

Epidemiology of *Pseudomonas aeruginosa* in diabetic foot infections: a global systematic review and meta-analysis

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Abstract

Pseudomonas aeruginosa is one of the most common causes of diabetic foot infection globally. This study aimed to determine the global distribution of *P. aeruginosa* isolated from diabetic foot ulcer infection.

PRISMA procedure was used to perform the current systematic review and meta-analysis. The Web of Science, MEDLINE/PubMed, Scopus, and other databases were searched for studies published in English from 2000 to 2022. Data was analyzed using the Comprehensive Meta-Analysis software (CMA). Keywords and MESH phrases included *Pseudomonas aeruginosa*, diabetic foot ulcer, *P. aeruginosa*, and diabetic foot infection.

As a result of this review, 16.6% of diabetic foot wound infections were caused by *P. aeruginosa*. About 37.9% of strains were multidrug resistant (MDR). *P. aeruginosa* infection rates in diabetic foot ulcers ranged from 0.5 to 100% globally. In total, the prevalence rates of *P. aeruginosa* in diabetic foot ulcer infection from Asia, Africa, and Western countries were reported at 18.5%, 16.3%, and 11.1%, respectively.

Data have shown that the prevalence of *P. aeruginosa*, particularly MDR strains, isolated from diabetic foot ulcer infection was relatively high; inherent resistance to antibiotics is also high; the wound either does not heal or if it does, it will be delayed. Therefore, timely treatment is essential.

Keywords *Pseudomonas aeruginosa*, diabetic ulcer, diabetic foot, foot ulcer, prevalence.

Introduction

Diabetes is a major public health concern worldwide. The number of patients suffering from diabetes has increased from 108 million in 1980 to 442 million in 2014, and the disease's prevalence is growing year after year.¹ Diabetes already affects 7% of the global population, and is expected to rise to 8.3% by 2030.² Diabetes can cause many complications such as renal failure, heart attack, blindness, stroke, and amputations of the lower limbs. Diabetic foot ulcers are a

major health concern worldwide, and they are one of the most prevalent diseases among diabetic people. A diabetic foot ulcer is one of the main causes of hospitalization in patients with diabetes. If the wound becomes infected, the length of hospitalization rises, causing more issues for the patient and increasing treatment expenses. About 25% of all wounds do not heal, and this can result in the amputation of the lower leg.²

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In Europe, predominantly Gram-positive bacteria such as *Staphylococcus aureus* are prevalent, but in Asia and Africa, mostly Gram-negative bacteria, particularly *P. aeruginosa* are prominent.³ In general, Gram-negative bacteria are the most common cause of diabetic foot infection.^{2,4} *P. aeruginosa* causes serious injury in patients with diabetic foot ulcers and should never be considered contamination or natural flora, since this microorganism is always a pathogen in this patient population, and the leading cause of diabetes-associated sepsis and amputation.⁵ *P. aeruginosa* is susceptible to few antibiotics due to the intrinsic poor permeability of its cell wall, making it a particularly deadly infection.^{6,7} Furthermore, effective antibiotics against *P. aeruginosa* such as ceftazidime, ciprofloxacin, levofloxacin, amikacin, and piperacillin have only been found to be effective in 64 to 80% of cases.⁸

Diabetic foot wound infection is more difficult to cure and is treated later than in non-diabetic patients.⁵ Numerous factors contribute to the enhancement of diabetic foot ulcer infection, including vascular system abnormalities, peripheral neuropathy, a high glycemic index, and immune system suppression, which all lead to infection by microorganisms.⁹

Poor blood sugar management is linked to biofilm development in diabetic foot ulcer infections. *P. aeruginosa* can create a biofilm in the wound, making it stronger and more difficult to heal.¹⁰ Biofilm production increases the expression of inflammatory factors, which eventually leads to vascular system damage and delayed wound healing. On the other hand, *P. aeruginosa* is found in chronic wound infections more frequently than other microorganisms, and inhibits wound healing.^{11,12} Antibiotic resistance is becoming a major global issue due to the high inherent resistance in *P. aeruginosa*, and produced infections are typically difficult to cure.¹³ Antibiotic resistance in *P. aeruginosa* is currently spreading.⁵ Despite several studies to investigate the prevalence and resistance of *P. aeruginosa* in various countries, a global study of the prevalence and antibiotic resistance of this microorganism in diabetic foot infection has seldom been

conducted. Thus, the aim of this study is to provide an overview of the prevalence of *P. aeruginosa* and its antibiotic resistance in people with diabetic foot ulcers worldwide.

Methods

Literature search

The search was conducted in Scopus, PubMed, Web of Science (ISI), and other databases for studies giving the prevalence of *Pseudomonas aeruginosa* retrieved from diabetic foot infections (DFI) all over the world between 2000 and end of 2022. MESH terms and Entry words included *Pseudomonas*, *Pseudomonas* spp., *Pseudomonas aeruginosa*, *P. aeruginosa*, diabetic ulcer, diabetic foot, foot ulcer, diabetic feet, foot diseases, prevalence, frequency, and occurrence.

Eligibility criteria

Studies that presented the prevalence of *P. aeruginosa* in DFI patients, which used the correct methods of sampling, processing, detection and isolation of bacteria were included in the present review. For sampling, needle aspiration under aseptic conditions is recommended by the protocol. For ulcers and other open wounds, biopsy was essential. Microbiological and biochemical methods such as culture on McConkey agar, chocolate agar, appearance of pyocyanin pigment on cetrimide-based media, growth at 42°C, oxidase and catalase test, nitrate reduction, and motility were used to determine this microorganism.¹⁴ Studies before 2000, studies with missed/unclear information, meeting abstracts, case reports, and reviews were omitted.

Quality assessment

Quality assessment was evaluated through Critical Appraisal Skills Programme (CASP) checklist for cross-sectional studies (www.casp-uk.net). Based on the criteria included in this protocol, the studies were classified into three categories: weak, strong and moderate. Finally, poor studies were excluded from the current review.

Data extraction

As shown in Supplementary Table 1, two authors independently considered the selected studies and extracted the appropriate data such as: first author, location (country), published year, sample size (all bacteria), event (*Pseudomonas aeruginosa*), multidrug resistant (MDR) strains, age, sex (male, female), and stage of disease.

Meta-analysis

Analysis was done with the Comprehensive Meta-Analysis software (Version 3.3.070, Biostat, USA). The prevalence was calculated by 95% confidence intervals (CIs). The possible statistical heterogeneity between studies was evaluated by Cochran's Q-test, and I^2 . Due to significant statistical heterogeneity, the random-effect model was applied. Moreover, Egger's regression asymmetry test, and Funnel plot were used for judging publication bias in the included studies.

Results

Study selection and characteristics of included studies

A total of 1702 studies were retrieved in the initial search. After all assessments for titles, abstracts, and full-texts, finally, 100 studies met eligibility criteria, were approved and included the present review (Figure 1). Of these 100 studies, 69, 25, and 5 were from Asian, European, and African countries, respectively.

Overall effects

As shown in Figure 2, the combined prevalence of *P. aeruginosa* in diabetic ulcer infections varied between 0.5-100% all over the world. In general, the pooled prevalence of *P. aeruginosa* in the world from 2000 to 2022 was reported at 16.6% (95%CI: 14.7-18.8), of which 37.9% (95%CI: 25.3-16.5) were MDR strains. The prevalence of *P. aeruginosa* in Asian, African and Western countries was 18.5% (95%CI: 16.2-20.9), 16.3% (95%CI: 9.4-26.8), and 11.1% (95% CI: 8.7-14.2), respectively. In Asian countries, the highest and lowest prevalence of *P. aeruginosa* isolated from diabetic ulcer infection were 100% and 1.63%, respectively. Also, the highest and lowest prevalence of this

microorganism from African countries were 32.2% and 9.4%, respectively. Similarly, values of 0.5% and 50% were reported from Western countries.

Heterogeneity and publication bias

Data showed the heterogeneity between studies included ($Q=1919.7$ and $Z=21.5$, and $I^2=94.8$). Funnel plot showed the bias in the studies. Egger's linear regression test was performed to further investigate this subject. According to Egger's linear regression, publication bias was not confirmed between studies ($p=0.43$).

Discussion

Diabetic foot is a chronic complication in patients with diabetes around the world.¹⁵ Every 30 seconds in the world, a lower limb is amputated due to diabetes,¹⁶ and the risk of amputation in patients with diabetic foot infection is 154.5 times higher than in people without infection.¹⁷ One of the common causes of diabetic foot infection is *P. aeruginosa*, and now, the prevalence of this bacterium in diabetic foot wound infection worldwide is 16.6%.

As mentioned in the results, the prevalence of *P. aeruginosa* in diabetic foot ulcer infection in Asia varied from 1.63% to 100%. This rate is related to 69 studies included in this review from the Asian continent and in Western countries it varied from 0.5 to 50%, with most of the mentioned studies having reported less than 20%. Also, according to the review, the prevalence of *P. aeruginosa* in diabetic foot ulcers in Africa varied from 9.4% to 32.2%, which is related to 6 studies, but in Africa, most of the data reported was above 10%, which indicated a higher prevalence of infection in Africa, although the numbers of studies in Africa are lower than in Asia and Western countries, which needs further investigation. In total, the prevalence of *P. aeruginosa* in diabetic foot ulcer infection in Asia, Africa, and Western countries is 18.5%, 16.3%, and 11.1%, respectively.

The bacteria causing diabetic foot ulcer infection in the studies included may be different, and the reasons for this difference are:

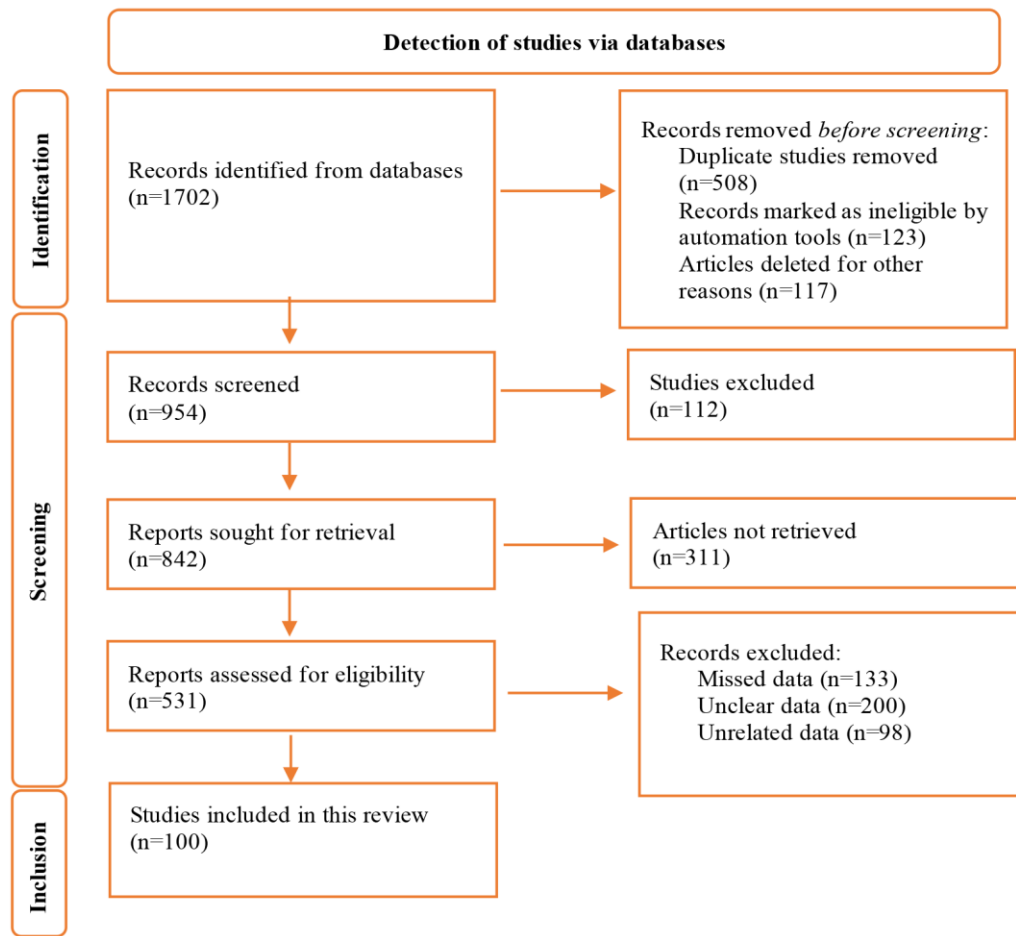
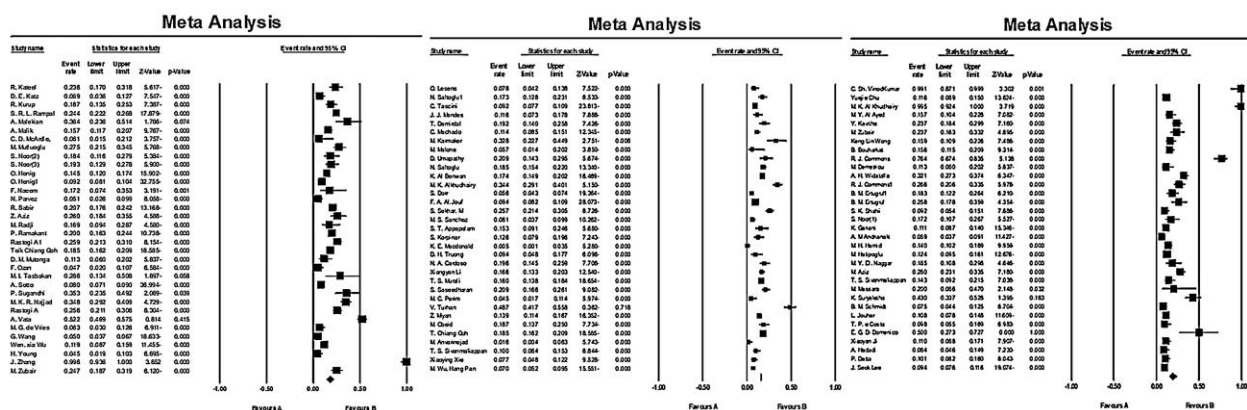


Figure 1. Flow diagram of the study selection process



A forest plot is a valuable graphical presentation of results from a meta-analysis. It provides crucial data to notify our interpretation of the findings. The typical forest plot contains a box, proving the point estimate for each subgroup, and a line, demonstrating the 95% confidence interval. The precision of the point estimate of each subgroup is characterized by the size of the box.

Figure 2. Forest plot of the meta-analysis of the prevalence of *P. aeruginosa* isolated from diabetic foot infections.

1. Differences in the bacteria causing the infection, 2. Geographical changes, 3. The type and intensity of the infection, and 4. Methods used in the isolation of bacteria.¹⁸ In general, the highest rate of prevalence of *P. aeruginosa* in diabetic foot ulcer infection was found in Asia, Africa, and, lastly, Western countries.

The most common cause of diabetic foot ulcer infection in European and North American countries is *S. aureus*, but in Asian, African, and South American countries, Gram-negative bacteria such as *P. aeruginosa* were common, for example, the prevalence of diabetic foot ulcer infection with *S. aureus* in Asian countries such as China, India, Thailand, Iran, Turkey, Saudi Arabia, Kuwait, and Malaysia varied from 11.4% to 44%,¹⁹ but in studies such as the one conducted by Amanda Thurler Palomo et al. in Brazil, the prevalence of Gram-negative bacilli (88%) was more than that of Gram-positive cocci, with a prevalence of 68%.²⁰ Also, in other studies included in the current review, such as the studies carried out by Esaki Muthu et al.²¹ and Sivanmaliappan et al.,⁵ both from India, Alkhudhairy et al.²² in Iraq, Saltoglu et al.²³ in Turkey, Xiangyan et al.²⁴ in China, and Agwuet et al.²⁵ in Nigeria, the predominant microorganism isolated from diabetic foot ulcer infection was *P. aeruginosa*.

In general, no relationship has been observed between the prevalence of *P. aeruginosa* in diabetic foot ulcer infection and age. Among patients who have recently been treated with antibiotics or patients whose foot wound infection has become chronic, the infection usually occurs in the form of polymicrobial infection, and so, the simultaneous infection with aerobic Gram-negative bacilli and obligate anaerobic bacteria also occurs.¹⁸

Among Gram-negative bacteria, *P. aeruginosa* causes important inflammatory responses and mediators that delay wound healing due to the assembly of many virulence contributors like hemolysins, collagenase, protease, and resistance to phagocytosis. Also, *P. aeruginosa* is potentially dangerous due to its quorum sensing systems, induction of passive resistance, and sharing of metabolic substances and DNA in the wound.¹⁸

One of the other reasons for the lack of healing seen in diabetic foot ulcers is the formation of biofilm by microorganisms. Biofilm reduces local immunity, hinders angiogenesis, creates a barrier between antibiotics and the bacterial environment, causes the colonization with other bacteria in the wound, and postpones wound healing.²⁶

P. aeruginosa has the ability to form a biofilm in the wound, which makes it stronger and harder to cure; the formation of biofilm in the wound causes the wound to become chronic.²⁷ The biofilm created by *P. aeruginosa* creates an inflammatory condition in the wound, subsequently, the host cannot eradicate the biofilm and the healing of the wound is delayed.²⁸

P. aeruginosa can lead to gangrene in chronic conditions of DFU such as osteomyelitis.²⁹ New treatment methods include debridement, antibiotic therapy, and hyperbaric oxygen therapy, which have provided hope for treating chronic cases of impaired repair infections.²⁹ Acyl-homoserine lactones, as a group of quorum sensing molecules, regulate biofilm formation by *P. aeruginosa* strains. These factors also provide colonization grounds for opportunistic pathogens.²⁹

In disease conditions, biofilms hinder the process of angiogenesis and delay wound healing, as mentioned above. Multiple drug-resistant microorganisms use these mechanisms to resist different antibiotic classes, including Gram-negative microorganisms such as *P. aeruginosa* and *Klebsiella* spp., which have a high tendency to create a strong biofilm.³⁰

According to the Infectious Diseases Society of America (IDSA), the risk factors considered for *P. aeruginosa* infection in DFI include a high local prevalence of *P. aeruginosa*, hot and humid weather, excessive exposure of the foot to water,³¹ immunocompromised status, failed outpatient DFI antibiotic therapy.³² Also, Lebowitz et al.³³ and Michael P. Veve et al.³² reported that patients who had recurrent diabetic foot infections had a higher rate of *P. aeruginosa* compared to people who did not. Another problem in the treatment of diabetic foot wound infection is the prevalence

of multidrug-resistant strains in wounds, including Gram-negative extended spectrum betalactamase-producing bacilli and, especially, multidrug-resistant *P. aeruginosa*, which makes their treatment more difficult.³⁴

Repeated exposure to common antibiotics against *Pseudomonas* causes the emergence of drug-resistant strains, so that highly efficient antibiotics against *P. aeruginosa* are difficult to find today.³⁵ In this review, 37.9% of *P. aeruginosa* strains isolated from diabetic foot ulcers were MDR, this rate varied in different parts of the world, and was around 28% in European countries,³⁴ but it varied between 47% and 62% in African and Latin American countries.³⁶

Investigating the prevalence of MDR *P. aeruginosa* strains is very important, because these bacteria can be able to transfer resistance genes to other bacteria through mobile genetic elements such as transposons, integrons, and plasmids. The level of resistance in different countries has been reported to be related to the pattern of prescribing antibiotics, the number of foreign devices used in the patient's body, and the care facilities in each country.¹⁴ The occurrence of resistance in *P. aeruginosa*, especially the formation of resistance to carbapenems, occurs for three main reasons: 1. a defect in the oprD porin, 2. production of the carbapenemase enzyme, 3. overexpression of the efflux pumps.³⁷

Amputation of the patient's limb is the last option in patients with diabetic foot ulcers when the injured tissue becomes necrotic.³⁸ The presence of infection caused by multidrug resistant bacteria worsens the situation, and response to single-drug treatments is usually suboptimal. In these cases, combined therapy with proteins, nanoparticles, herbal extracts, or other nutritional substances can be useful to some extent.³⁹ For more than a decade, there has been no completely efficient treatment for multidrug-resistant strains of *P. aeruginosa*. Moreover, the gene transfer that takes place during the phenomenon of biofilm formation makes *Pseudomonas* resistant to different combinations of antibiotics.⁴⁰

Improving diabetic foot ulcers through different strategies as well as studying the

microbiome in different stages of the disease, both acute and chronic, may provide better knowledge regarding the prescription of antibiotics.

Conclusions

Data have shown that the prevalence of *P. aeruginosa*, particularly MDR strains, isolated from diabetic foot ulcer infection was relatively high; inherent resistance to antibiotics is also high; the wound either does not heal or if it does, it will be delayed. Therefore, timely treatment is essential.

Author contributions statement: MG, and SMT conceptualized the study; HM and ZF carried out the search process; AK interpreted the findings; AS edited and revised the manuscript. All authors read and approved the final version of the manuscript.

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Availability of data: The data supporting the findings are available from the corresponding author, upon reasonable request.

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Supplementary Table 1. Characteristics of selected studies

Study	Countries	Published year	Sample size (all bacteria)	Event (<i>Pseudomonas</i>)	MDR	Male	Female	G1W	G2W	G3W	G4W	G5W
O. Lesens	France	2010	129	10								
N. Saltoglu	Turkey	2015	208	36								
C. Tascini	Italy	2011	1295	119								
J. J. Mendes	Portugal	2011	147	17	7							
T. Demirdal	Turkey	2018	172	33								
C. Machado	Portugal	2020	359	41								
M. Karmaker	Bangladesh	2015	67	22								
M. Malone	Australia	2017	35	2								
D. Umapathy	India	2018	110	23								
N. Saltoglu	Turkey	2018	536	99	21							
K. Al Benwan	Kuwait	2011	777	135								
M. K. Alkhudhairy	Iraq	2020	282	97	12	43	54					
S. Dorr	Germany	2020	888	50								
F. A. Al. Jouf	Egypt	2020	1803	170								
S. Sekhar	India	2018	354	91								
M. S. Sanchez	Mexico	2017	246	15								
S. T. Appapalam	India	2019	85	13					6	7		
S. Korpinar	Turkey	2020	127	16				2	5	7	2	
K. E. Macdonald	Scotland	2020	200	1								
D. H. Truong	USA	2021	85	8								
N. A. Cardoso	Brazil	2017	189	37								
X. Li	China	2018	435	72								
T. S. Murali	India	2014	940	150								
S. Saseedharan	India	2018	282	59								
M. C. Perim	Brazil	2015	89	4								
V. Turhan	Turkey	2013	191	93								48
Z. Miyan	Pakistan	2017	671	93	28							2
M. Obeid	Lebanon	2018	182	34								
T. Chiang Goh	Malaysia	2020	1040	192								
M. Anvarinejad	Iran	2015	122	2								
T. S. Sivanmaliappan	India	2011	180	18	10							
Xiaoying Xie	China	2017	207	16								
M. Wu	China	2018	555	39				2	8	9	17	3

Study	Countries	Published year	Sample size (all bacteria)	Event (<i>Pseudomonas</i>)	MDR	Male	Female	G1W	G2W	G3W	G4W	G5W
C. Sh. VinodKumar	India	2011	54	54		32	22					
Yuejie Chu	China	2015	439	51								
M. K. Al Khudhairy	Iraq	2020	97	97		54	43					
M. Y. Al Ayed	Saudi Arabia	2018	134	21								
Y. Kavitha	India	2017	207	49								
M. Zubair	India	2011	97	23								
K. L. Wong	Singapore	2013	151	24								
B. Bouharkat	Algeria-France	2020	231	36								
R. J. Commons	Australia	2018	106	81								
M. Demetriou	Greece	2013	80	9								
A. H. Wadataalla	Sudan	2012	330	106								
R. J. Commons	New Zealand	2015	177	47								
B. M. Ertugrul	Turkey	2012	115	21								
B. M. Ertugrul	Turkey	2017	89	23								
S. K. Shahi	India	2016	142	13								
S. Noor (1)	India	2016	87	15								
K. Gariani	Switzerland	2018	551	61								
A. M Andrianaki	Greece	2020	307	18								
M. H. Hamid	Sudan	2020	250	35								
M. Hatipoglu	Turkey	2016	387	48								
M. Y. El. Naggar	Egypt	2016	65	12								
M. Aziz	Pakistan	2019	286	80								
T. S. Sivanmaliappan	India	2011	126	18								
M. Massara	Italy	2015	15	3								
K. Suryaleta	India	2017	100	43								
B. M. Schmidt	USA	2020	173	13								
L. Jouhar	Lebanon	2020	314	34	0							
T. P. e Costa	Portugal	2020	112	11	4							
E. G. Di Domenico	Italy	2020	16	8								
X. Ji	China	2014	146	16	12							
A. Hadadi	Iran	2014	119	10								
P. Datta	India	2019	149	15								
J. Seok Lee	Korea	2017	832	78								
R. Kateel	India	2017	127	30								
D. E. Katz	Israel	2016	131	9								

Study	Countries	Published year	Sample size (all bacteria)	Event (<i>Pseudomonas</i>)	MDR	Male	Female	G1W	G2W	G3W	G4W	G5W
R. Kurup	Guyana	2019	166	31								
S. R. L. Rampal	Malaysia	2019	1356	331								
A. Malekian	Iran	2019	44	16								
A. Malik	India	2013	255	40								
C. D. McArdle	Ireland	2018	33	2								
M. Mutluoglu	Turkey	2012	178	49								
S. Noor (2)	India	2017	87	16								
S. Noor (3)	India	2018	109	21								
O. Henig	USA	2020	648	94	0							
O. Henig	USA	2018	2450	225	0							
F. Naeem	Pakistan	2019	29	5								
N. Parvez	India	2012	157	8								
R. Sabir	Pakistan	2014	585	121								
Z. Aziz	Singapore	2011	100	26								
M. Radji	Indonesia	2014	59	10								
P. Ramakant	India	2010	375	75								
A. Rastogi	India	2016	313	81								
T. C. Goh	Malaysia	2020	1040	192								
D. M. Mutonga	Kenya	2019	80	9								
F. Ozan	Turkey	2017	107	5								
M. I. Tasbakan	Turkey	2017	21	6								
A. Sotto	France	2010	3117	250								
P. Sugandhi	India	2014	51	18								
M. K. R. Najjad	Pakistan	2014	250	87						83	4	
A. Rastogi	India	2016	317	81								
A. Vata	Turkey	2017	339	177								
M. G. de Vries	Netherlands	2013	111	7								
G. Wang	China	2015	844	42	33							
W. Wu	China	2017	312	37								
H. Young	USA	2015	112	5								
J. Zhang	China	2014	117	117	74	80	37					
M. Zubair	India	2011	162	40								

WG1: Wagner Grade 1; WG 2: Wagner Grade 2; WG 3: Wagner Grade 3; WG 4: Wagner Grade 4; WG 5: Wagner Grade 5.