Int J Clin Exp Med 2017;10(2):4057-4076
www.ijcem.com /ISSN:1940-5901/IJCEM0035141

Review Article

Identification accuracy of matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) for clinical pathogenic bacteria and fungi diagnosis: a meta-analysis

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Received July 6, 2016; Accepted November 15, 2016; Epub February 15, 2017; Published February 28, 2017

Abstract: Recently, matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) has been enthusiastically adopted in clinical microbial identification by virtue of its rapid process, easy operation, relatively low cost and high throughput. However, its identification accuracy for common clinical pathogens is still inconclusive. Therefore, we conducted this meta-analysis to systematically assess the performance of MALDI-TOF MS in identifying clinical pathogenic bacteria and fungi by meta-analysis. After a comprehensive literature search through PubMed and Web of Science databases (up to January 2016), 50 articles involving 35406 bacteria isolates and 30 articles involving 14250 fungi isolates were included. Overall analysis demonstrated that the accuracy of MALDI-TOF MS for bacteria identification increased from 0.849 (95% confidence interval (CI) = 0.812-0.879) at the species level to 0.909 (95% CI = 0.883-0.933) at the genus level; the accuracy of MALDI-TOF MS for fungi identification increased from 0.922 (95% CI = 0.900-0.941) at the species level to 0.942 (95% CI = 0.926-0.956) at the genus level. Then we performed univariate and multivariate meta-regression analyses to explore potential factors of heterogeneity. Subgroup analyses were also carried out to further evaluate the identification accuracy of MALDI-TOF MS in various clinical situations, which including different strain categories, pre-treatments, specimen types and detection systems. In summary, our meta-analysis not only strongly suggests that MALDI-TOF MS truly is a good diagnostic tool for clinical microbiology, but also provides several hints to improve its performance in the coming future.

Keywords: MALDI-TOF MS, identification accuracy, bacteria identification, fungi identification

Introduction

Fast identification of clinically relevant microorganisms is crucial to guide timely therapeutic decisions. However, traditional phenotypic and biochemical methods, such as Vitek-II, API and biochemical tests, often take one or more days [1]. Moreover, they have limitations to recognize certain pathogens. Recent molecular methods, including polymerase chain reaction (PCR) and sequencing analysis, partly reduce the duration and have good performance on sensitivity and specificity, but the complicate operations, strict environmental requirements and demand of specialized staff limit their widespread application in clinical diagnosis. Thus, it is imperative to find a simple and effective method to rapidly identify pathogenic microorganisms for better clinical care [2-4].

Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) is frequently used for pathogen identification in current years, which can rapidly detect pathogens and distinguish bacteria/fungi with similar [5]. Many microorganisms including most bacteria and fungi can be effectively identified by this method in a few minutes per sample. Its rapid, accurate and cost-effective advantages have made MALDI-TOF MS more and more popular in modern microbiological laboratories [3, 6, 7]. While MALDI-TOF MS is widely used for microorganism identification using colonies after culture, its performance on

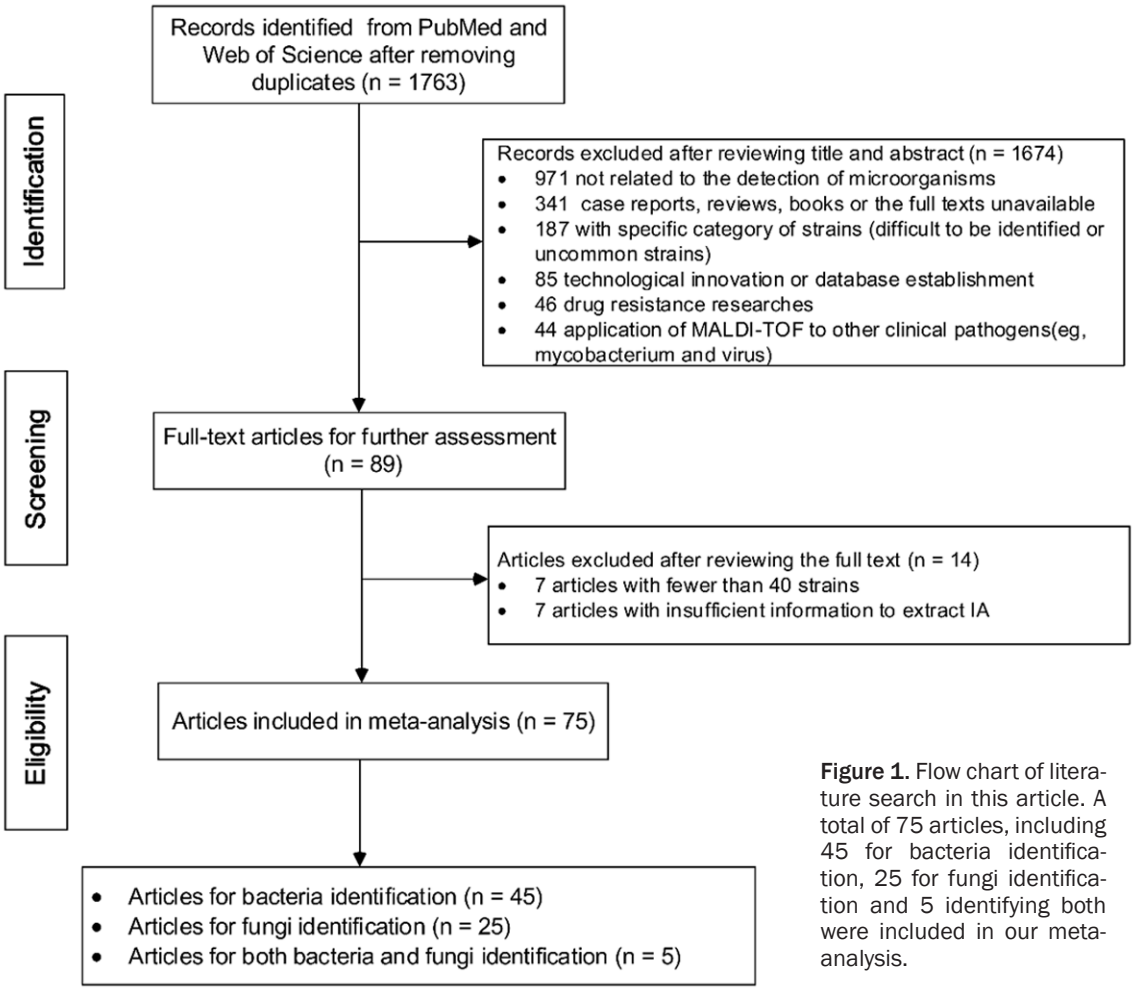

Figure 1. Flow chart of literature search in this article. A total of 75 articles, including 45 for bacteria identification, 25 for fungi identification and 5 identifying both were included in our meta-analysis.

direct detection of clinical specimens (eg, positive blood cultures, urine and cerebrospinal fluid samples) has drawn a lot of attention and showed inconclusive results [8]. In addition, factors likely to influence the accurate detection of MALDI-TOF MS, such as different strain categories, pre-treatments, specimen types and detection systems, are also the issue of its further extension in the clinic.

Currently, MALDI-TOF MS is considered as "a revolution in clinical microbiology" [9], and many studies have evaluated its accuracy of microorganism identification [10, 11]. However, there was wide variation of identification accuracy in previous researches, systematic meta-analysis of evaluating its performance on clinically relevant microorganisms has been relatively rare. Existing inconsistent results and increasing demands of fast microorganism identification urge people to wonder about whether MALDI-TOF MS could be well applied in general clinical laboratories. Although detection of mycobacterium and virus is capable [3], main clinical applications of MALDI-TOF MS are still for detecting bacteria and fungi so far. Therefore, we carried out this meta-analysis to comprehensively assess the accuracy of MALDI-TOF MS for the identification of common bacteria and fungi and further evaluated its performance in subgroups including different strain categories, pre-treatments, specimen types and detection systems.

Materials and methods

Search strategy

We searched PubMed and Web of Science (up to January 2016) with the following keywords: "MALDI-TOF MS", "matrix-assisted laser desorption/ionization time-of-flight mass spectrometry", identification and detection. Except for the

Table 1. Main characteristics of 50 studies including 66 trials eligible for bacteria identification

Study	Geographical distribution of strains	Strain categories	Specimen types	Detection systems	S.(Software) or/and D.(database) V(version)	Threshold	Pre-treatments	Reference method(s)
Eigner 2009	Europe	Bacteria	Mixed	Bruker Biotyper	S.V2.0	S	C	MO, MB, BI
Seng 2009	Europe	Bacteria	Mixed	Bruker Biotyper	S.V2.0	S	C	MO, MB, BI
Bizzini 2010	Europe	Bacteria	Mixed	Bruker Biotyper	S.V3.0	S	C.Extra	MO, MB, BI
Cherkaoui 2010	Europe	Bacteria	Mixed	Bruker Biotyper	NR	S	C	MB, BI
	Europe	Bacteria	Mixed	Saramis	NR	S	C	MB, BI
Christner 2010	Europe	Bacteria	B	Bruker Biotyper	S.V2.0	S	D	MO, MB, BI
Ferreira 2010	Europe	Bacteria	U	Bruker Biotyper	S.V2.0	S	D	MO, BI
Moussaoui 2010	Europe	Bacteria	B	Bruker Biotyper	S.V2.0 and D.V2.0.4.0	S	D	MO, BI
Stevenson 2010	America	Bacteria	B	Bruker Biotyper	S.V2.0 and D.V2.0.4	S	D	MB, BI
van Veen 2010*	Europe	Bacteria	Mixed	Bruker Biotyper	S.V2.0	S	C.Extra	MB, BI
	Europe	Bacteria	Mixed	Bruker Biotyper	S.V2.0	S	C.Extra	MB, BI
Alatoom 2011	America	GPB	Mixed	Bruker Biotyper	S.V2.0 and D.V2.0	S	C.Extra	MO, MB, BI
	America	GPB	Mixed	Bruker Biotyper	S.V2.0 and D.V2.0	S	C	MO, MB, BI
Benagli 2011	Europe	Bacteria	Mixed	Saramis	NR	NR	C	MO, MB, BI
Bessede 2011	Europe	Bacteria	Mixed	Bruker Biotyper	S.V2.0	S	C	MO, MB, BI
	Europe	Bacteria	Mixed	Bruker Biotyper	S.V2.0	S	C.Extra	MO, MB, BI
Buchan 2011	America	Bacteria	B	Bruker Biotyper	S.V3.0	S	D.Sep	MO, BI
Ferreira 2011	Europe	Bacteria	B	Bruker Biotyper	S.V2.0	S	D	MO, BI
	Europe	Bacteria	U	Bruker Biotyper	S.V2.0	S	D	MO, BI
Juiz 2011	Europe	Bacteria	B	Bruker Biotyper	S.V3.0	S	D.Sep	MO, MB, BI
Kok 2011	Australia	Bacteria	B	Bruker Biotyper	S.V2.0	S	D.Sep	MO, BI
Neville 2011	Australia	Bacteria	Mixed	Bruker Biotyper	S.V3.1.1.0	S	C.Extra	MB, BI
Schubert 2011	Europe	Bacteria	B	Bruker Biotyper	S.V3.0 and D.V3.1.1.0	S	D	MO, MB, BI
Bille 2012	Europe	Bacteria	Mixed	Andromas	S.V2010	S	C	MO, MB, BI
Dubois 2012	Europe	Bacteria	Mixed	Vitek MS	S.V1.0.0	S	C	MB, BI
Fernandez-Olmos 2012	Europe	NFGNB	R	Bruker Biotyper	S.V2.0	S	C	MO, MB, BI
Klein 2012	Europe	Bacteria	B	Bruker Biotyper	S.V2.0 and D.V5	S	D.Sep	MO, MB, BI
	Europe	Bacteria	B	Bruker Biotyper	S.V2.0 and D.V5	S	D	MO, MB, BI
Lagace-Wiens 2012	America	Bacteria	B	Bruker Biotyper	S.V3.0	S	D.Sep	MO, MB, BI
Loonen 2012	Europe	Bacteria	B	Bruker Biotyper	S.V2.0	S	D.Sep	MO, BI, MALDI-TOF MS(colony)
	Europe	Bacteria	B	Bruker Biotyper	S.V2.0	S	D	MO, BI, MALDI-TOF MS(colony)
Marko 2012	America	NFGNB	R	Bruker Biotyper	S.V3.0	S	C.Extra	MO, MB, BI
	America	NFGNB	R	Vitek MS	SARAMIS D.V3.62	S	C.Extra	MO, MB, BI
Martiny 2012	Europe	Bacteria	B	Bruker Biotyper	S.V2.0 and D.V3.1.1.0	S	D.Sep	MO, BI, MALDI-TOF MS
Martiny 2012	Europe	Bacteria	Mixed	Bruker Biotyper	S.V2.0 and D.V3.1.1.0	S	C	MO, MB, BI
	Europe	Bacteria	Mixed	Vitek MS	Vitek MS IVD D.V5.1	S	C	MO, MB, BI
Meex 2012	Europe	Bacteria	anaerobic B	Bruker Biotyper	S.V2.0 and D.V3.1.2.0.	S	D.Sep	MO, MALDI-TOF MS(colony)
Chen 2013	Asian	Bacteria	B	Bruker Biotyper	S.V3.0	S	D.Sep	MO, MB, BI
	Asian	Bacteria	B	Vitek MS	NR	S	D.Sep	MO, MB, BI

Jamal 2013	Asian	Bacteria	B	Bruker Biotyper	S.V3.0	S	D.Sep	MO, MB, BI
Moon 2013	Asian	GPB	Mixed	Vitek MS	Vitek MS D.V2	S	C	MO, MB, BI
Nonnemann 2013	Europe	Bacteria	B	Bruker Biotyper	S.V2.0	S	D.Sep	MO, BI
Schulthess 2013*	Europe	GPB	Mixed	Bruker Biotyper	S.V3.0 and D.V3.1.2.0	S	C	MO, MB, BI
	Europe	GPB	Mixed	Bruker Biotyper	S.V3.0 and D.V3.1.2.0	S	C.Extra	MO, MB, BI
	Europe	GPB	Mixed	Bruker Biotyper	S.V3.0 and D.V3.1.2.0	S	C.Extra	MO, MB, BI
Wang 2013	Asian	Bacteria	U	Bruker Biotyper	NR	S	D	MO, MB, BI
Rychert 2013	America	GPB	Mixed	Vitek MS	D.V2.0	S	C	MB
Homem 2014	America	NFGNB	R	Vitek MS	SARAMIS D.V3.62	S	C	MB, BI
Jamal 2014	Asian	Bacteria	Mixed	Bruker Biotyper	S.V3.0	S	C	MB, BI
	Asian	Bacteria	Mixed	Vitek MS	Vitek D.	S	C	MB, BI
Konnerth 2014	Europe	Bacteria	B	Saramis	SARAMIS D.V4.09	S	D	MO, BI
Martinez 2014	America	Bacteria	B	Bruker Biotyper	S.V3.0	S	D.Sep	MO, MB, BI
Panda 2014	Asian	Bacteria	Mixed	Bruker Biotyper	S.V1.1	S	C.Extra	MO, BI
Schieffer 2014	America	Bacteria	B	Bruker Biotyper	S.V3.0 and D.V3.1.2	S	D.Sep	MO, MB, BI
Wang 2014	Asian	Bacteria	Mixed	Vitek MS	S.V2.0	S	C	MO, MB, BI
AbdulWahab 2015	Asian	Bacteria	R	Bruker Biotyper	S.V3.0	S	C	MO, MB, BI
Deak 2015	America	Bacteria	Mixed	Bruker Biotyper	S.V3.0	S	C.Extra	MO, MB, BI
	America	Bacteria	Mixed	Vitek MS	S.V2.0	S	C.Extra	MO, MB, BI
Desai 2015	America	Bacteria	R	Bruker Biotyper	D.V3.0.2	S	C	MO, MB, BI
Egli 2015	Europe	Bacteria	B	Bruker Biotyper	S.V3.1	S	D.Sep	MB, BI
Handal 2015	Europe	Bacteria	B	Bruker Biotyper	D.V4.0.0.1	S	C	MB
	Europe	Bacteria	B	Bruker Biotyper	D.V4.0.0.1	S	C.Extra	MB
Kim 2015	Asian	Bacteria	U	Vitek MS	Vitek D.V2.0	S	D	MO, BI
Levesque 2015	America	Bacteria	Mixed	Bruker Biotyper	S.V3.1	S	C.Extra	MO, MB, BI
	America	Bacteria	Mixed	Vitek MS	D.V2.0	S	C.Extra	MO, MB, BI
Luo 2015	Asian	Bacteria	Mixed	Vitek MS	NR	S	C	MO, MB, BI

Note: GPB, gram-positive bacteria; NFGNB, Nonfermenting Gram-Negative Bacilli; B, blood specimens; Mixed, various clinical isolates; R, respiratory specimens; U, urine specimens; S, standard threshold recommended by manufacturer; NR, no report; C, culture without protein extraction; C.Extra, culture with protein extraction; D, direct detection; D.Sep, direct detection with "Sepsityper" kit; MO, morphology; MB, molecular biology; BI, biochemistry. *conducting both retrospective and prospective researches in one article.

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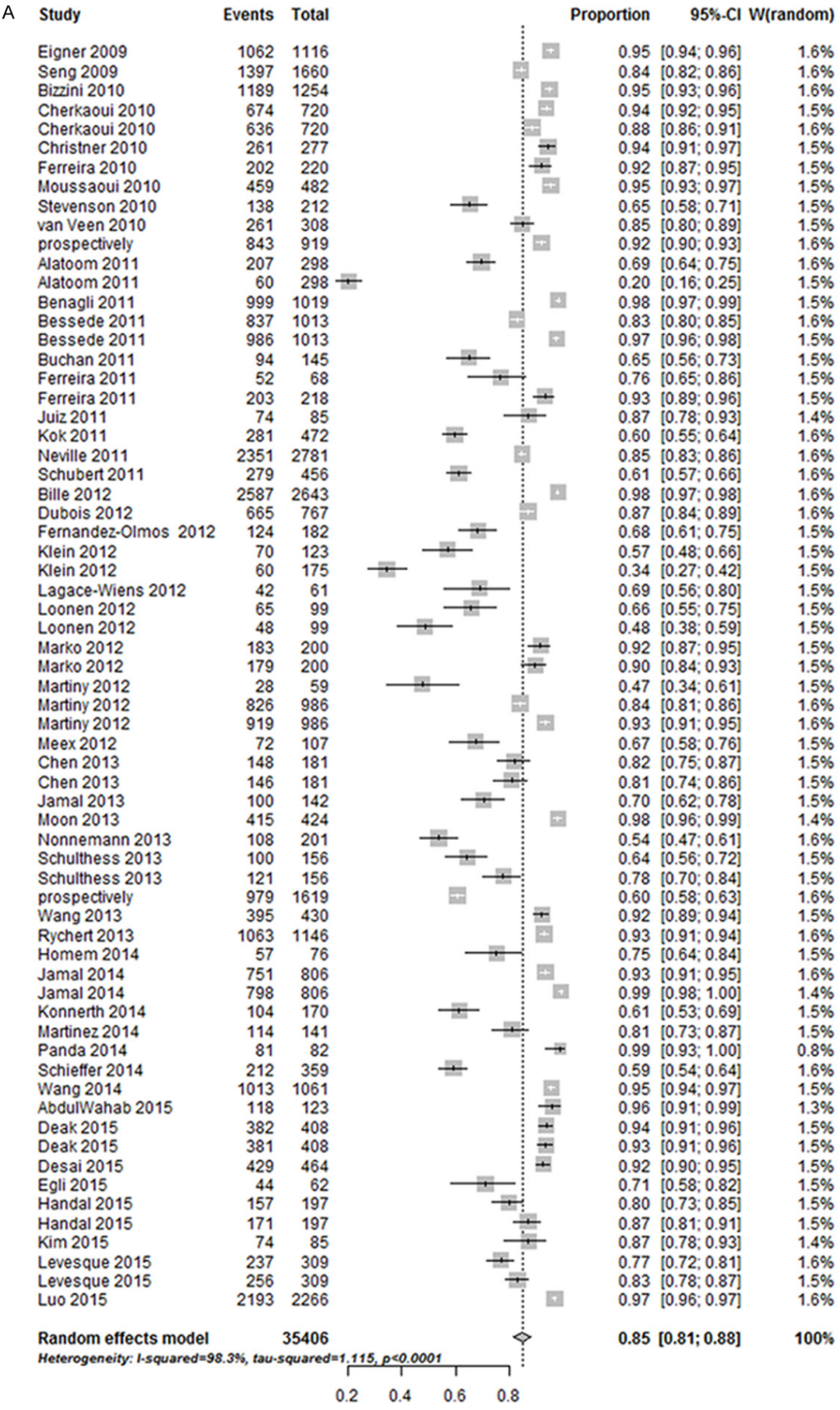
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Eigner 2009 1062 1116 0.95 [0.94; 0.96] 1.6%
Seng 2009 1397 1660 0.84 [0.82; 0.86] 1.6%
Bizzini 2010 1189 1254 0.95 [0.93; 0.96] 1.6%
Cherkaoui 2010 674 720 0.94 [0.92; 0.95] 1.5%
Cherkaoui 2010 636 720 0.88 [0.86; 0.91] 1.6%
Christner 2010 261 277 0.94 [0.91; 0.97] 1.5%
Ferreira 2010 202 220 0.92 [0.87; 0.95] 1.5%
Moussaoui 2010 459 482 0.95 [0.93; 0.97] 1.5%
Stevenson 2010 138 212 0.65 [0.58; 0.71] 1.5%
van Veen 2010 261 308 0.85 [0.80; 0.89] 1.5%
prospectively 843 919 0.92 [0.90; 0.93] 1.6%
Alatoom 2011 207 298 0.69 [0.64; 0.75] 1.6%
Alatoom 2011 60 298 0.20 [0.16; 0.25] 1.5%
Benagli 2011 999 1019 0.98 [0.97; 0.99] 1.5%
Bessede 2011 837 1013 0.83 [0.80; 0.85] 1.6%
Bessede 2011 986 1013 0.97 [0.96; 0.98] 1.5%
Buchan 2011 94 145 0.65 [0.56; 0.73] 1.5%
Ferreira 2011 52 68 0.76 [0.65; 0.86] 1.5%
Ferreira 2011 203 218 0.93 [0.89; 0.96] 1.5%
Juiz 2011 74 85 0.87 [0.78; 0.93] 1.4%
Kok 2011 281 472 0.60 [0.55; 0.64] 1.6%
Neville 2011 2351 2781 0.85 [0.83; 0.86] 1.6%
Schubert 2011 279 456 0.61 [0.57; 0.66] 1.6%
Bille 2012 2587 2643 0.98 [0.97; 0.98] 1.6%
Dubois 2012 665 767 0.87 [0.84; 0.89] 1.6%
Fernandez-Olmos 2012 124 182 0.68 [0.61; 0.75] 1.5%
Klein 2012 70 123 0.57 [0.48; 0.66] 1.5%
Klein 2012 60 175 0.34 [0.27; 0.42] 1.5%
Lagace-Wiens 2012 42 61 0.69 [0.56; 0.80] 1.5%
Loonen 2012 65 99 0.66 [0.55; 0.75] 1.5%
Loonen 2012 48 99 0.48 [0.38; 0.59] 1.5%
Marko 2012 183 200 0.92 [0.87; 0.95] 1.5%
Marko 2012 179 200 0.90 [0.84; 0.93] 1.5%
Martiny 2012 28 59 0.47 [0.34; 0.61] 1.5%
Martiny 2012 826 986 0.84 [0.81; 0.86] 1.6%
Martiny 2012 919 986 0.93 [0.91; 0.95] 1.6%
Meex 2012 72 107 0.67 [0.58; 0.76] 1.5%
Chen 2013 148 181 0.82 [0.75; 0.87] 1.5%
Chen 2013 146 181 0.81 [0.74; 0.86] 1.5%
Jamal 2013 100 142 0.70 [0.62; 0.78] 1.5%
Moon 2013 415 424 0.98 [0.96; 0.99] 1.4%
Nonnemann 2013 108 201 0.54 [0.47; 0.61] 1.6%
Schulthess 2013 100 156 0.64 [0.56; 0.72] 1.5%
Schulthess 2013 121 156 0.78 [0.70; 0.84] 1.5%
prospectively 979 1619 0.60 [0.58; 0.63] 1.6%
Wang 2013 395 430 0.92 [0.89; 0.94] 1.5%
Rychert 2013 1063 1146 0.93 [0.91; 0.94] 1.6%
Homem 2014 57 76 0.75 [0.64; 0.84] 1.5%
Jamal 2014 751 806 0.93 [0.91; 0.95] 1.6%
Jamal 2014 798 806 0.99 [0.98; 1.00] 1.4%
Konnerth 2014 104 170 0.61 [0.53; 0.69] 1.5%
Martinez 2014 114 141 0.81 [0.73; 0.87] 1.5%
Panda 2014 81 82 0.99 [0.93; 1.00] 0.8%
Schieffer 2014 212 359 0.59 [0.54; 0.64] 1.6%
Wang 2014 1013 1061 0.95 [0.94; 0.97] 1.5%
AbdulWahab 2015 118 123 0.96 [0.91; 0.99] 1.3%
Deak 2015 382 408 0.94 [0.91; 0.96] 1.5%
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Desai 2015 429 464 0.92 [0.90; 0.95] 1.5%
Egli 2015 44 62 0.71 [0.58; 0.82] 1.5%
Handal 2015 157 197 0.80 [0.73; 0.85] 1.5%
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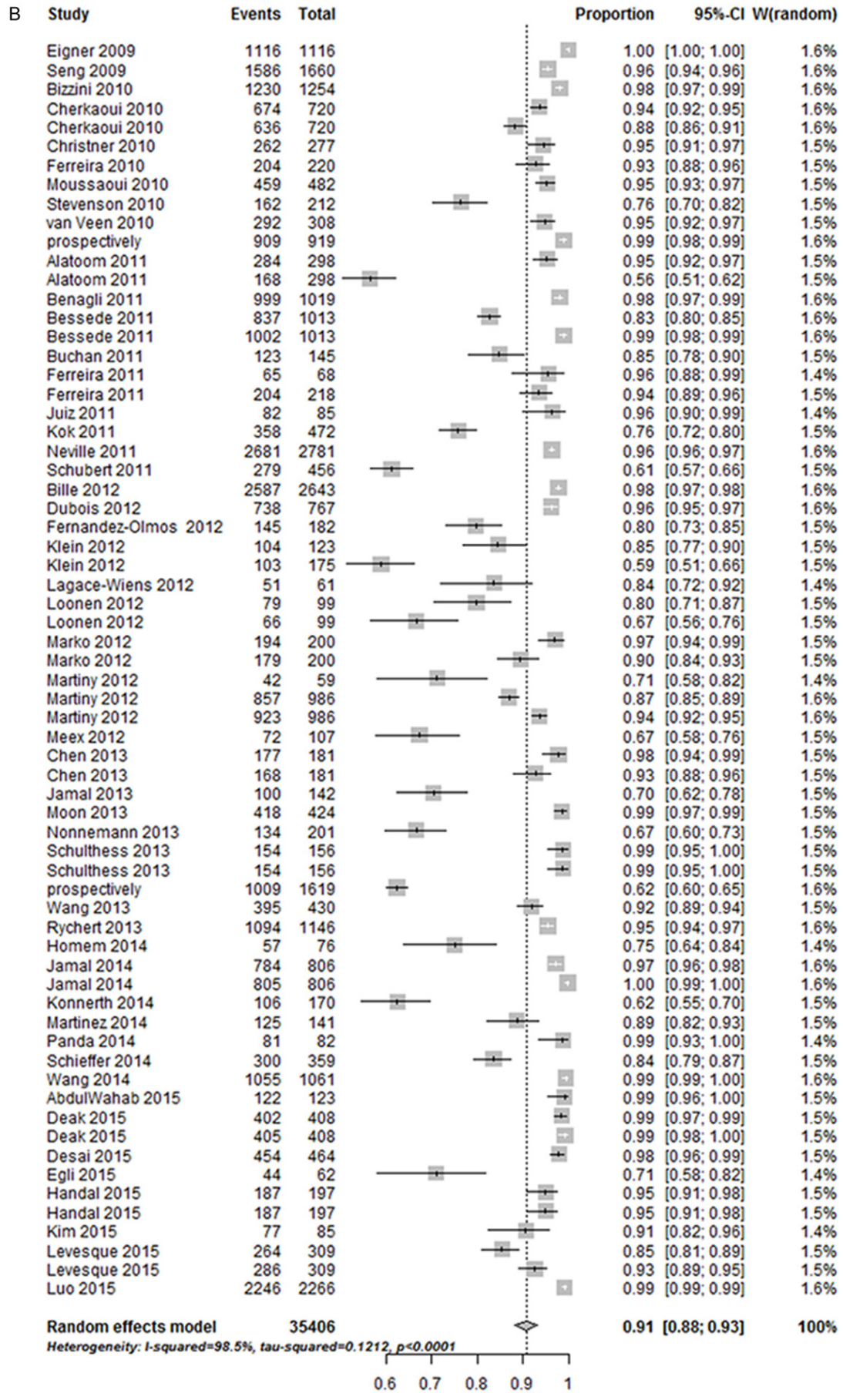
Kim 2015 74 85 0.87 [0.78; 0.93] 1.4%
Levesque 2015 237 309 0.77 [0.72; 0.81] 1.6%
Levesque 2015 256 309 0.83 [0.78; 0.87] 1.5%
Luo 2015 2193 2266 0.97 [0.96; 0.97] 1.6%
Random effects model 35406 0.85 [0.81; 0.88] 100%
Heterogeneity: I-squared=98.3%, tau-squared=1.115, p<0.0001
0.2 0.4 0.6 0.8


B
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Martiny 2012 857 986 0.87 [0.85; 0.89] 1.6%
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Luo 2015 2246 2266 0.99 [0.99; 0.99] 1.6%
Random effects model 35406 0.91 [0.88; 0.93] 100%
Heterogeneity: I-squared=98.5%, tau-squared=0.1212, p<0.0001
0.6
0.7
0.8
0.9
1

Figure 2. Forest plots of the overall IA for bacteria identification by random-effects model. A: Overall IA at the species level. B: Overall IA at the genus level.

Table 2. Results of univariate and multivariate meta-regressions for bacteria identification

Moderator	Estimate	SE	*P*
Univariate meta-regression analysis			
Publication year	0.027	0.078	0.727
Geographic distribution of isolates	0.234	0.272	0.388
Strain categories	-0.522	0.342	0.127
Specimen types	1.311	0.248	< 0.0001
Pre-treatments	-1.114	0.250	< 0.0001
Detection systems	1.069	0.275	< 0.0001
Multivariate meta-regression analysis			
Specimen types	-0.044	0.378	0.908
Pre-treatments	1.005	0.399	0.012
Detection systems	0.675	0.268	0.012

Note: SE, standard error.

filters of Humans and English language, publication status and geographical distribution were not restricted. The reference lists of the retrieved articles and reviews were also checked for potential studies. Our meta-analysis was carried out according to the PRISMA guidelines [12]. Two authors independently searched the literature and extracted data. Disagreements were resolved through mutual discussion or consultation by a third party.

Study selection criteria and data extraction

Studies assessing the accuracy of MALDI-TOF MS for identification of clinical specimens (including bacteria and/or fungi by comparison with conventional methods) were included; Data on frozen clinical isolates confirmed by gold standard methods (molecular methods) previously were included; We also included articles about comparing accuracy of MALDI-TOF MS using different systems. An additional premise of all the enrolled studies was using a commercial database.

Studies were excluded if they met one of the following criteria: (1) studies used MALDI-TOF MS for identification of certain specific clinical strains (eg, difficult to be identified or uncommon strains); (2) studies focused on technological innovation (eg, in-house pre-treatment verification), in-house database establishment or drug resistance; (3) studies detected fewer than 40 specimens; (4) studies were case reports, reviews, books or full text unavailable.

Two independent authors extracted the data from each study as follows: the first author's name, publication year, geographical distribution of strains, specimen types, strain categories, pre-treatments, detection systems and its software and/or database version (when it was possible), threshold, reference methods, total isolates and correctly identified number. If one article contained different specimen types, pre-treatments, detection systems or conducting both retrospective and prospective researches, they were considered as different trials, and data were extracted separately.

Statistics analysis

Identification accuracy (IA) was evaluated for each study, which was a ratio of correctly identified isolates divided by the total number of isolates. Normality test was performed before data synthesis. If the IA did not obey normal distribution, normalized transforms were used for further analysis. The pooled IA was estimated by random-effects model [13]. Cochran's Q test and the I^2 index were used to test for heterogeneity, which was considered statistical significance when $P < 0.100$ or $I^2 > 50.0\%$. Because species identification is more meaningful than genus identification in the clinic, we performed the following analyses at the species level. The univariate and multivariate meta-regression analyses were performed to explore the potential source of heterogeneity. We also conducted subgroup analyses to evaluate the IA of MALDI-TOF in different strain categories, pre-treatments, specimen types and detection systems. To evaluate the robustness of the pooled results, we performed sensitivity analysis. Finally, we used Begg's [14] and Egger's test [15] to assess the publication bias. When the publication bias was observed, we further used the "trim-and-fill" method to evaluate its influence on the pooled IA [16]. All the analyses above were carried out by R software version 3.2.3 (Vienna, Austria), and the level of

Table 3. Heterogeneity and pooled IA in the subgroup analyses for bacteria identification

Sub analyses	No. of total isolates (no. of studies)	*P*	I^2	IA (95% CI)
Strain categories				
GNB	4783 (30)	< 0.0001	88.9%	0.865 (0.827-0.895)
GPB	8257 (32)	< 0.0001	98.8%	0.685 (0.585-0.777)
Pre-treatments				
After culture detection	30096 (39)	< 0.0001	98.5%	0.899 (0.864-0.925)
Direct detection	5310 (27)	< 0.0001	97.1%	0.726 (0.652-0.795)
Specimens types				
Positive blood cultures	4751 (25)	< 0.0001	97.5%	0.689 (0.619-0.759)
Urine samples	953 (4)	0.401	0.0%	0.916 (0.896-0.932)
Respiratory samples	1245 (6)	< 0.0001	93.9%	0.878 (0.774-0.938)
Various clinical isolates	28457 (31)	< 0.0001	98.8%	0.905 (0.868- 0.933)
Detection systems				
Biotyper	22139 (49)	< 0.0001	98.1%	0.809 (0.763-0.848)
Vitek MS (including Saramis)	10624 (16)	< 0.0001	96.8%	0.919 (0.879-0.947)

significance was set a two-sided $P \leq 0.05$ unless otherwise specified.

Results

Literature search

Figure 1 was the flow chart of literature search. A total of 1763 records were obtained by searching PubMed and Web of Science after removing duplicate items. 1674 records were subsequently removed after reviewing title and abstract, because they were case reports, reviews, irrelevant to the detection of clinical bacteria and fungi, focused on technological innovation, database establishment, or other clinical pathogens such as mycobacterium and virus. Then we got 89 full-text articles for further assessment, of which 7 articles were excluded for strains fewer than 40 and 7 articles were excluded with insufficient information to extract IA. Finally, a total of 75 articles, including 45 for bacteria identification [5, 6, 17-59], 25 for fungi identification [60-84] and 5 for identification of both bacteria and fungi [1, 11, 85-87], were eligible in our meta-analysis.

In consideration that there are huge inherent differences between bacteria and fungi, we carried out this meta-analysis about them respectively.

The accuracy of MALDI-TOF MS for bacteria identification

Study characteristics: 50 studies including 66 trials with a total of 35406 isolates were included for bacteria identification (**Table 1**). Among them, 25 trials were from positive blood cultures, 6 were respiratory specimens, 4 were urine samples and 31 were isolated from various clinical specimens. Bruker Biotyper was the most popular detection system (49/66), the second was Vitek MS (including Saramis) (16/66) and then was Andromas (1/66). In addition, when the discrepancy occurred between MALDI-TOF MS and conventional methods (phenotypic testing), most of the included studies applied molecular method as a golden standard to resolve the problem.

Overall results: We used the random-effects model to summarize the overall IA at the species and genus levels, respectively (**Figure 2A** and **2B**). Results showed that the pooled IA was 0.849 (95% CI = 0.812-0.879) at the species level and increased to 0.909 (95% CI = 0.883-0.933) at the genus level. High heterogeneity was found in both levels (Species level: I^2 = 98.3%, P < 0.0001; Genus level: I^2 = 98.5%, P < 0.0001).

Meta-regression and subgroup analyses: Because species identification is more meaningful than genus identification in the clinic, we performed further analyses at the species level. We first performed meta-regression analysis to explore source of heterogeneity. Six potential factors including publication year, geographic distribution of isolates, specimen types, strains categories, pre-treatments and detection systems were analyzed in the univariate meta-regression analysis. Results indicat-

Table 4. Main characteristics of 30 studies including 42 trials eligible for fungi identification

Study	Geographical distribution of strains	Strain categories	Specimen types	Detection systems	S.(Software) or/and D.(database) V(version)	Threshold	Pre-treatments	Reference method(s)
Marklein 2009	Europe	Yeasts	Mixed	Bruker Biotyper	S.V2.0	S	C.Extra	MO, MB, BI
Bader 2010	Europe	Yeasts	Mixed	Bruker Biotyper	S.V2.0 and D.V3.0	S	C.Extra	MO, MB, BI
	Europe	Yeasts	Mixed	Saramis	Superspectra D.V3.3.1	S	C.Extra	MO, MB, BI
Van Veen 2010	Europe	Yeasts	Mixed	Bruker Biotyper	S.V2.0	S	C.Extra	MO, MB,BI
Dhiman 2011	America	Yeasts	Mixed	Bruker Biotyper	S.V3.0 and D.V3.0	S	C.Extra	MO, MB, BI
Pinto 2011	Australia	Yeasts	Mixed	Bruker Biotyper	S.V3.1.2.0	S	C.Extra	MB, BI
Bille 2012	Europe	Fungi	Mixed	Andromas	Andromas S.V2010	S	C.Extra	MO, MB, BI
Iriart 2012	Europe	Fungi	Mixed	Vitek MS	NR	NR	C	MO, MB, BI
Yaman 2012	Asian	Candida	B	Bruker Biotyper	S.V2.0	S	C.Extra	MO, MB, BI
Theel 2012	America	Yeasts	Mixed	Bruker Biotyper	S.V3.0 and D.V3.0	S	C.Extra	MO, MB, BI
Chen 2013	Asian	Yeasts	Mixed	Bruker Biotyper	S.V3.0	S	C.Extra	MO, MB, BI
	Asian	Yeasts	Mixed	Vitek MS	D.V2.0	S	C.Extra	MO, MB, BI
Ferreira 2013	Europe	Fungi	Mixed	Bruker Biotyper	S.V2.0	S	C.Extra	MO, MB, BI
Lohmann 2013	Europe	Yeasts	Mixed	Bruker Biotyper	D.V2.0.4.0	S	C.Extra	MO, MB, BI
	Europe	Yeasts	Mixed	Saramis	D.V4.07	S	C.Extra	MO, MB, BI
Mancini 2013	Europe	Yeasts	Mixed	Bruker Biotyper	D.V3.0	S	C.Extra	MO, MB, BI
	Europe	Yeasts	Mixed	Vitek MS	S.V1.2.0	S	C.Extra	MO, MB, BI
Pulcrano 2013	Europe	Yeasts	B	Bruker Biotyper	S.V2.0 and D.V2.0	S	C.Extra	MB, BI
Sendid 2013	Europe	Yeasts	Mixed	Bruker Biotyper	S.V2.0	S	C.Extra	MO, MB, BI
Westblade 2013	America	Yeasts	Mixed	Vitek MS	D.V2.0	S	C.Extra	MB
Won 2013	Asian	Yeasts	B	Vitek MS	NR	S	C.Extra	MO, MB, BI
Rosenvinge 2013	Europe	Yeasts	Mixed	Saramis	Saramis SuperSpectra D.V4.09	Modified	C.Extra	MO, MB, BI
	Europe	Yeasts	Mixed	Bruker Biotyper	D.V3.1.2.0	Modified	C.Extra	MO, MB, BI
Chao 2014	Europe	Yeasts	Mixed	Bruker Biotyper	S.V3.1 and D.V3.1.66	S	C.Extra	MB
	Europe	Yeasts	Mixed	Vitek MS	D.V2.0 and D.V4.10	S	C.Extra	MB
Duran-Valle 2014	Europe	Yeasts	Mixed	Vitek MS	D.V2.0	Modified	C.Extra	MO, MB, BI
Hamprecht 2014	Europe	Yeasts	Mixed	Bruker Biotyper	S.V3.0 and D.V3.0.10.0.	Modified	C.Extra	MO, MB, BI
	Europe	Yeasts	Mixed	Vitek MS	S.V3.2.0 and D.V2.0	S	C.Extra	MO, MB, BI
Jamal 2014	Asian	Yeasts	Mixed	Bruker Biotyper	S.V3.3	S	C.Extra	MO, MB, BI
	Asian	Yeasts	Mixed	Vitek MS	VITEK MS D.	S	C.Extra	MO, MB, BI
Lacroix 2014	Europe	Candida	Mixed	Andromas	NR	Modified	C.Extra	MO, MB, BI
	Europe	Candida	Mixed	Bruker Biotyper	S.V3.0	S	C.Extra	MO, MB, BI
Lima-Neto 2014	America	Candida	Mixed	Saramis	NR	NR	C.Extra	MO, MB, BI
Schulthess 2014*	Europe	Molds	Mixed	Bruker Biotyper	S.V3.0 and the Filamentous Fungi D.V1.0	S	C.Extra	MO, MB, BI
	Europe	Molds	Mixed	Bruker Biotyper	S.V3.0 and the Filamentous Fungi D.V1.0	S	C.Extra	MO, MB, BI
Wang 2014	Asian	Yeasts	Mixed	Vitek MS	D.V2.0	S	C.Extra	MO, MB, BI

Zhang 2014	Asian	Yeasts	Mixed	Vitek MS	D.V2.0	S	C.Extra	MB
Deak 2015	America	Yeasts	Mixed	Bruker Biotyper	S.V3.0	S	C.Extra	MO, MB, BI
	America	Yeasts	Mixed	Vitek MS	D.V2.0	S	C.Extra	MO, MB, BI
Levesque 2015	America	Fungi	Mixed	Bruker Biotyper	S.V3.1	S	C.Extra	MB
	America	Fungi	Mixed	Vitek MS	D.V2.0	S	C.Extra	MB
Panda 2015	Asian	Fungi	Mixed	Bruker Biotyper	S.V3.1	S	C.Extra	MO, BI

Note: B, blood specimens; Mixed, various clinical isolates; S, standard threshold recommended by manufacturer; NR, no report; C, culture without protein extraction; C.Extra, culture with protein extraction; MO, morphology; MB, molecular biology; BI, biochemistry. *conducting both retrospective and prospective researches in one article.

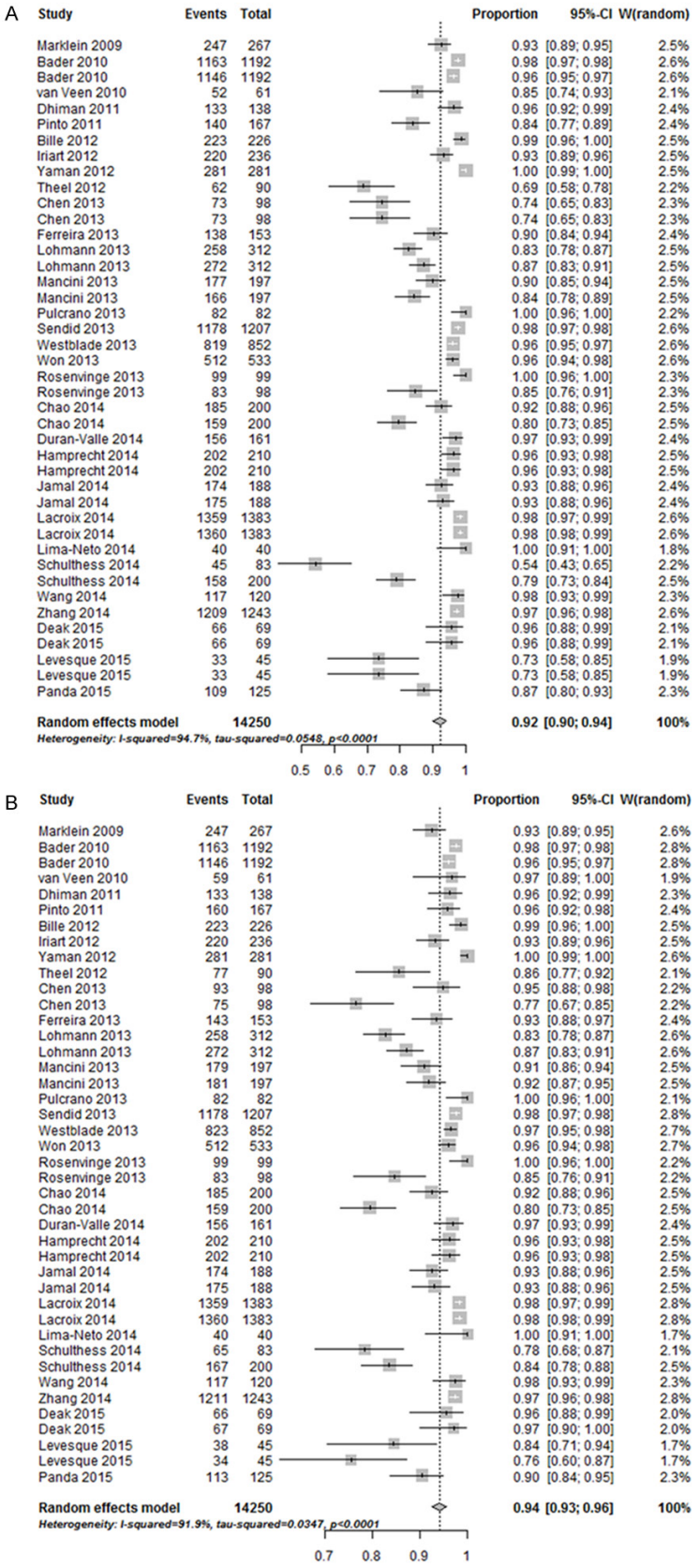

Figure 3. Forest plots of the overall IA for fungi identification by random-effects model. A: Overall IA at the species level. B: Overall IA at the genus level.

ed that specimen types (P < 0.0001), pre-treatments (P < 0.0001) and detection systems (P < 0.0001) significantly contributed to the heterogeneity (**Table 2**). Further multivariate meta-regression analysis suggested that specimen types (P = 0.012) and detection systems (P = 0.012) were the main source of the between-study heterogeneity (**Table 2**).

Then we performed subgroup analyses to explore the IA of MALDI-TOF MS in different situations (**Table 3**). In the subgroup of strain categories, gram-negative bacteria (GNB) (IA = 0.865, 95% CI = 0.827-0.895, I^2 = 88.9%, P < 0.0001) had better accuracy than gram-positive bacteria (GPB) (IA = 0.685, 95% CI = 0.585-0.777, I^2 = 98.8%, P < 0.0001). In the subgroup of pre-treatments, the MALDI-TOF MS accuracy for detecting colonies after culture (IA = 0.899, 95% CI = 0.864-0.925, I^2 = 98.5%, P < 0.0001) was superior to direct detection (IA = 0.726, 95% CI = 0.652-0.795, I^2 = 97.1%, P < 0.0001). In the subgroup of specimens types, the MALDI-TOF MS accuracy was the highest in urine samples (IA = 0.916, 95% CI = 0.896-0.932, I^2 = 0%, P = 0.401) and the lowest in positive blood cultures (IA = 0.689, 95% CI = 0.619-0.759, I^2 = 97.5%, P < 0.0001). In different detection systems, we found that Vitek MS (including Saramis) (IA = 0.919, 95% CI = 0.879-0.946, I^2 = 96.8%, P < 0.0001) had an advantage over Bruker Biotyper (IA = 0.809, 95% CI = 0.763-0.848, I^2 = 98.1%, P < 0.0001) for bacteria identification.

Sensitivity analysis and publication bias: The sensitivity

Table 5. Results of univariate and multivariate meta-regressions for fungi identification

Moderator	Estimate	SE	*P*
Univariate meta-regression analysis			
Publication year	-0.024	0.027	0.377
Geographic distribution of isolates	-0.049	0.080	0.535
Strain categories	-0.301	0.095	0.002
Specimen types	0.412	0.147	0.005
Pre-treatments*	-	-	-
Detection systems	0.144	0.079	0.068
Multivariate meta-regression analysis			
Strain categories	-0.269	0.096	0.005
Specimen types	0.358	0.142	0.011

Note: SE, standard error. *All used after culture detection.

analysis indicated that the pooled IA was quite stable by removing each study at a time (data not shown). Begg's test and Egger's test of funnel plot asymmetry at the species level showed no significant publication bias in the meta-analysis of bacteria identification (P_{Begg} = 0.479, P_{Egger} = 0.075).

The accuracy of MALDI-TOF MS for fungi identification

Study characteristics: 30 studies including 42 trials with a total of 14250 isolates were included for fungi identification (details shown in **Table 4**). Among them, 39 trials detected fungi from different clinical specimens, 3 from positive blood cultures and all of them employed detecting after culture method. In addition, 2 trials focused on molds, 34 focused on yeasts and 6 focused on both of them.

Overall results: Overall analysis of fungi detection by the random-effects model showed that the pooled IA was 0.922 (95% CI = 0.900-0.941) at the species level and 0.942 (95% CI = 0.926-0.956) at the genus level. We also observed significant heterogeneity at the both levels (Species level: I^2 = 94.7%, P < 0.0001; Genus level: I^2 = 91.9%, P < 0.0001) (**Figure 3A** and **3B**).

Meta-regression and subgroup analyses: For same reason, we performed further analyses at the species level. We conducted meta-regression analysis to explore the source of heterogeneity and summarized results in **Table 5**. Strain categories (P = 0.002) and specimen types (P = 0.005) were the significant factors suggested by the univariate meta-regression analysis and further multivariate meta-regression results demonstrated that Strain categories was the main source of heterogeneity (P = 0.005).

Table 6 presented the results of subgroup analyses for fungi identification. For strain categories, the MALDI-TOF MS accuracy was better for yeasts (IA = 0.942, 95% CI = 0.924-0.958, I^2 = 93.7%, P < 0.0001) than molds (IA = 0.661, 95% CI = 0.553-0.790, I^2 = 81.8%, P = 0.0002). For specimen types, the MALDI-TOF MS accuracy in positive blood cultures (IA = 0.995, 95% CI = 0.951-1.000, I^2 = 94.2%, P < 0.0001) outperformed that in various specimens (IA = 0.914, 95% CI = 0.889-0.934, I^2 = 94.8%, P < 0.0001). In addition, Bruker Biotyper (IA = 0.901, 95% CI = 0.861-0.936, I^2 = 95.8%, P < 0.0001) and Vitek MS (including Saramis) (IA = 0.935, 95% CI = 0.907-0.958, I^2 = 92.1%, P < 0.0001) had a good and comparable performance for fungi identification.

Sensitivity analysis and publication bias: Results from sensitivity analysis presented a stable pooled IA for fungi identification (data not shown). Significant publication bias was observed at the species level (P_{Begg} = 0.005, P_{Egger} < 0.0001). Further trim-and-fill analysis revealed that after incorporating the "missing" studies, the adjusted pooled IA was increased from 0.922 (95% CI = 0.900-0.941) to 0.966 (95% CI = 0.949-0.980), suggesting that the actual MALDI-TOF MS accuracy for fungi identification might be better than our estimation.

Discussion

This present meta-analysis demonstrated that MALDI-TOF MS had a good IA for clinical common bacteria and fungi identification at the species level (0.849 for bacteria and 0.922 for fungi) and better at the genus level (0.909 for bacteria and 0.942 for fungi). That was consistent with previous reports (about 84.1-93.6% for routine bacteria identification [4] and 95.5% for fungi identification [88]). Further subgroup analyses showed the performance of MALDI-TOF MS was stable in most subgroups.

Table 6. Heterogeneity and pooled IA in the subgroup analyses for fungi identification

Subanalyses	No. of total isolates (no. of studies)	*P*	I^2	IA (95% CI)
Strain categories				
Molds	396 (5)	0.0002	81.8%	0.661 (0.553- 0.790)
Yeasts	13538 (37)	< 0.0001	93.7%	0.942 (0.924- 0.958)
Pre-treatments*	-	-	-	-
Specimens types				
Positive blood cultures	896 (3)	< 0.0001	94.2%	0.995 (0.951- 1)
Various clinical isolates	13354 (39)	< 0.0001	94.8%	0.914 (0.889-0.934)
Detection systems				
Biotyper	6846 (23)	< 0.0001	95.8%	0.901 (0.861-0.936)
Vitek MS (including Saramis)	5795 (17)	< 0.0001	92.1%	0.935 (0.907-0.958)

Note: *All used after culture detection.

The accuracy of MALDI-TOF MS for bacteria identification

GPB and GNB are two major categories of bacteria. Our results revealed that MALDI-TOF MS had much better performance on the detection of GNB than GPB at the species level (0.865 versus 0.685), which was in accord with other reports [89]. MALDI-TOF MS is considered to have the ability to directly identify pathogens in blood, urine or cerebrospinal fluid specimens. However, we found that different pre-treatments (direct detection or after culture identification) might influence the accuracy of MALDI-TOF MS. Its IA without bacteria culture was significantly lower than that with culture (0.726 versus 0.899 at the species level). Given that direct detection from positive blood cultures is the most common in enrolled studies, one possible explanation of its low IA is that blood cells and charcoal in the flask may affect the performance [2]. The results also suggested that appropriate pre-treatment could be an effective way to increase IA of MALDI-TOF MS. Bruker has currently developed a commercial lysis kit called “Sepsityper” [90], which is reported to be better at performance improvement of MALDI-TOF MS than other pre-treatments [38, 42].

We also found that the MALDI-TOF MS exhibited different performance on different specimen types. The lowest IA of MALDI-TOF MS was seen in blood cultures, possibly resulting from the influence of blood cells and charcoal, which was in consistent with the results of pre-treatment subgroup. Interestingly, we observed that MALDI-TOF MS was quite suitable for bacteria identification in urine specimens. In the included studies containing 954 urine specimens (bacteria load > 10^5 CFU/mL), the accuracy by direct detection was as high as 0.916 with no heterogeneity. Ferreira et al. once noted that MALDI-TOF was able to identify 92.7% and 91.8% of uropathogens to genus and species level respectively, providing samples with a high bacteria load (> 10^5 CFU/mL) [91]. The previous studies and our work strongly suggested that MALDI-TOF MS would have a great application prospect in direct detection of bacteria in the urine specimens.

In addition, we investigated the performance of MALDI-TOF MS in different detection systems and surprisingly found that Vitek had higher accuracy than Bruker (0.919 versus 0.809). In consideration of more popularity of Bruker in the clinical detection, we further conducted meta-analysis restricted in studies focusing on the comparison between these two detection systems, and observed that their performance gap obviously narrowed (0.899 for Vitek versus 0.885 for Bruker). Thus based on the previous studies [10] and our work, we speculated that different databases and/or determination algorithms might contribute to the discrepancy in MALDI-TOF MS performance among different detection systems [92].

The accuracy of MALDI-TOF MS for fungi identification

Our results demonstrated that MALDI-TOF MS had an excellent accuracy for fungi identification at both species and genus levels, which was in accordance with the previous meta-analysis by Ling, et al. [88]. However, MALDI-TOF MS showed much lower IA on molds in our

study than that in Ling, et al.'s report (0.661 versus 0.934). The discrepancy might result from the different inclusion criteria that we only included studies focusing on clinical fungi detected by commercial databases with standard procedure according to manufacture instructions. While Ling et al. did not exclude studies about fungi identification using in-house databases.

MALDI-TOF MS showed a good IA (> 0.90) for detecting fungi in different specimen types and especially in positive blood cultures (IA = 0.995), for all of them detected after culture. Furthermore, we observed comparable performance on fungi identification between Bruker and Vitek detection systems.

Usually, the accuracy of MALDI-TOF MS for fungi identification is considered to be worse than bacteria because of the thick cell wall of fungi. However, our meta-analysis showed opposite results that MALDI-TOF MS had a better performance on fungi identification at both species and genus levels. There are several possible explanations: (1) the diversity of bacteria is higher and the current databases are unable to identify all of them; (2) all the fungi specimens were detected after culture in our included studies, while many bacteria specimens were detected directly (such as blood and urine samples, etc.); (3) many fungi are difficult to be identified with insufficient data in the commercial databases. Studies focusing on these fungi identification were excluded according to our criteria.

Based on large data, we revealed some significant findings of MALDI-TOF MS for bacteria and fungi identification. However, there were some limitations in this present meta-analysis. First, only studies about common clinical bacteria and fungi identification were included, which might lead to an overestimation of the accuracy of MALDI-TOF MS. Second, the included studies were restricted in using commercial databases. Although using in-house or expanded databases may improve the performance of MALDI-TOF MS [93], it is difficult to find a unified standard to compare these results. Thus we failed to evaluate the accuracy of MALDI-TOF MS in these studies. Third, as MALDI-TOF having limitation in directly identifying polymicrobial samples [89], their IA were not analyzed in this paper. Finally, large heterogeneity was observed in our meta-analysis. Many reasons, such as different culture situations [20], operating skills and thresholds (although most of the eligible studies used standard threshold recommended by manufacturers), as well as frequently updated databases, may contribute to the severe heterogeneity. Future studies are still required in more homogeneous situations.

In conclusion, our meta-analysis offered a strong evidence that MALDI-TOF MS had a good accuracy on common bacteria and fungi identification at both species and genus levels. Moreover, we not only revealed several factors likely to influence the accuracy of MALDI-TOF MS, but also assessed its performance in various clinical situations including different strain categories, pre-treatments, specimen types and detection systems. Our work could provide meaningful hints for the application of mass spectrometry technology in the clinical laboratories.

Acknowledgements

This work was supported by The National Mega Project on Major Infectious Diseases Prevention [2014yligzknljs03]. The funders had no role in study design, data collection and the decision to submit the work for publication. All authors were responsible for the integrity and accuracy of the data analysis.

Disclosure of conflict of Interest

None.

Abbreviations

MALDI-TOF MS, Matrix-assisted laser desorption ionization-time of flight mass spectrometry; IA, Identification accuracy; GNB, gram-negative bacteria; GPB, gram-positive bacteria.

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