,ab 898

#18 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 148158

#19 #5 AND #18 in Cochrane Reviews 14

Search 2 – Clinical Trials/Comparative Studies

Search date: August 26, 2019

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present, Embase Classic+Embase 1947 to 2019 August 26; Wiley Cochrane

Limits: Humans

Excluded: Letters, notes, comments, editorials, case reports

Study design filter: RCTs/Clinical Trials/Comparative Studies

Ovid MEDLINE(R), Embase

#	Searches	Results
1	exp Pneumonia/	392105
2	exp Pneumococcal Infections/ use ppez or pneumococcal infection/ use emczd or exp Streptococcus pneumoniae/ use ppez	39521
3	(pneumoni* or peripneumoni* or pleuropneumoni* pneumococc* or lobitis or ((pulmon* or lung*) adj inflammation*)).ti,ab,kf,kw.	451975
4	or/1-3	629397
5	exp Polymerase Chain Reaction/	1301486
6	*C-Reactive Protein/ use ppez	16974
7	*C Reactive Protein/ use emczd	23166
8	*Procalcitonin/	4560
9	*Spectrometry, Mass, Matrix-Assisted Laser Desorption-Ionization/ use ppez	8561
10	*matrix-assisted laser desorption-ionization mass spectrometry/ use emczd	729
11	exp Molecular Diagnostic Techniques/ use ppez	16600

12	*In Situ Hybridization, Fluorescence/ use ppez	6384
13	exp molecular diagnosis/ use emczd or *fluorescence in situ hybridization/ use emczd	24103
14	exp Rapid Test/ use emczd	10856
15	exp Point-of-Care Systems/ use ppez	13065
16	exp "point of care testing"/ use emczd	12073
17	*Biological Markers/	82823
18	exp *Immunoassay/	107103
19	((rapid* or real?time or point of care or poc or bedside) adj2 (test* or detect* or identification or diagnos* or assay* or immunoassay* or immunofluores* or microimmunofluores*)).ti,ab,kf,kw.	156152
20	((nucleic acid amplification or crp or c reactive protein or procalcitonin) adj2 (test* or assay*)).ti,ab,kf,kw.	9744
21	((Enzyme adj2 immunoassay) or (urinary adj antigen*) or (urine adj antigen*) or lateral flow assay*).ti,ab,kf,kw.	55179
22	or/5-21	1754327
23	4 and 22	37094
24	animals/ not (humans/ and animals/)	5954601
25	23 not 24	35366

26	limit 24 to (case reports or comment or congress or editorial or letter or conference abstract or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher,Embase; records were retained]	125057
27	Case Report/	4535252
28	25 not (26 or 27)	30705
29	Randomized Controlled Trial/ or exp Randomized Controlled Trials as Topic/ or "Randomized Controlled Trial (topic)"/ or Controlled Clinical Trial/ or exp Controlled Clinical Trials as Topic/ or "Controlled Clinical Trial (topic)"/ or Randomization/ or Random Allocation/ or Double-Blind Method/ or Double Blind Procedure/ or Double-Blind Studies/ or Single-Blind Method/ or Single Blind Procedure/ or Single-Blind Studies/ or Placebos/ or Placebo/ or (random* or sham or placebo*).ti,ab,hw,kf,kw. or ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. or ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. or (control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw. or (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw. or ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw. or ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw. or (pragmatic study or pragmatic studies).ti,ab,hw,kf,kw. or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw. or ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw. or allocated.ti,ab,hw. or (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	4990885
30	exp comparative study/	3221893
31	(compare or compared or comparing or comparative or comparison).ti,kf,kw.	1366028
32	or/29-31	8199461
33	28 and 32	5564
34	remove duplicates from 33	4615

Wiley Cochrane

ID	Search	Hits
#1	MeSH descriptor: [Pneumonia] explode all trees	3179
#2	MeSH descriptor: [Pneumococcal Infections] explode all trees	678
#3	MeSH descriptor: [Streptococcus pneumoniae] explode all trees	550
#4	(pneumoni* or peripneumoni* or pleuropneumoni* pneumococc* or lobitis or ((pulmon* or lung*) next/1 inflammation*)):ti,ab	12577
#5	#1 or #2 or #3 or #4	13729
#6	MeSH descriptor: [Polymerase Chain Reaction] explode all trees	2196
#7	MeSH descriptor: [C-Reactive Protein] explode all trees	4407
#8	MeSH descriptor: [Procalcitonin] explode all trees	10
#9	MeSH descriptor: [Spectrometry, Mass, Matrix-Assisted Laser Desorption-Ionization] explode all trees	64
#10	MeSH descriptor: [Molecular Diagnostic Techniques] explode all trees	54
#11	MeSH descriptor: [In Situ Hybridization, Fluorescence] explode all trees	219
#12	MeSH descriptor: [Point-of-Care Systems] explode all trees	450
#13	MeSH descriptor: [Biomarkers] explode all trees	19321
#14	MeSH descriptor: [Immunoassay] explode all trees	4679
#15	((rapid* or real-time or real time or point of care or poc or bedside) near/2 (test* or detect* or identification or diagnos* or assay* or immunoassay* or immunofluores* or microimmunofluores*)):ti,ab	121559
#16	((nucleic acid amplification or crp or c reactive protein or procalcitonin) near/2 (test* or assay*)):ti,ab	2470
#17	((Enzyme near/2 immunoassay) or (urinary near/1 antigen*) or (urine near/1 antigen*) or lateral flow assay*):ti,ab	898
#18	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17	148158
#19	#5 AND #18 in Trials	1975

Search 3

Search date: July 24, 2019

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present, Embase Classic+Embase 1947 to 2019 July 23; Wiley Cochrane

Limits: Humans

Exclusions: Letters, notes, editorials, conferences/congresses, comments, case reports

Ovid MEDLINE(R), Embase

#	Searches	Results
1	exp Pneumonia/	389908
2	(pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) adj inflammation*)).ti,ab.	444330
3	1 or 2	609710
4	*bacterial infection/di [Diagnosis]	12781
5	*Virus Diseases/di [Diagnosis]	9026
6	*virus diagnosis/ use emczd	806
7	*Polymerase Chain Reaction/	66945
8	*Molecular Diagnostic Techniques/ use ppez	6407
9	*In Situ Hybridization, Fluorescence/ use ppez	6369
10	*diagnostic test/ use emczd or *molecular diagnosis/ use emczd or *fluorescence in situ hybridization/ use emczd	23579
11	or/4-10	123225
12	exp Time Factors/ use ppez or exp Time Factor/ use emczd	1185135
13	exp Turnaround Time/ use emczd	4519
14	12 or 13	1189649
15	11 and 14	2796
16	exp Rapid Test/ use emczd	10704

17	(rapid* adj2 (test* or detect* or identification or diagnos* or assay*)).ti,ab.	130149
18	15 or 16 or 17	137858
19	3 and 18	4773
20	animals/ not (humans/ and animals/)	5939551
21	19 not 20	4676
22	limit 21 to (case reports or comment or congress or editorial or letter or conference abstract or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher,Embase; records were retained]	874
23	Case Report/	4515579
24	21 not (22 or 23)	3521
25	remove duplicates from 24	2268

Wiley Cochrane

ID Search Hits

#1 MeSH descriptor: [Pneumonia] explode all trees 3175

#2 (pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) adj inflammation*)):ti,ab 12177

#3 #1 or #2 12926

#4 MeSH descriptor: [Bacterial Infections] explode all trees 16280

#5 MeSH descriptor: [Virus Diseases] explode all trees 26077

#6 MeSH descriptor: [Polymerase Chain Reaction] explode all trees 2193

#7	MeSH descriptor: [Molecular Diagnostic Techniques] explode all trees	54
#8	MeSH descriptor: [In Situ Hybridization, Fluorescence] explode all trees	219
#9	#4 or #5 or #6 or #7 or #8	42907
#10	MeSH descriptor: [Time Factors] explode all trees	62663
#11	#9 and #10	3165
#12	(rapid* near/2 (test* or detect* or identification or diagnos* or assay*)):ti,ab	2311
#13	#11 or #12	5408
#14	#3 and #13	215

Question 2. In hypoxemic patients with sCAP, can either non-invasive mechanical ventilation (NIV) or high-flow nasal oxygen (HFNC) be used initially—rather than supplemental standard oxygen administration—to avoid intubation and reduce mortality?

Search date: June 9, 2019

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present, Embase Classic+Embase 1947 to 2019 June 07; Wiley Cochrane

Limits: Human

Search Filters: Systematic Reviews, Meta-Analyses, Randomized Controlled Trials, Health Technology Assessments

Ovid MEDLINE(R), Embase

#	Searches	Results
1	exp Pneumonia/	386414
2	(pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) adj inflammation*)).ti,ab,kf,kw.	450431
3	1 or 2	610378
4	exp Noninvasive Ventilation/	9851
5	exp Oxygen Inhalation Therapy/ use ppez	24890
6	exp oxygen therapy/ use emczd	33445
7	(non?invasive adj4 ventilation).ti,ab,kf,kw.	10440
8	((high Flow or high-flow) adj2 (oxygen* or cannula* or therap*)).ti,ab,kf,kw.	3803
9	(hfno or hfnot or hfnc or hfn or niv).ti,ab,kf,kw.	9745
10	or/4-9	79089
11	3 and 10	6788

12	animals/ not (humans/ and animals/)	5920571
13	11 not 12	6748
14	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/	540730
15	Meta Analysis.pt.	101693
16	(meta analy* or metaanaly* or health technolog* assess*).ti,ab,kf,kw.	359116
17	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	691949
18	(((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pub med or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab,kf,kw.	715101
19	(cochrane or (health adj2 technology assessment) or evidence report).jw.	43712
20	(Randomized Controlled Trial or Pragmatic Clinical Trial).pt. or exp Randomized Controlled Trials as Topic/ or "Randomized Controlled Trial (topic)"/ or Randomized Controlled Trial/ or Randomization/ or Random Allocation/ or Double-Blind Method/ or Double Blind Procedure/ or Double-Blind Studies/ or Single-Blind Method/ or Single Blind Procedure/ or Single-Blind Studies/ or Placebos/ or Placebo/ or (random* or sham or placebo*).ti,ab,hw,kf,kw. or ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. or ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	3386335
21	or/14-20	4029325
22	13 and 21	894
23	remove duplicates from 22	741

Wiley Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Pneumonia] explode all trees	3163
#2	(pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) NEAR inflammation*)):ti,ab	13108
#3	#1 or #2	13804
#4	MeSH descriptor: [Noninvasive Ventilation] explode all trees	186
#5	MeSH descriptor: [Oxygen Inhalation Therapy] explode all trees	1415
#6	(non?invasive NEAR/4 ventilation):ti,ab	2057
#7	((high Flow or high-flow) NEAR/2 (oxygen* or cannula* or therap*)):ti,ab	4249
#8	(hfno or hfnot or hfnc or hfn or niv):ti,ab	1160
#9	#4 or #5 or #6 or #7 or #8	7403
#10	#3 and #9	312

Antibiotics in SCAP (one common search for PICOs, 3, 4, 7)

Search 1 – SRs/MAs/HTAs

Search date: April 29, 2019

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present, Embase Classic+Embase 1947 to 2019 April 26; Wiley Cochrane Library

Ovid MEDLINE(R), Embase

#	Searches	Results
1	exp Pneumonia/	383548
2	(pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) adj inflammation*)).ti,ab.	436390
3	1 or 2	599159
4	exp Anti-Bacterial Agents/ use ppez or exp antibiotic agent/ use emczd	2124393
5	exp Quinolones/ use ppez or exp quinolone derivative/ use emczd	203031
6	exp Macrolides/ use ppez	105054
7	exp beta-Lactams/ use ppez	124562
8	(((anti?bacterial or anti?mycobacterial or bacteriocidal) adj agent) or antibiotic* or bacteriocide* or quinolon* or fluoroquinolon* or aripiprazole* or Carteolol* or PQQ Cofactor* or Ciprofloxacin* or Enoxacin* or Enrofloxacin* or Gatifloxacin* or Gemifloxacin* or Moxifloxacin* or Norfloxacin* or Ofloxacin* or Pefloxacin* or Levofloxacin* or Fleroxacin* or Nalidixic Acid* or Nedocromil* or Oxolinic Acid* or macrolid* or Fidaxomicin* or Lucensomycin* or Maytansine* or Mepartricin* or Miocamycin* or Natamycin* or Nystatin* or Oleandomycin* or Oligomycin* or Sirolimus or Tylosin or Tacrolimus or beta?lactam* or carbapenem* or imipenem* or Ertapenem* or Meropenem* or Doripenem* or Thienamycin* or clavulanic acid* or sulbactam* or tazobactam* or amoxicillin* or penicillin* or ampicillin* or cephalosporin* or monobactam* or Moxalactam*).ti,ab,kf,kw.	1117935

9	or/4-8	2571969
10	3 and 9	171862
11	animals/ not (humans/ and animals/)	5902057
12	10 not 11	167922
13	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/	531189
14	Meta Analysis.pt.	100250
15	(meta analy* or metaanaly* or health technolog* assess*).ti,ab,kf,kw.	352428
16	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	679749
17	(((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pub med or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab,kf,kw.	702731
18	(cochrane or (health adj2 technology assessment) or evidence report).jw.	43467
19	or/13-18	954041
20	12 and 19	4408
21	remove duplicates from 20	3418

Wiley Cochrane Library

#1 MeSH descriptor: [Pneumonia] explode all trees 3131

#2 (pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) NEXT/1 inflammation*)):ti,ab 12214

#3 #1 or #2 12920

#4 MeSH descriptor: [Anti-Bacterial Agents] explode all trees 11090

#5 MeSH descriptor: [Quinolones] explode all trees 4527

#6 MeSH descriptor: [Macrolides] explode all trees 8038

#7 MeSH descriptor: [beta-Lactams] explode all trees 8954

#8 (((anti?bacterial or anti?mycobacterial or bacteriocidal) adj agent) or antibiotic* or bacteriocide* or quinolon* or fluoroquinolon* or aripiprazole* or Carteolol* or PQQ Cofactor* or Ciprofloxacin* or Enoxacin* or Enrofloxacin* or Gatifloxacin* or Gemifloxacin* or Moxifloxacin* or Norfloxacin* or Ofloxacin* or Pefloxacin* or Levofloxacin* or Fleroxacin* or Nalidixic Acid* or Nedocromil* or Oxolinic Acid* or macrolid* or Fidaxomicin* or Lucensomycin* or Maytansine* or Mepartricin* or Miocamycin* or Natamycin* or Nystatin* or Oleandomycin* or Oligomycin* or Sirolimus or Tylosin or Tacrolimus or beta?lactam* or carbapenem* or imipenem* or Ertapenem* or Meropenem* or Doripenem* or Thienamycin* or clavulanic acid* or sulbactam* or tazobactam* or amoxicillin* or penicillin* or ampicillin* or cephalosporin* or monobactam* or Moxalactam*):ti,ab 10223

#9 #4 or #5 or #6 or #7 or #8 30516

#10 #3 and #9 in Cochrane Reviews 43

Search 2 - RCTs

Search date: February 9, 2020

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present, Embase Classic+Embase 1947 to 2020 February 07; Wiley Cochrane (Trials)

Limits: Humans

Filters: RCTs

Ovid MEDLINE(R), Embase

#	Searches	Results
1	exp Pneumonia/	401913
2	(pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) adj inflammation*)).ti,ab.	459813
3	1 or 2	628964

4 exp Anti-Bacterial Agents/ use ppez or exp antibiotic agent/ use emczd 2263032

5 exp Quinolones/ use ppez or exp quinolone derivative/ use emczd 213236

6 exp Macrolides/ use ppez 108087

7 exp beta-Lactams/ use ppez 127094

8 (((anti?bacterial or anti?mycobacterial or bacteriocidal) adj agent) or antibiotic* or bacteriocide* or quinolon* or fluoroquinolon* or aripiprazole* or Carteolol* or PQQ Cofactor* or Ciprofloxacin* or Enoxacin* or Enrofloxacin* or Gatifloxacin* or Gemifloxacin* or Moxifloxacin* or Norfloxacin* or Ofloxacin* or Pefloxacin* or Levofloxacin* or Fleroxacin* or Nalidixic Acid* or Nedocromil* or Oxolinic Acid* or macrolid* or Fidaxomicin* or Lucensomycin* or Maytansine* or Mepartricin* or Miocamycin* or Natamycin* or Nystatin* or Oleandomycin* or Oligomycin* or Sirolimus or Tylosin or Tacrolimus or beta?lactam* or carbapenem* or imipenem* or Ertapenem* or Meropenem* or Doripenem* or Thienamycin* or clavulanic acid* or sulbactam* or tazobactam* or amoxicillin* or penicillin* or ampicillin* or cephalosporin* or monobactam* or Moxalactam*).ti,ab,kf,kw. 1178355

9 or/4-8 2713271

10 3 and 9 183305

11 animals/ not (humans/ and animals/) 6009818

12 10 not 11 179208

13 (Randomized Controlled Trial or Pragmatic Clinical Trial).pt. or exp Randomized Controlled Trials as Topic/ or "Randomized Controlled Trial (topic)"/ or Randomized Controlled Trial/ or Randomization/ or Random Allocation/ or Double-Blind Method/ or Double Blind Procedure/ or Double-Blind Studies/ or Single-Blind Method/ or Single Blind Procedure/ or Single-Blind Studies/ or Placebos/ or Placebo/ or (random* or sham or placebo*).ti,ab,hw,kf,kw. or ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. or ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. 3546963

14 12 and 13 13969

15 limit 14 to yr="2012 -Current" 5788

16 remove duplicates from 15 4719

Wiley Cochrane (Trials)

#1 MeSH descriptor: [Pneumonia] explode all trees 3435

#2 (pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) NEXT/1 inflammation*)):ti,ab 13539

#3 #1 or #2 14312

#4 MeSH descriptor: [Anti-Bacterial Agents] explode all trees 11806

#5 MeSH descriptor: [Quinolones] explode all trees 4956

#6 MeSH descriptor: [Macrolides] explode all trees 8826

#7 MeSH descriptor: [beta-Lactams] explode all trees 9408

#8 (((anti?bacterial or anti?mycobacterial or bacteriocidal) NEXT/1 agent) or antibiotic* or bacteriocide* or quinolon* or fluoroquinolon* or aripiprazole* or Carteolol* or PQQ Cofactor* or Ciprofloxacin* or Enoxacin* or Enrofloxacin* or Gatifloxacin* or Gemifloxacin* or Moxifloxacin* or Norfloxacin* or Ofloxacin* or Pefloxacin* or Levofloxacin* or Fleroxacin* or Nalidixic Acid* or Nedocromil* or Oxolinic Acid* or macrolid* or Fidaxomicin* or Lucensomycin* or Maytansine* or Mepartricin* or Miocamycin* or Natamycin* or Nystatin* or Oleandomycin* or Oligomycin* or Sirolimus or Tylosin or Tacrolimus or beta?lactam* or carbapenem* or imipenem* or Ertapenem* or Meropenem* or Doripenem* or Thienamycin* or clavulanic acid* or sulbactam* or tazobactam* or amoxicillin* or penicillin* or ampicillin* or cephalosporin* or monobactam* or Moxalactam*):ti,ab 46534

#9 #4 or #5 or #6 or #7 or #8 56576

#10 #3 and #9 with Publication Year from 2012 to 2020, in Trials 1720

Question 5: Should oseltamivir be added to standard therapy in patients with sCAP and confirmed influenza?

Search 1 – SRs/MAs/HTAs

Search date: September 5, 2019

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present, Embase Classic+Embase 1947 to 2019 September 04; Wiley Cochrane

Limits: Humans

Filters: Systematic reviews/Meta-Analyses, Health Technology Assessments

Ovid MEDLINE(R), Embase

#	Searches	Results
1	exp Pneumonia/	392788
2	(pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) adj inflammation*)).ti,ab,kf,kw.	458190
3	1 or 2	620484
4	exp Antiviral Agents/ use ppez	344307
5	exp antivirus agent/ use emczd	952351
6	*Enzyme Inhibitors/ use ppez	52071
7	exp Neuraminidase/ai [Antagonists & Inhibitors]	2032
8	exp sialidase inhibitor/ use emczd	12464
9	((Neuraminidase or sialidase) adj2 inhibit*).ti,ab,kf,kw.	6243
10	(Zanamivir or Relenza or Laninamivir or Inavir or Peramivir or oseltamivir or tamiflu or anti?viral* or anti?virus*).ti,ab,kf,kw.	207870
11	or/4-10	1422031

12	3 and 11	41824
13	animals/ not (humans/ and animals/)	5959678
14	12 not 13	40354
15	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/	561978
16	Meta Analysis.pt.	104478
17	(meta analy* or metaanaly* or health technolog* assess*).ti,ab,kf,kw.	374080
18	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	719184
19	(((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pub med or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab,kf,kw.	741476
20	(cochrane or (health adj2 technology assessment) or evidence report).jw.	44142
21	or/15-20	1002550
22	14 and 21	1252
23	remove duplicates from 22	1134

Wiley Cochrane

ID	Search	Hits
#1	MeSH descriptor: [Pneumonia] explode all trees	3186

#2 (pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) NEAR inflammation*)):ti,ab 13460

#3 #1 or #2 14159

#4 MeSH descriptor: [Antiviral Agents] explode all trees 7828

#5 MeSH descriptor: [Enzyme Inhibitors] this term only 2098

#6 MeSH descriptor: [Neuraminidase] explode all trees 111

#7 ((Neuraminidase or sialidase) near/2 inhibit*):ti,ab 184

#8 (Zanamivir or Relenza or Laninamivir or Inavir or Peramivir or oseltamivir or tamiflu or anti?viral* or anti?virus*):ti,ab 5953

#9 #4 or #5 or #6 or #7 or #8 14300

#10 #3 and #9 in Cochrane Reviews 9

Search 2 – RCTs/SRs/MAs/HTAs

Search date: May 31, 2019

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present, Embase Classic+Embase 1947 to 2019 May 30; Wiley Cochrane

Limits: Human

Search filters: RCTs, Systematic Reviews, Meta-Analyses, and Health Technology Assessments

Ovid MEDLINE(R), Embase

Searches Results

1 exp Pneumonia/ 385783

2 (pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) adj inflammation*)).ti,ab,kf,kw. 449816

3 1 or 2 609380

4 exp Antiviral Agents/ use ppez 341216

5 exp antivirus agent/ use emczd 930688

6 *Enzyme Inhibitors/ use ppez 51616

7 exp Neuraminidase/ai [Antagonists & Inhibitors] 2004

8 exp sialidase inhibitor/ use emczd 12187

9 ((Neuraminidase or sialidase) adj2 inhibit*).ti,ab,kf,kw. 6121

10 (Zanamivir or Relenza or Laninamivir or Inavir or Peramivir or oseltamivir or tamiflu or anti?viral* or anti?virus*).ti,ab,kf,kw. 202896

11 or/4-10 1394953

12 3 and 11 40991

13 animals/ not (humans/ and animals/) 5917254

14 12 not 13 39541

15 meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ 539419

16 Meta Analysis.pt. 101403

17 (meta analy* or metaanaly* or health technolog* assess*).ti,ab,kf,kw. 357853

18 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. 689845

19 (((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pub med or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab,kf,kw. 712983

20 (cochrane or (health adj2 technology assessment) or evidence report).jw. 43684

21 (Randomized Controlled Trial or Pragmatic Clinical Trial).pt. or exp Randomized Controlled Trials as Topic/ or "Randomized Controlled Trial (topic)"/ or Randomized Controlled Trial/ or Randomization/ or Random Allocation/ or Double-Blind Method/ or Double Blind Procedure/ or Double-Blind Studies/ or Single-Blind Method/ or Single Blind Procedure/ or Single-Blind Studies/ or Placebos/ or Placebo/ or (random* or sham or placebo*).ti,ab,hw,kf,kw. or ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. or ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. 3380440

22 or/15-21 4021666

23 14 and 22 4995

24 remove duplicates from 23 4659

Wiley Cochrane

#1 MeSH descriptor: [Pneumonia] explode all trees 3163

#2 (pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) NEAR inflammation*)):ti,ab 13108

#3 #1 or #2 13804

#4 MeSH descriptor: [Antiviral Agents] explode all trees 7758

#5 MeSH descriptor: [Enzyme Inhibitors] this term only 2090

#6 MeSH descriptor: [Neuraminidase] explode all trees 111

#7 ((Neuraminidase or sialidase) near/2 inhibit*):ti,ab 175

#8 (Zanamivir or Relenza or Laninamivir or Inavir or Peramivir or oseltamivir or tamiflu or anti?viral* or anti?virus*):ti,ab 83

#9 #4 or #5 or #6 or #7 or #8 9998

#10 #3 and #9 91

Question 6. Does the addition of steroids to antibiotic therapy in specific sCAP populations lead to better outcomes in comparison to when steroid therapy is not used?

Search 1 – RCTs

Search date: August 27, 2019

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present, Embase Classic+Embase 1947 to 2019 August 26; Wiley Cochrane

Limits: Humans, Randomized Controlled Trials; Year 2000 onwards

Ovid MEDLINE(R), Embase

#	Searches	Results
1	exp Pneumonia/	385414
2	(pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) adj inflammation*)).ti,ab,kf,kw.	449222
3	1 or 2	608748
4	exp Adrenal Cortex Hormones/ use ppez	385182
5	exp Steroids/ use ppez	831891
6	exp Steroid/ use emczd	1580549
7	(steroid* or adrenal cortex hormone* or corticosteroid* or corticoid* or glucocorticoid* or glucocorticosteroid* or Prednisone* or Methylprednisolone* or Hydrocortisone* or Fludrocortisone*).ti,ab,kf,kw.	1023594
8	or/4-7	2799425
9	3 and 8	62862
10	animals/ not (humans/ and animals/)	5915564

11	9 not 10	61615
12	(Randomized Controlled Trial or Pragmatic Clinical Trial).pt. or exp Randomized Controlled Trials as Topic/ or "Randomized Controlled Trial (topic)"/ or Randomized Controlled Trial/ or Randomization/ or Random Allocation/ or Double-Blind Method/ or Double Blind Procedure/ or Double-Blind Studies/ or Single-Blind Method/ or Single Blind Procedure/ or Single-Blind Studies/ or Placebos/ or Placebo/ or (random* or sham or placebo*).ti,ab,hw,kf,kw. or ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. or ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	3376790
13	11 and 12	6473
14	limit 13 to yr="2000 -Current"	5998
15	remove duplicates from 14	5421

Wiley Cochrane

#1 MeSH descriptor: [Pneumonia] explode all trees 3148

#2 (pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) NEXT/1 inflammation*)):ti,ab 12332

#3 #1 or #2 13041

#4 MeSH descriptor: [Steroids] explode all trees 53921

#5 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees 13714

#6 (steroid* or adrenal cortex hormone* or corticosteroid* or corticoid* or glucocorticoid* or glucocorticosteroid* or Prednisone* or Methylprednisolone* or Hydrocortisone* or Fludrocortisone*) 67138

#7 #4 or #5 or #6 100508

#8 #3 and #7 with Publication Year from 2000 to 2019, in Trials 911

Search 2 – SRs/MAs/HTAs

Search date: May 11, 2019

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present, Embase Classic+Embase 1947 to 2019 May 09; Wiley Cochrane Library

Limits: Systematic Reviews, Meta-Analyses, Health Technology Assessments

Ovid MEDLINE(R), Embase

#	Searches	Results
1	exp Pneumonia/	384181
2	(pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) adj inflammation*)).ti,ab,kf,kw.	447139
3	1 or 2	606031
4	exp Adrenal Cortex Hormones/ use ppez	384655
5	exp Steroids/ use ppez	830640
6	exp Steroid/ use emczd	1575477
7	(steroid* or adrenal cortex hormone* or corticosteroid* or corticoid* or glucocorticoid* or glucocorticosteroid* or Prednisone* or Methylprednisolone* or Hydrocortisone* or Fludrocortisone*).ti,ab,kf,kw.	1018991
8	or/4-7	2789942
9	3 and 8	62553
10	animals/ not (humans/ and animals/)	5905715
11	9 not 10	61309
12	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/	534252
13	Meta Analysis.pt.	100522
14	(meta analy* or metaanaly* or health technolog* assess*).ti,ab,kf,kw.	354367
15	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	683263
16	(((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pub med or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab,kf,kw.	706043
17	(cochrane or (health adj2 technology assessment) or evidence report).jw.	43551
18	or/12-17	958118
19	11 and 18	2110
20	remove duplicates from 19	1830

Wiley Cochrane Library

#1 MeSH descriptor: [Pneumonia] explode all trees 3148

#2 (pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) NEXT/1 inflammation*)):ti,ab 12334

#3 #1 or #2 13043

#4 MeSH descriptor: [Steroids] explode all trees 53922

#5 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees 13714

#6 (steroid* or adrenal cortex hormone* or corticosteroid* or corticoid* or glucocorticoid* or glucocorticosteroid* or Prednisone* or Methylprednisolone* or Hydrocortisone* or Fludrocortisone*):ti,ab 48899

#7 #4 or #5 or #6 89506

#8 #3 AND #7 in Cochrane Reviews 36

**Included Meduri et al. ICM 2022

Question 8. Do patients with sCAP and aspiration risk factors have better outcomes (mortality, LOS, treatment failure) if treated with a risk-based therapy regimen instead of standard sCAP antibiotics?

Search date: December 12, 2021

Databases searched: PubMed (1988 – 2021)

Search Filters: none

Search	Query	Results
#2	Search: **((Aspiration pneumonia) AND (severe) AND (community) AND (therapy))** ("pneumonia, aspiration"[MeSH Terms] OR ("pneumonia"[All Fields] AND "aspiration"[All Fields]) OR "aspiration pneumonia"[All Fields] OR ("aspiration"[All Fields] AND "pneumonia"[All Fields])) AND ("sever"[All Fields] OR "severe"[All Fields] OR "severed"[All Fields] OR "severely"[All Fields] OR "severer"[All Fields] OR "severes"[All Fields] OR "severing"[All Fields] OR "severities"[All Fields] OR "severity"[All Fields] OR "severs"[All Fields]) AND ("communal"[All Fields] OR "communalism"[All Fields] OR "communalities"[All Fields] OR "communality"[All Fields] OR "communally"[All Fields] OR "commune"[All Fields] OR "communes"[All Fields] OR "community s"[All Fields] OR "communitys"[All Fields] OR "residence characteristics"[MeSH Terms] OR ("residence"[All Fields] AND "characteristics"[All Fields]) OR "residence characteristics"[All Fields] OR "communities"[All Fields] OR "community"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields]) **Translations** **Aspiration pneumonia:** "pneumonia, aspiration"[MeSH Terms] OR ("pneumonia"[All Fields] AND "aspiration"[All Fields]) OR "aspiration pneumonia"[All Fields] OR ("aspiration"[All Fields] AND "pneumonia"[All Fields]) **severe:** "sever"[All Fields] OR "severe"[All Fields] OR "severed"[All Fields] OR "severely"[All Fields] OR "severer"[All Fields] OR "severes"[All Fields] OR "severing"[All Fields] OR "severities"[All Fields] OR "severity"[All Fields] OR "severs"[All Fields] **community:** "communal"[All Fields] OR "communalism"[All Fields] OR "communalities"[All Fields] OR "communality"[All Fields] OR "communally"[All Fields] OR "commune"[All Fields] OR "communes"[All Fields] OR "community's"[All Fields] OR "communitys"[All Fields] OR "residence characteristics"[MeSH Terms] OR ("residence"[All Fields] AND	108

Search	Query	Results
	"characteristics"[All Fields]) OR "residence characteristics"[All Fields] OR "communities"[All Fields] OR "community"[All Fields] **therapy:** "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[Subheading] OR "therapy"[All Fields] OR "therapy's"[All Fields] OR "therapys"[All Fields]	
#1	Search: **((Aspiration pneumonia) AND (severe)) AND (community)** ("pneumonia, aspiration"[MeSH Terms] OR ("pneumonia"[All Fields] AND "aspiration"[All Fields]) OR "aspiration pneumonia"[All Fields] OR ("aspiration"[All Fields] AND "pneumonia"[All Fields])) AND ("sever"[All Fields] OR "severe"[All Fields] OR "severed"[All Fields] OR "severely"[All Fields] OR "severer"[All Fields] OR "severes"[All Fields] OR "severing"[All Fields] OR "severities"[All Fields] OR "severity"[All Fields] OR "severs"[All Fields]) AND ("communal"[All Fields] OR "communalism"[All Fields] OR "communalities"[All Fields] OR "communality"[All Fields] OR "communally"[All Fields] OR "commune"[All Fields] OR "communes"[All Fields] OR "community s"[All Fields] OR "communitys"[All Fields] OR "residence characteristics"[MeSH Terms] OR ("residence"[All Fields] AND "characteristics"[All Fields]) OR "residence characteristics"[All Fields] OR "communities"[All Fields] OR "community"[All Fields]) **Translations** **Aspiration pneumonia:** "pneumonia, aspiration"[MeSH Terms] OR ("pneumonia"[All Fields] AND "aspiration"[All Fields]) OR "aspiration pneumonia"[All Fields] OR ("aspiration"[All Fields] AND "pneumonia"[All Fields]) **severe:** "sever"[All Fields] OR "severe"[All Fields] OR "severed"[All Fields] OR "severely"[All Fields] OR "severer"[All Fields] OR "severes"[All Fields] OR "severing"[All Fields] OR "severities"[All Fields] OR "severity"[All Fields] OR "severs"[All Fields] **community:** "communal"[All Fields] OR "communalism"[All Fields] OR "communalities"[All Fields] OR "communality"[All Fields] OR "communally"[All Fields] OR "commune"[All Fields] OR "communes"[All Fields] OR "community's"[All Fields] OR "communitys"[All Fields] OR "residence characteristics"[MeSH Terms] OR ("residence"[All Fields] AND "characteristics"[All Fields]) OR "residence characteristics"[All Fields] OR "communities"[All Fields] OR "community"[All Fields]	147