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Review

Metagenomic next-generation sequencing on treatment strategies and prognosis of patients with lower respiratory tract infections: A systematic review and meta-analysis

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ABSTRACT

Objectives: Controversy exists regarding the benefits of metagenomic next-generation sequencing (mNGS) in lower respiratory tract infections (LRTIs). We assessed the impact of mNGS on the treatment and prognosis of LRTI patients through a systematic review and meta-analysis.

Methods: A literature search was conducted in PubMed, Embase, and CENTRAL databases up to 19 February 2024. Studies investigating the clinical value of mNGS in patients with LRTIs were included. The Risk-of-Bias Tool for randomized controlled trials and the Newcastle–Ottawa scale for observational studies were used to assess risk of bias. Antibiotic change rates and prognostic outcomes were evaluated using random-effects analyses with 95% confidence intervals (CIs). This study is registered with PROSPERO, CRD42024509738.

Results: Twelve studies were included in the meta-analysis. The use of mNGS was associated with a higher rate of antibiotic change (odds ratio, 2.47; 95% CI, 1.42–4.28; $P < 0.01$). Consistent findings were observed in adults, patients with severe LRTIs, and in those who underwent mNGS testing exclusively on bronchoalveolar lavage fluid. We also observed a reduction in in-hospital mortality (odds ratio, 0.49; 95% CI, 0.36–0.67; $P < 0.01$), though no significant impact on length of hospital stay was observed (mean difference, −1.79; 95% CI, −5.20 −1.63; $P = 0.31$).

Conclusions: This meta-analysis indicates that the application of mNGS may lead to changes in antibiotic prescriptions for patients with LRTIs, and might reduce the risk of mortality. However, large-scale randomized controlled clinical trials are urgently needed to validate the findings of this study.

1. Introduction

Lower respiratory tract infections (LRTIs) are a prevalent type of respiratory infectious disease caused by various pathogenic microorganisms [1,2]. As the fourth leading cause of global mortality, LRTIs result in millions of deaths annually, making them one of the most common infectious diseases worldwide [3]. Identifying the causative pathogen is essential for the targeted treatment of LRTIs.

Metagenomic next-generation sequencing (mNGS) is a microbiologic diagnostic method that enables unbiased pathogen detection by sequencing all the nucleic acid in a sample [4]. With the advantages of short turnaround time and broad detection range,

Abbreviations: CIs, confidence intervals; mNGS, metagenomic next-generation sequencing; LRTIs, Lower respiratory tract infections; OR, odds ratio; RCTs, randomized controlled trials; aOR, adjusted odds ratio; MD, mean difference; BALF, bronchoalveolar lavage fluid.

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mNGS significantly enhances pathogen detection rates and is anticipated to change antimicrobial stewardship for LRTIs [5–7]. As a novel microbiologic test, mNGS is increasingly applied in the etiological diagnosis of LRTIs in China [8]. In recent years, growing studies have explored the value of mNGS in patients with LRTIs, providing evidence that mNGS could influence the treatment decision and thereby reduce mortality [9]. However, some studies have controversially reported that mNGS has little impact on treatment decisions, despite significantly increasing pathogen detection rates [10].

In this review, we conducted a meta-analysis of the relevant studies on the clinical value of mNGS in LRTIs, so as to comprehensively assess whether the application of mNGS provides benefits to patients, which is essential for the development of clinical pathways for managing LRTIs.

2. Methods

2.1. Search strategy and selection criteria

This systematic review and meta-analysis, registered at PROSPERO (CRD42024509738), was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [11]. The study aims to evaluate the impact of mNGS combined with conventional microbiologic tests on antimicrobial stewardship and prognosis in patients with LRTIs, compared to conventional microbiologic tests performed alone.

MEDLINE/PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched from inception to 19 February 2024. The search strategies were developed based on terms associated with mNGS and LRTIs (Supplementary Appendix 1). Original articles included in this review should meet all the following inclusion criteria: (1) Investigating the association between mNGS application and treatment strategies and/or clinical outcomes in patients with LRTIs; (2) including a control group that only performed conventional microbiologic test; (3) being randomized controlled trials (RCTs), cohort studies, or case-control studies published in English. Exclusion criteria were as follows: (1) Studies with an enrolment of 10 or fewer patients; (2) studies focusing on only a specific pathogen or a group of specific pathogens, such as non-tuberculous mycobacterial, mycobacterial tuberculous and fungal.

After excluding duplicates, two independent investigators (M.Y. and L.S.) initially screened the literature at the title and abstract levels using Endnote X9. Potentially eligible studies were then assessed at the full-text level. Any disagreements were resolved through discussion, and a third researcher (C.W.) was consulted for adjudication if necessary.

2.2. Data collection and quality assessment

Data extraction was performed in a custom electronic data extraction form by two investigators (M.Y. and L.S.) and was revalidated by a third investigator (C.W.) in case of disagreement. Extracted data included author, publication year, location, study design, patient characteristics, sample type, mNGS sequencing technology, and outcome information. The primary outcomes were proportion of patients with antibiotic change, length of hospital stay, and in-hospital mortality. Secondary outcomes were proportion of patients with antibiotic de-escalation, proportion of patients with antibiotic escalation, duration of mechanical ventilation, duration of ICU stay, 30-d all-cause mortality, and 90-d all-cause mortality. Mean and standard deviation of continuous outcomes were extracted for assessment [12,13], while for dichotomous outcomes, the number of events and the number of patients in each group were extracted from the articles. Effect measures, expressed as adjusted odds ratio (aOR) were also extracted. The quality of the included studies was assessed using the Risk-of-Bias Tool for RCTs and Newcastle–Ottawa scale for case-control and cohort studies [14,15].

2.3. Data analysis

The crude dichotomous data were reported as OR and 95% confidence intervals (CIs). Adjusted dichotomous outcomes were pooled by generic inverse variance method after converting aOR with 95% CIs to log-OR and standard error. The adjusted outcomes of binomial data are presented in the Supplementary Material. Continuous outcomes were analysed by generic inverse variance method and reported as mean difference (MD) and 95% CIs. Considering the potential heterogeneity across the studies, a random-effect model was used across the meta-analyses, and the statistical heterogeneity was assessed using the I^2 test and Q statistic. Heterogeneity was considered when $I^2 > 50$ and/or $P < 0.1$ of the Q statistic. Subgroup analysis of the primary outcomes was performed based on age (adults and infants), sequencing methods (DNA-seq, DNA-seq and RNA-seq, unknown), and sequencing platforms (BGISEQ, NextSeq, unknown), while sensitivity analyses were performed by excluding studies one by one. We also conducted analyses of the primary outcomes specifically for patients who underwent mNGS exclusively on bronchoalveolar lavage fluid (BALF) and for those with severe LRTIs. Univariable random-effects meta-regression were conducted on age, sample type of mNGS, severity of LRTIs, sequencing methods, and sequencing platforms to investigate potential sources of heterogeneity. Funnel plot and Egger's test were used to assess publication bias for the primary outcomes. Results for all outcomes were presented using forest plots. $P < 0.05$ was considered statistically significant. All statistical analyses were conducted with R, version 4.4.1, package 'meta'.

3. Results

3.1. Study selection and characteristics

Fig. 1 illustrated the study selection process. A total of 4964 records were retrieved from MEDLINE/PubMed, Embase, and CENTRAL databases, and after deduplication, 4098 records were screened by two independent reviewers. After removing irrelevant records, 396 articles underwent full-text assessment. Eventually, 12 studies were included in the systematic review and meta-analyses.

Table 1 summarizes the characteristics of the included studies. All studies were conducted in China at tertiary hospitals. Among them, three studies utilized a randomized design [16–18]. However, they were assessed as unclear risk in most bias domains due to the limited information of methodological information (Supplementary Table S1). The other included studies were observational studies, comprising eight cohort studies [9,10,19–24] and one nested case-control study [25]. Information related to mNGS sequencing technology, mNGS sequencing method, and mNGS sequencing conditions of the included studies is presented in Table S2. The Newcastle–Ottawa scale scores for the observational studies are provided in Supplementary Table S1 and ranged from 6 to 9.

3.2. mNGS and antibiotic change

Six studies reported the proportion of patients with antibiotic change in both the mNGS group and control group, 4 of which were cohort studies, 1 nested case-control study, and 1 RCT. The application of mNGS was associated with a higher rate of antibiotic change (OR, 2.47; 95% CI, 1.42–4.28; $P < 0.01$; $I^2 = 80\%$)

Table 1
Characteristics of studies investigating the impact of mNGS on treatment and prognosis of patients with LRTIs.

Study identification	Hospital	Study design	Population	Age	Type of sample	Sequencing methods	Sequencing platforms	Intervention	Control	Total	Adjusted
Zheng et al. [19]	Fujian Maternal and Child Health Hospital and Fujian Children's Hospital	Cohort	Patients with severe pneumonia after CHD admitted to CICU	Infants	BALF	DNA-seq	BGISEQ	CM+mNGS	CM	83	
Zhang, et al. [9]	Jiangmen Central Hospital	Cohort	Patients with severe pneumonia admitted to ICU, all with ARDS	Adults	BALF	DNA-seq	BGISEQ	CM+mNGS	CM	95	Yes
Zhang, et al. [20]	Zhongshan Hospital, Fudan University	Cohort	Immunocompromised patients with pulmonary infection	Adults	BALF, sputum, blood, pleural effusion	Unknown	BGISEQ	CM+mNGS	CM	356	
Yang et al. [25]	First Affiliated Hospital of the University of Science and Technology of China	Nested case-control	Patients with severe HAP admitted to ICU	Adults	BALF	DNA-seq	BGISEQ	CM+mNGS	CM	99	Yes
Yan et al. [10]	China-Japan Friendship Hospital	Cohort	Patients with LRTIs	Adults	BALF	Unknown	Unknown	CM+mNGS	CM	306	Yes
Xu et al. [21]	The Second Affiliated Hospital of Harbin Medical University	Cohort	Patients with pneumonia with pleural effusion	Adults	Pleural effusion	DNA-seq	NextSeq	CM+mNGS	CM	80	
Xie et al. [22]	Shanghai General Hospital	Cohort	Patients with severe pneumonia admitted to ICU	Adults	Sputum, blood, BALF	Unknown	Unknown	CM+mNGS	CM	178	
Xie et al. [16]	People's Liberation Army General Hospital	RCT	Patients with CAP admitted to RICU	Adults	Plasma, sputum, BALF	DNA-seq	NextSeq	CM+mNGS	CM	159	
Wang et al. [17]	The First Affiliated Hospital of Anhui Medical University	RCT	Pneumonia	Premature infants	Sputum, BALF	DNA-seq	NextSeq	CM+mNGS	CM	100	
Liu et al. [23]	Affiliated Hospital of Qingdao University	Cohort	Patients with pulmonary infection admitted to the ICU	Adults	Sputum, blood, BALF	Unknown	Unknown	CM+mNGS	CM	164	
Liu et al. [24]	Xiangya Hospital of Central South University	Cohort	CAP	Adolescents and Adults	BALF	DNA-seq and RNA-seq	NextSeq	BALF culture +mNGS	BALF or sputum culture	346	
Lu et al. [18]	People's Hospital of Xinjiang Uygur Autonomous Region	RCT	SCAP	Adults	BALF	DNA-seq and RNA-seq	BGISEQ	CM+mNGS	CM	158	

ARDS, acute respiratory distress syndrome; BALF, bronchoalveolar lavage fluid; CAP, community-acquired pneumonia; CHD, congenital heart disease; CICU, cardiac intensive care unit; CM, conventional microbiological test; HAP, hospital-acquired pneumonia; ICU, intensive care unit; LRTIs, lower respiratory tract infections; mNGS, metagenomic next-generation sequencing; RCT, randomized controlled trial; RICU, respiratory intensive care unit; SCAP, severe community-acquired pneumonia.

Table 2
Summary of the pooled outcomes of the meta-analyses.

Outcomes	No. of studies	No. of patients	No. of patients in the mNGS group	OR/MD	95% CI	*P*-value	I^2	*P*-value (Q test)	*P*-value (subgroup differences)
Antibiotic change rates									
Antibiotic change rates (total)	6	1098	432	2.47	1.42, 4.28	**<0.01**	80%	<0.01	NA
Adjusted with effect measures	6	1098	432	2.43	1.36, 4.35	**<0.01**	77%	<0.01	NA
Subgroup of age									0.25
Subgroup of adults	5	1015	389	2.25	1.22, 4.14	**<0.01**	82%	<0.01	
Subgroup of infants	1	83	43	4.29	1.71, 10.75	**<0.01**	NA	NA	
Subgroup of sequencing methods									0.59
Subgroup of DNA-seq	4	436	177	2.95	1.89, 4.61	**<0.01**	0%	0.64	
Subgroup of Unknown methods	2	662	255	1.92	0.43, 8.58	0.39	95%	<0.01	
Subgroup of sequencing platforms									**<0.01**
Subgroup of BGISEQ	4	633	220	3.77	2.62, 5.42	**<0.01**	0%	0.89	
Subgroup of unknown platforms	1	306	153	0.90	0.57, 1.41	0.65	NA	NA	
Subgroup of NextSeq	1	159	59	1.85	0.75, 4.59	0.18	NA	NA	
Patients who underwent mNGS exclusively on BALF	4	583	271	2.29	1.07, 4.88	**0.03**	80%	<0.01	NA
Patients with severe LRTIs	4	436	177	2.95	1.89, 4.61	**<0.01**	0%	0.64	NA
In-hospital mortality									
In-hospital mortality (total)	6	1226	518	0.49	0.36, 0.67	**<0.01**	0%	0.92	NA
Adjusted with effect measures	6	1226	518	0.48	0.35, 0.67	**<0.01**	0%	0.93	NA
Subgroup of age									0.66
Subgroup of adults	5	1143	475	0.49	0.36, 0.68	**<0.01**	0%	0.92	
Subgroup of infants	1	83	43	0.29	0.03, 2.95	0.30	NA	NA	
Subgroup of sequencing methods									0.67
Subgroup of DNA-seq	2	242	102	0.42	0.19, 0.96	**0.04**	0%	0.74	
Subgroup of Unknown methods	3	826	337	0.54	0.37, 0.79	**<0.01**	0%	0.77	
Subgroup of DNA-seq and RNA-seq	1	158	79	0.38	0.18, 0.81	**0.01**	NA	NA	
Subgroup of sequencing platforms									0.57
Subgroup of BGISEQ	3	597	224	0.43	0.27, 0.66	**<0.01**	0%	0.87	
Subgroup of unknown platforms	2	470	235	0.61	0.37, 1.01	0.06	0%	0.89	
Subgroup of NextSeq	1	159	59	0.45	0.19, 1.06	0.07	NA	NA	
Patients who underwent mNGS exclusively on BALF	3	547	275	0.49	0.30, 0.80	**<0.01**	0%	0.56	NA
Patients with severe LRTIs	4	564	263	0.45	0.29, 0.71	**<0.01**	0%	0.86	NA
Length of hospital stay									
Length of hospital stay (total)	7	1069	509	−1.79	−5.20, 1.63	0.31	83%	<0.01	NA
Subgroup of age									0.54
Subgroup of adults	5	886	402	−0.82	−6.37, 4.73	0.77	87%	<0.01	
Subgroup of infants	2	183	107	−2.60	−4.15, −1.05	**0.01**	46%	0.17	
Subgroup of sequencing methods									0.10
Subgroup of DNA-seq	3	263	147	−4.46	−8.31, −0.62	**0.02**	91%	<0.01	
Subgroup of Unknown methods	3	648	283	2.79	−2.69, 8.27	0.32	54%	0.11	
Subgroup of DNA-seq and RNA-seq	1	158	79	−2.61	−8.15, 2.93	0.36	NA	NA	
Subgroup of sequencing platforms									0.07
Subgroup of BGISEQ	2	241	122	−1.86	−3.43, −0.30	**0.02**	0%	0.78	
Subgroup of unknown platforms	2	648	283	2.79	−2.69, 8.27	0.32	54%	0.11	
Subgroup of NextSeq	3	180	104	−5.83	−10.78, −0.89	**0.02**	92%	<0.01	
Patients who underwent mNGS exclusively on BALF	3	547	275	−1.70	−3.26, −0.14	**0.03**	24%	0.27	NA
Patients with severe LRTIs	4	583	252	−0.72	−3.20, 1.77	0.57	48%	0.12	NA
Other outcomes									
Antibiotic escalation rates	2	389	196	1.45	0.28, 6.44	0.71	87%	<0.01	NA
Antibiotic de-escalation rates	3	445	206	1.33	0.86, 2.07	0.20	0%	0.45	NA
Duration of mechanical ventilation	5	619	248	2.09	−0.53, 4.07	0.12	85%	0.01	NA
Duration of ICU stay	6	677	333	1.41	−2.34, 5.17	0.46	86%	<0.01	NA
30-d mortality rates	5	1074	398	0.57	0.33, 0.98	**0.04**	56%	0.06	NA
90-d mortality rates	2	277	81	0.55	0.14, 2.23	0.41	82%	0.02	NA

BALF, bronchoalveolar lavage fluid; CI, confidence interval; ICU, intensive care unit; LRTIs, lower respiratory tract infections; MD, mean difference; mNGS, metagenomic next-generation sequencing; NA, not applicable; OR, odds ratio.
The bolded P values indicate statistical significant at $P < 0.05$.

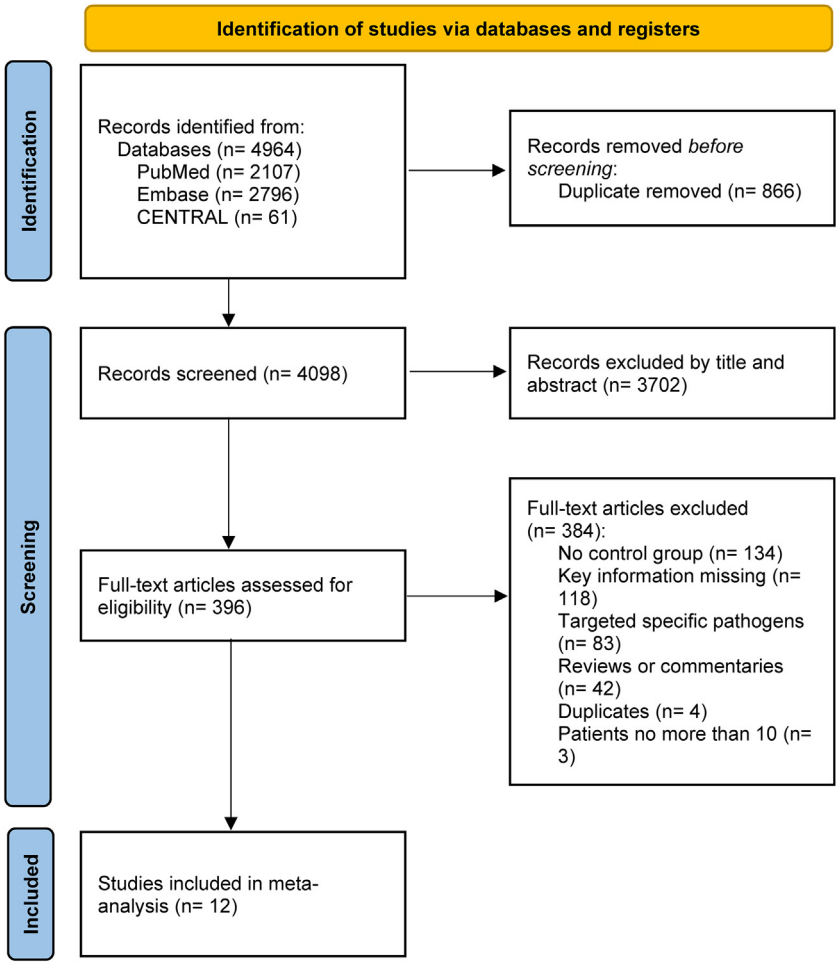

Fig. 1. Study flowchart. CENTRAL, Cochrane Central Register of Controlled Trials.

(Fig. 2A and Table 2). Subgroup analyses indicated consistently elevated rates of antibiotic changes in the mNGS group compared to the control group across adults, infants, and patients who underwent DNA sequencing alone, although age and sequencing methods were not sources of heterogeneity (Supplementary Figs. 1A and 2A, Table S3 and Table 2). Subgroup analyses based on sequencing platforms showed that heterogeneity was significantly reduced ($P < 0.01$) (Supplementary Fig. 3A, Table S3 and Table 2). Similar findings were observed in studies that specifically performed mNGS on BALF and in those targeting patients with severe LRTIs (Supplementary Fig. 4, Table 2 and Table S3). Sensitivity analyses excluding each study individually did not alter the conclusion (Supplementary Fig. 5A). There was no evidence of publication bias (Egger test, $P = 0.34$) (Supplementary Fig. 6A and 6D). Only one study provided adjusted measures for antibiotic change, and meta-analysis after adjustment yielded results consistent with those of the crude analysis (Supplementary Fig. 7A and Table 2).

3.3. mNGS and in-hospital mortality

The outcomes of in-hospital mortality were available in 6 studies, comprising 4 cohort studies and 2 RCTs. Meta-analysis showed that mNGS was associated with a decreased risk of in-hospital mortality (OR, 0.49; 95% CI, 0.36–0.67; $P < 0.01$; $I^2 = 0$) (Fig. 2B and Table 2). Meta-regression was not performed due to the low heterogeneity in pooled analysis. Consistent results were observed among adult patients (Supplementary Fig. 1B and Table 2), subgroups based on different sequencing methods (Supplementary Fig. 2B and Table 2), patients who underwent mNGS on the BGISEQ platform (Supplementary Fig. 3B and Table 2), patients with severe LRTIs (Supplementary Fig. 8A and Table 2), those who underwent mNGS exclusively on BALF (Supplementary Fig. 8B and Table 2), and in sensitivity analyses (Supplementary Fig. 5B). One study provided adjusted measure of OR, and the pooled aOR with crude OR yielded similar results (OR, 0.48; 95% CI, 0.35–0.67; $P < 0.01$; $I^2 = 0$) (Supplementary Fig. 7B and Table 2). On the contrary, the in-hospital mortality was not altered by mNGS application in infants, though data were limited with only one study in this subgroup (Supplementary Fig. 1B and Table 2). No publication bias was detected, as evidenced by the funnel plot and Egger's test (Egger test, $P = 0.31$) (Supplementary Fig. 6B and 6E).

3.4. mNGS and length of hospital stay

The length of hospital stay was compared between the mNGS group and control group in 7 studies, and meta-analysis showed that the length of hospital stay was not altered by mNGS application (MD, −1.79; 95% CI, −5.20 to 1.63; $P = 0.31$; $I^2 = 83\%$) (Fig. 2C and Table 2). The effect of mNGS on length of hospital stay remained insignificant in adult patients (Supplementary Fig. 1C and Table 2), those who underwent mNGS with unspecified sequencing methods or platforms (Supplementary Figs. 2C and 3C and Table 2), and in populations with severe LRTIs (Supplementary Fig. 9A and Table 2). However, the results differed in the subgroups of infants (Supplementary Fig. 1C and Table 2), patients who underwent DNA-seq only (Supplementary Fig. 2C and Table 2), pa-

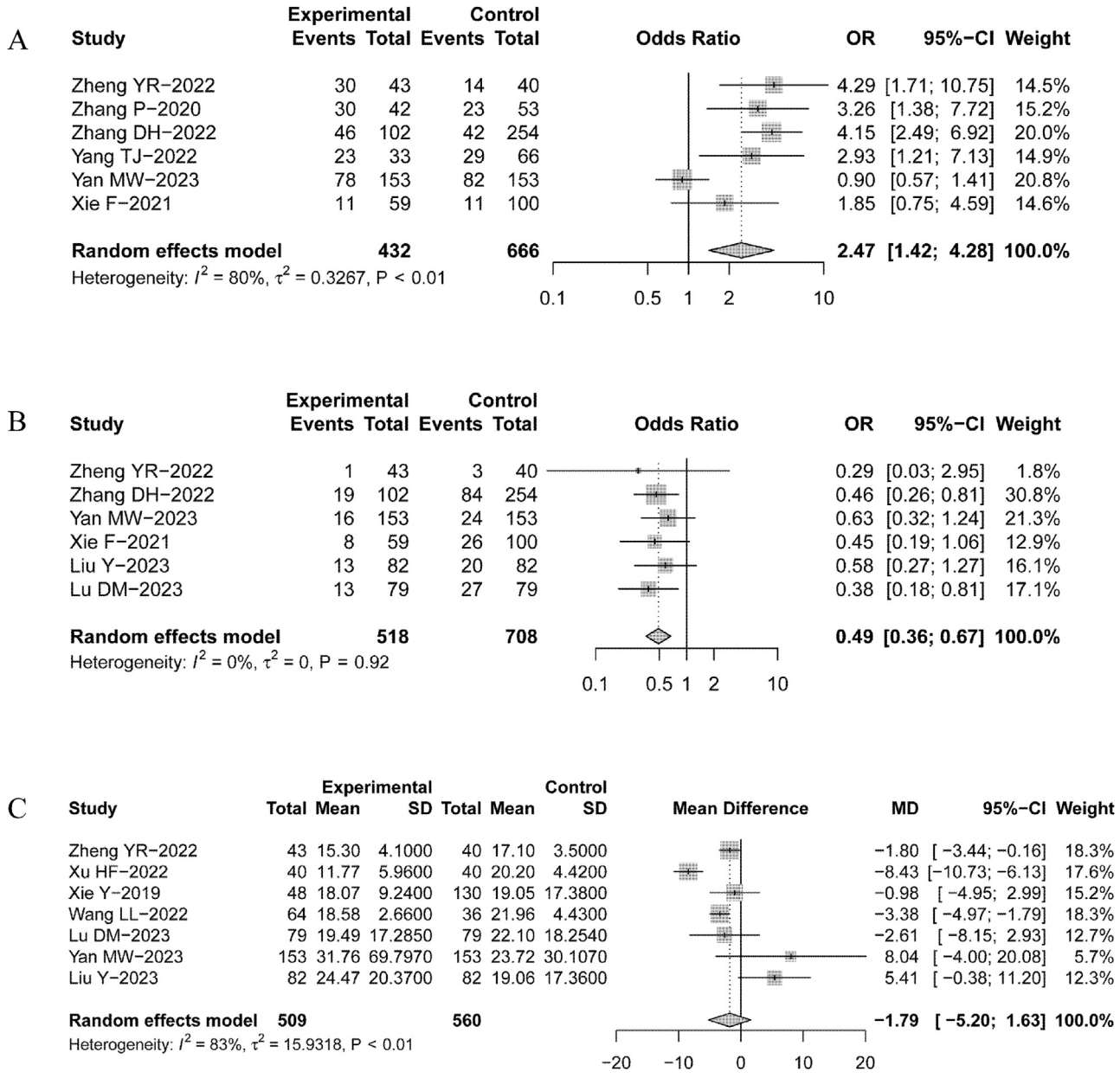

Fig. 2. Forest plot of the impact of mNGS on antibiotic change rates (A); in-hospital mortality (B); and length of hospital stay (C) in patients with LRTIs. CI, confidence interval; MD, mean difference; OR, odds ratio.

tients who underwent mNGS on the BGISEQ or NextSeq platforms (Supplementary Fig. 3C and Table 2), and patients with mNGS performed only on BALF (Supplementary Fig. 9B and Table 2), showing that mNGS was associated with shorter hospital stays. Meta-regression analysis showed that mNGS sequencing platform was a significant source of heterogeneity (P = 0.04) (Supplementary Table S3). Sensitivity analyses did not eliminate the heterogeneity of studies (Supplementary Fig. 5C). Funnel plot and Egger regression test suggested a low likelihood of publication bias (Egger test, P = 0.38) (Supplementary Fig. 6C and 6F).

3.5. mNGS and secondary outcomes

The application of mNGS did not affect the proportion of patients with antibiotic escalation or antibiotic de-escalation, based on 2 studies and 3 studies, respectively (OR for antibiotic escalation, 1.35; 95% CI, 0.28–6.44; P = 0.71; OR for antibiotic de-escalation, 1.33; 95% CI, 0.86–2.07; P = 0.20) (Supplementary Fig. 10A and 10B and Table 2). Analysis of 5 observational studies indicated that mNGS usage did not influence the duration of mechanical ventilation (d) (MD, 2.09; 95% CI, −0.53 to 4.70; P = 0.12) (Supplementary Fig. 10C and Table 2). Similarly, the duration of ICU stay was not affected by the use of mNGS across 6 studies (MD, 1.41; 95% CI, −2.34 to 5.17; P = 0.46) (Supplementary Fig. 10D and Table 2). Regarding the impact of mNGS on mortality, pooled data from 5 trials suggested a potential reduction in 30-d mortality (OR, 0.57; 95% CI, 0.33–0.98; P = 0.04) (Supplementary Fig. 10E and Table 2). In contrast, the pooled data from 2 cohort studies did not indicate any significant impact of mNGS on 90-d mortality (OR, 0.55; 95% CI, 0.14–2.23; P = 0.41) (Supplementary Fig. 10F and Table 2).

4. Discussion

The effectiveness of mNGS in LRTIs has been a persistent concern for clinicians, limiting the broader adoption of mNGS. This

systematic review and meta-analysis, to the best of our knowledge, represents the first comprehensive attempt to address this issue scientifically. We have synthesized the available evidence regarding the impact of mNGS on antibiotic use and prognosis. Our findings suggest that mNGS increases the likelihood of adjusting antibiotics in patients with LRTIs. These results were consistent across adult patients, those with severe LRTIs, and populations where mNGS was conducted on BALF samples. We observed that mNGS might potentially reduce the in-hospital mortality among patients with LRTIs. However, mNGS did not demonstrate a significant effect on reducing the length of hospital stays for LRTIs. Based on existing clinical studies, we believe that mNGS may have the potential to influence treatment strategies for patients with LRTIs.

Most evidence suggests that mNGS has advantages over conventional microbiologic test in the detection of pathogens in LRTIs. A review summarizing the diagnostic efficacy of mNGS found that compared to conventional methods, mNGS achieves higher detection rates for bacteria, viruses, and fungi in patients with pulmonary infections [26]. A systematic review and meta-analysis evaluating the pathogen diagnostic performance of mNGS on BALF in patients with pulmonary infections indicated that mNGS achieves a sensitivity of 78% and a specificity of 77% for pathogens detection [27]. In another meta-analysis including nine studies, researchers explored the pathogen diagnostic performance of mNGS for *Pneumocystis jirovecii* pneumonia, finding that mNGS has a sensitivity of 97.4% and a specificity of 94.3% [28]. However, the respiratory tract, being a non-sterile site, naturally harbours a complex microbiota [29,30]. The non-targeted characteristic of mNGS inevitably results in detection influenced by commensal microbiota, opportunistic pathogens, and sample contamination, posing challenges in interpreting mNGS results [31,32]. To date, robust evidence-based medical research on the potential impact of mNGS on antimicrobial stewardship remains scarce. Within the scope of this review, we substantiate that, grounded in existing clinical evidence, mNGS has influenced the treatment strategies of antibiotic of LRITs.

Early targeted antibiotic therapy, compared to empirical treatment, could improve the prognosis of patients with LRTIs [33]. The high sensitivity and broad-spectrum detection capabilities of mNGS enable clinicians to identify pathogens that are difficult to detect with conventional methods, allowing for earlier and more targeted antibiotic therapy. This may explain the observed reduction in mortality among patients in the mNGS group. Additionally, targeted antibiotic treatment strategies avoid the unnecessary use of broad-spectrum antibiotics, reducing the development of drug-resistance bacteria and thereby improving treatment outcomes. Meanwhile, compared to culture methods, mNGS has faster turnaround time. Conventional microbiologic tests typically take more than 3 d to produce results, whereas mNGS has a rapid turnaround time of only 1–2 d [25,34]. For patients with LRTIs, especially those severe patients, rapid diagnosis and treatment are crucial for reducing mortality. Among the six studies in the mortality analysis, four targeted patients with severe LRTIs, and one targeted on immunocompromised patients, who were identified in the mNGS application consensus as likely to benefit from its use [8]. This appropriate patient selection might also account for the improved prognosis. Similarly, in the analyses targeting severe and immunocompromised patients, a decrease in mortality was observed. However, it is important to note that four of the studies included in the mortality analysis were observational, with only two being randomized studies that had small sample sizes and unclear study designs. Therefore, it is challenging to draw definitive conclusions about the impact of mNGS on improving prognosis based solely on the existing observational data. Future high-quality clinical trials are needed to validate the efficacy of mNGS in LRTI patients. mNGS is associated with high costs, requires specialized technical expertise, and its results are often challenging to interpret, which typically relegates it to a supplementary role in pathogen diagnosis for LRTIs [35]. Consequently, patients undergoing mNGS testing often present with more complex and severe conditions. Although some studies conducted baseline matching to enhance the reliability of their conclusions, the characteristic of observational studies limits the direct comparability between mNGS and control groups, which may explain why no benefit was observed in clinical outcomes including hospital length of stay, length of ICU stays, and duration of mechanical ventilation in this study.

In 2022, NCBI announced that it would be updating how it classifies and names 42 phyla of bacteria and archaea [36]. The changes in microbial nomenclature can lead to discrepancies in microbial taxonomy, thereby influencing the mNGS results. Since most of the included studies are retrospective, all patients were enrolled by 2022. Additionally, delayed updates to the reference microbial databases used by researchers and sequencing companies are common, so the impact of changes in taxonomy and nomenclature of bacteria and archaea on the mNGS results in this study is minimal.

The potential role of sequencing platforms as a source of heterogeneity in the pooled antibiotic change rates and length of hospital stay draw our attention. Among the included studies, the sequencing platform was unknown in some retrospective studies, possibly because clinicians were free to choose different companies for mNGS sequencing in these studies, leading to the use of multiple sequencing platforms within the same study. In China, due to the lack of in-hospital mNGS testing laboratories, clinical mNGS is currently conducted by sequencing companies. Therefore, the use of diverse sequencing platforms is common in clinical practice. Further research is needed to explore the impact of sequencing platforms on the diagnostic accuracy of mNGS, in order to optimize its application in patients with LRTIs.

This review has several limitations. First, there is clinical heterogeneity among the included studies, with variations in age, sample types, disease severity, sequencing methods, and sequencing platforms potentially influencing study outcomes. We conducted subgroup analyses, meta regression analyses and sensitivity analyses to address this limitation. Additionally, most of the studies included in this review are observational, and there is a lack of RCTs to validate these findings.

5. Conclusion

Overall, our meta-analysis indicates that the use of mNGS in patients with LRTIs may lead to changes in antibiotic treatment strategies. We propose that mNGS could serve as a viable pathogen diagnostic tool for LRTIs, particularly in cases of severe LRTIs, where the benefits outweigh the testing costs. However, there remains a need for high-quality prospective studies to rigorously evaluate the clinical efficacy of mNGS, especially focusing on its benefits for severe and immunocompromised patients.

Sequence information

Not applicable.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2024.107440.

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