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Original Article

Features and global impact of invasive fungal infections caused by *Pneumocystis jirovecii*: A systematic review to inform the World Health Organization fungal priority pathogens list

Brendan McMullan[1,2], Hannah Yejin Kim[3,4,5], Ana Alastruey-Izquierdo[6], Evelina Tacconelli[7], Aiken Dao[5,8], Rita Oladele[9], Daniel Tanti[2,10], Nelesh P. Govender[11,12,13,14], Jong-Hee Shin[15], Jutta Heim[16], Nathan Paul Ford[17,18], Benedikt Huttner[19], Marcelo Galas[20], Saskia Andrea Nahrgang[21], Valeria Gigante[22], Hatim Sati[22], Jan Willem Alffenaar[3,4,5], C. Orla Morrissey[23,24] and Justin Beardsley[5,8,*]

[1]Faculty of Medicine and Health, UNSW, Sydney, New South Wales, Australia
[2]Department of Immunology and Infectious Diseases, Sydney Children's Hospital, Sydney, New South Wales, Australia
[3]Sydney Pharmacy School, Faculty of Medicine and Health, University of Sydney, Camperdown, New South Wales, Australia
[4]Department of Pharmacy, Westmead Hospital, Western Sydney LHD, North Parramatta, New South Wales, Australia
[5]Sydney Infectious Diseases Institute, The University of Sydney, Camperdown, New South Wales, Australia
[6]Mycology Reference Laboratory, National Centre for Microbiology, Instituto de Salud Carlos III, Majadahonda, Madrid, Spain
[7]Department of Diagnostics and Public Health, Verona University, Verona, Italy
[8]Westmead Hospital, Western Sydney LHD, North Parramatta, New South Wales, Australia
[9]Department of Medical Microbiology and Parasitology, College of Medicine, University of Lagos, Lagos, Nigeria
[10]Discipline of Paediatrics, Faculty of Medicine and Health, University of NSW, Sydney, Australia
[11]Division of the National Health Laboratory Service, National Institute for Communicable Diseases, Johannesburg, South Africa
[12]Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[13]Institute of Infection and Immunity, St George's University of London, London , UK
[14]MRC Centre for Medical Mycology, University of Exeter, Exeter , UK
[15]Department of Laboratory Medicine, Chonnam National University School of Medicine, Gwangju, South Korea
[16]Scientific Advisory Committee, Helmholtz Centre for Infection Research, Germany
[17]Department of HIV, Viral Hepatitis and STIs, World Health Organization, Geneva, Switzerland
[18]Centre for Infectious Disease Epidemiology and Research, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa
[19]Essentials Medicines List Team, WHO, Geneva, Switzerland
[20]Antimicrobial Resistance Special Program, Communicable Diseases and Environmental Determinants of Health, Pan American Health Organization, Washingdom, District of Columbia, USA
[21]Antimicrobial Resistance Programme, World Health Organization European Office, Copenhagen, Denmark
[22]AMR Division, WHO, Geneva, Switzerland
[23]Department of Infectious Diseases, Alfred Health, Melbourne, Victoria, Australia
[24]Department of Infectious Diseases, Monash University, Clayton, Victoria, Australia

*To whom correspondence should be addressed. Justin Beardsley, MBChB, FRACP, PhD, University of Sydney, Sydney Infectious Diseases Institute, Sydney, Tel: +61 2 9351 2222. E-mail: justin.beardsley@sydney.edu.au

Abstract

This systematic review evaluates the current global impact of invasive infections caused by *Pneumocystis jirovecii* (principally pneumonia: PJP), and was carried out to inform the World Health Organization Fungal Priority Pathogens List. PubMed and Web of Science were used to find studies reporting mortality, inpatient care, complications/sequelae, antifungal susceptibility/resistance, preventability, annual incidence, global distribution, and emergence in the past 10 years, published from January 2011 to February 2021. Reported mortality is highly variable, depending on the patient population: In studies of persons with HIV, mortality was reported at 5%–30%, while in studies of persons without HIV, mortality ranged from 4% to 76%. Risk factors for disease principally include immunosuppression from HIV, but other types of immunosuppression are increasingly recognised, including solid organ and haematopoietic stem cell transplantation, autoimmune and inflammatory disease, and chemotherapy for cancer. Although prophylaxis is available and generally effective, burdensome side effects may lead to discontinuation. After

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a period of decline associated with improvement in access to HIV treatment, new risk groups of immunosuppressed patients with PJP are increasingly identified, including solid organ transplant patients.

Key words: *Pneumocystis jirovecii*, pneumonia, immunosuppression, PCP, invasive fungal infection.

Introduction

Pneumocystis jirovecii is a globally ubiquitous fungus capable of colonising human pulmonary alveoli transiently, but it is also an opportunistic infection in immunocompromised individuals leading to severe illness, including *Pneumocystis* pneumonia (PJP),[1] which has been widely reported among those with HIV infection. The natural history of *P. jirovecii* is of a human-specific pathogen exhibiting parasitic behaviour: Healthy individuals are frequently exposed but have asymptomatic or mild infection; pneumonia and severe infection generally occur only in the presence of immune compromise.[2] In human immunodeficiency virus (HIV)-associated PJP, it was recognised that more than 90% of cases occurred in patients with CD4 + T lymphocyte counts <200 cells/mm^3, and PJP is listed as an AIDS-defining illness.[3,4] A combination of primary prophylaxis with trimethoprim–sulfamethoxazole (TMP/SMX) and increasingly early and effective antiretroviral therapy has led to a substantial decline in PJP incidence in individuals with HIV.[5–7]

More recently, it has been recognised that other groups vulnerable to PJP include people with impaired T-lymphocyte immunity due to primary immunodeficiency or medical immunosuppression, including that associated with treatment of malignancy, solid organ transplantation (SOT) or haemopoietic stem cell transplantation (HSCT), or long-term corticosteroid use.[8] While onset of symptoms in HIV-infected individuals is typically gradual, appearing over weeks, it can be more abrupt in non-HIV-infected individuals.[5]

Diagnosis of PJP may be challenging, as, firstly, *P. jirovecii* is extremely difficult to culture *in vitro*.[9] Traditionally, the diagnosis of PJP relied on a combination of clinical and radiographic findings in populations with known risk factors, supplemented by immunofluorescent or other staining and microscopy of respiratory specimens to visualise organisms. This approach is limited by poor sensitivity and has largely been superseded by molecular diagnosis, where available. Molecular diagnosis usually involves PCR performed on bronchoalveolar lavage or induced sputum samples. While molecular diagnosis is more sensitive than the traditional approach, differentiating colonisation from disease may be challenging. Efforts have been made in recent years to standardise testing and interpretation for the diagnosis of PJP in non-HIV populations, with consensus guidelines now available for use in haematological malignancy and solid organ transplant.[10,11] More recently, serum (1,3)-β-D-glucan testing has been used to aid diagnosis of PJP, with high sensitivity (95%–96%) and specificity (84%–86%) overall.[10] Sensitivity may be lower in patients without HIV and with haematological malignancy: estimated at 64% in one small recent study.[12] It should be noted, however, that(1,3)-β-D-glucan is a cell wall polysaccharide common to several clinically significant fungi and therefore unable to confirm the disease.[10] In addition, it follows that approximately 5% of genuine PJP may occur without concomitant positive β-D-glucan testing in the blood.[13] This emphasises the need for complementary diagnostic approaches to confirm PJP diagnosis.

The gold-standard test for PJP requires sophisticated and well-resourced laboratories and healthcare systems, typically unavailable in resource-constrained settings where people are at highest risk of PJP. Thus, *P. jirovecii* is an under-diagnosed and under-recognised threat to global health, causing substantial morbidity and mortality. Global incidence has been estimated at over 400 000 cases annually.[14,15] *Pneumocystis jirovecii* is one of a number of important fungal pathogens, causing in excess of 1.6 million global deaths each year.[16]

Recognising the growing global threat of fungal pathogens, the World Health Organization (WHO) established an expert group in 2020 to identify priority fungal pathogens for the development of the first fungal priority pathogen list (FPPL).[17] The WHO FPPL was based on broad international consultation using a survey consisting of a discrete choice experiment, and 19 individual pathogens were ranked subsequently based on the information from systematic reviews, including this one. This WHO prioritisation exercise underlines the importance of addressing invasive fungal infections through research and development of novel therapeutics and diagnostics as well as through public health interventions in the context of global health. Following this process, *P. jirovecii* was classified as a medium-priority pathogen, reflecting lower urgent research and development needs than some other fungi, although it achieved a high priority ranking for public health significance.[17]

The specific aims of this systematic review were to evaluate the features and global impact of invasive infections caused by *P. jirovecii*. This review also sought to determine knowledge gaps for *P. jirovecii* and highlight research needs.

Materials and methods

The systematic review was conducted according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.[18] Studies were identified by searching the following electronic databases: PubMed and Web of Science from 1 January 2011 to 19 February 2021. A detailed search strategy is listed in the Supplementary material available online.

Included articles were original reports in English among humans of all ages (adults and children), which included data on *P. jirovecii* and at least one of the following outcomes of interest: mortality, inpatient care, complications/sequelae, antifungal susceptibility/resistance, preventability, annual incidence, global distribution, and emergence in the past 10 years. To assess preventability, we considered available preventive measures and risk factors for infection. Included study types were retrospective/prospective observational studies, randomised controlled trials, epidemiological studies, and surveillance reports that were published within the prior 10 years (2011–2021). References of all included articles and guidelines were reviewed to identify additional original studies. Studies with fewer than 50 participants, case reports, conference abstracts, and review articles were excluded, as were studies reporting

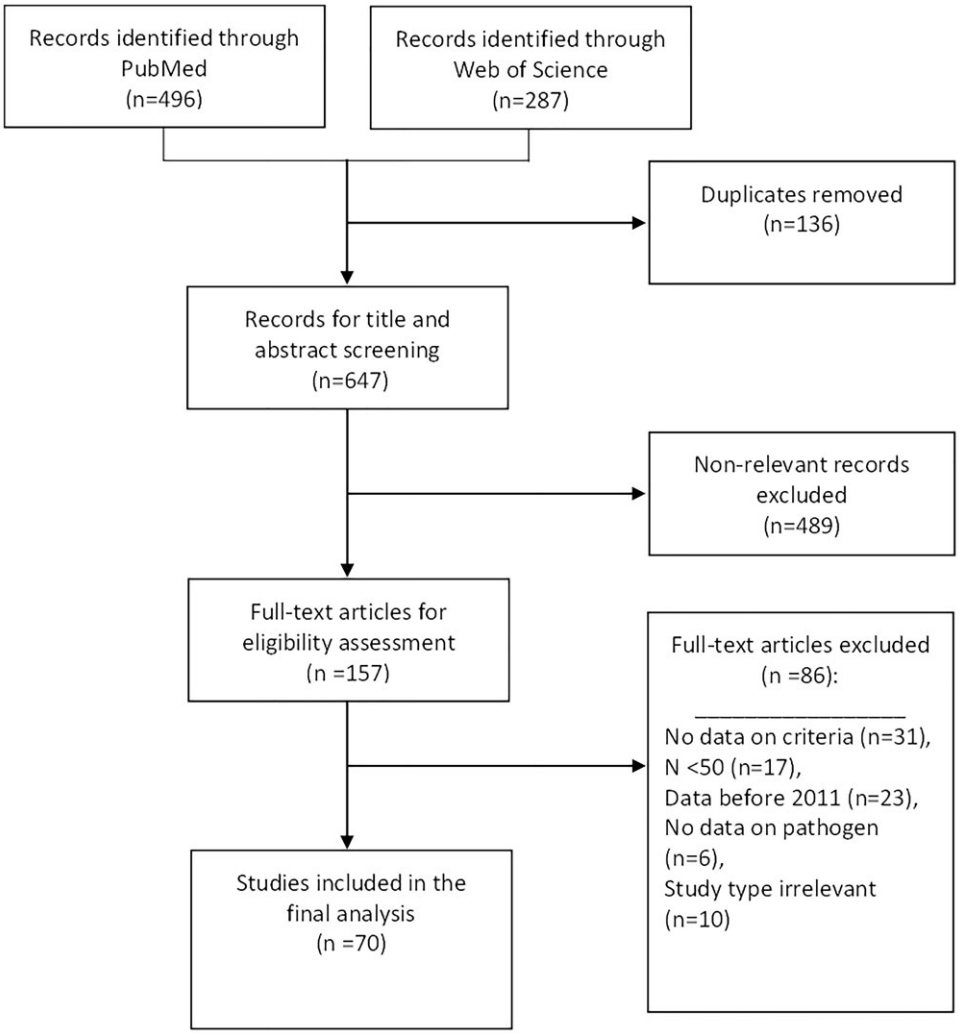

Figure 1. Flow diagram for the selection of studies included in the systematic review. Based on Page et al.[18].

only on novel drugs or diagnostic tools not registered for clinical use.

The final search results from each database were incorporated into the online systematic review software, Covidence® (Veritas Health Innovation, Australia). Duplicates were removed, and the remaining articles underwent title and abstract screening based on the inclusion criteria. Full text screening was performed for the final eligible articles. The title/abstract screening and full text screenings were performed independently by two reviewers with discrepancies to be resolved by discussion, with a third reviewer, if required, to achieve consensus. The first reviewer extracted data, which was checked by the second reviewer.

Risk of bias assessment was performed for the included studies on relevant bias criteria, depending on the type of data extracted using either Risk of Bias Tool for Randomized Trials version 2 (RoB 2)[19] or the Risk of Bias in Non-Randomised Studies (RoBANS) tool.[20] Using RoBANS tool, the studies were rated as low, high, or unclear risk. We used each outcome criterion (mortality, inpatient care, etc.) as an outcome of the study and assessed if any bias was expected based on the study design, data collection, or analysis in that study. Studies classified as unclear or high overall risk were still considered for analysis, but this is highlighted where relevant. The risk of bias assessment provides a comprehensive evaluation of the quality and reliability of the included studies, enhancing the robustness of the findings.

Results

The initial search yielded 783 articles; after removing duplicates, 648 articles underwent title/abstract screening, 157 articles underwent full text screening, and 69 studies were included in the final analysis (Figure 1). Detailed age information was not always available, but most included patients were adults (aged at least 18 years), where this information was available (Tables 2–8 and Supplementary Table 1).

The overall risk of bias for each study is presented in Table 1. Of the included studies, 40 studies (58%) were classified as low risk of bias in all domains assessed. A further 26 (37.7%) were classified as unclear risk of bias due to selection bias caused by unclear eligibility criteria or population groups, or unclear confirmation/consideration of confounding variables. Three studies (4.4%) were classified as a high risk of bias because of selection bias or confounding.

Table 1. Risk of bias of studies included in the review.

Author	Year	Risk level
Amona et al.	2020	Unclear
Anand et al.	2011	Unclear
Argy et al.	2018	High
Attia et al.	2015	Low
Awad et al.	2020	Unclear
Azoulay et al.	2018	Low
Báez-Saldaña et al.	2015	Low
Barreto et al.	2016	Unclear
Basiaga et al.	2018	Low
Beardsley et al.	2015	Unclear
Chen et al.	2020	Low
Choi et al.	2018	Unclear
Coelho et al.	2014	Unclear
Coyle et al.	2012	High
Creemers-Schild et al.	2016	Low
de Boer et al.	2011	Low
Evernden et al.	2020	Low
Faini et al.	2015	Unclear
Figueiredo-Mello et al.	2017	Low
Gabardi et al.	2012	Unclear
Gaborit et al.	2019	Low
Garg et al.	2018	Low
Haeusler et al.	2013	Low
Inoue and Fushimi	2019	Unclear
Kim et al.	2014	Low
Kim et al.	2015	Unclear
Kim et al.	2016	Low
Kim et al.	2017	Low
Kim et al.	2019	Low
Kitazawa et al.	2019	Unclear
Lagrou et al.	2015	Unclear
Lee et al.	2013	Low
Lee et al.	2019	High
Lee et al.	2020	Low
Lee et al.	2021	Unclear
Li et al.	2017	Low
Li et al.	2020	Low
Liu et al.	2020	Low
Lopez-Sanchez et al.	2015	Low
Lum et al.	2020	Unclear
Maartens et al.	2018	Low
Macedo-Viñas and Denning	2018	Unclear
Matsumura et al.	2014	Unclear
Mundo et al.	2020	Unclear
Nam et al.	2020	Low
Neofytos et al.	2018	Low
Nunokawa et al.	2019	Low
Ohmura et al.	2019	Low
Özenci et al.	2019	Unclear
Panizo et al.	2020	Unclear
Park et al.	2020	Low
PERCH Study Group	2019	Low
Quinn et al.	2018	Low
Rego de Figueiredo et al.	2019	Unclear
Rekhtman et al.	2019	Unclear
Saeed et al.	2015	Unclear
Schmidt et al.	2018	Low
Schoffelen et al.	2013	Low
Shi et al.	2020	Low
Singh et al.	2015	Unclear
Singh et al.	2019	Low
Solodokin et al.	2019	Low
Tanaka et al.	2015	Unclear
Tufa and Denning	2019	Unclear
Wang et al.	2019	Low
Wei et al.	2018	Low
Yanagisawa et al.	2020	Low
Yu et al.	2017	Low
Yukawa et al.	2018	Low

Mortality

Mortality in patients with PJP was highly variable, ranging from 4% to 76% across 33 studies (Table 2).[21–53] These were all observational studies, mostly retrospective case control or cohort studies ($n = 27$),[21–50] with three prospective cohort studies.[51–53] The patient populations and comorbidities addressed were diverse, as were measures of mortality, including deaths specific to PJP and all-cause or in-hospital mortality. For patients without HIV, mortality ranged from 4% to 76%.[26,43] Three studies compared mortality between HIV+ and HIV− patients with PJP and reported significantly higher mortality in non-HIV patients (33%–71%) than HIV-positive patients receiving highly active antiretroviral therapy (13%–18%).[26,40,44] Three studies also reported on PJP with and without cytomegalovirus coinfection but reported no significant differences in mortality.[42,50,53] For patients in one study without HIV, with severe PJP, adjunctive corticosteroids were associated with a lower risk of 60-day mortality (HR 0.71; 95% confidence interval 0.55–0.91) and significantly decreased mortality rates (24.7% vs. 36.6%, $P = .006$), but differences were not significant in moderately severe PJP.[37]

Inpatient care

Information on inpatient care and length of stay (LOS) was reported in six studies,[28,32,42,44,47,48] of which one study specifically reported on ICU LOS[42] and the rest hospital LOS. Hospital LOS varied, with a minimum reported median of 13 days [28] and a maximum mean of 29 days,[44] ranging from 0 to 123 days (details shown in Table 3).

Complications and sequelae

Long-term complications or sequelae of PJP were reported in 1 study, as shown in Table 4.[54] This was a study of renal transplant patients, reporting an increased hazard of long-term graft failure from PJP [HR 3.33 (95% CI 1.30–8.53)].[54]

Antifungal susceptibility and resistance

Clinical breakpoints defining resistance in *P. jirovecii* are not available. However, we identified one paper reporting on *DHPS* gene mutations[48] in which the prevalence of mutant *DHPS* (novel substitution at position 288) accounted for 3/12 (25%) of infected patients tested for mutations. The authors suggested that this mutation may be associated with resistance leading to treatment failure, as all three died despite treatment with TMP–SMX. Another paper reported *DHFR* gene polymorphisms of uncertain clinical significance for TMP–SMX treatment,[55] while a third paper reported cytochrome *b* mutants associated with failure of atovaquone prophylaxis in heart transplant patients.[56] Details of these three studies are provided in Table 5.

Preventability and risk factors

Measures to prevent PJP were reported in 13 studies shown in Table 6.[27,28,33,36,41,54,57–63] These refer to prophylaxis, either with TMP–SMX or with alternatives pentamidine (aerosolised or intravenous) or atovaquone. The studies included 1 study of HIV-positive [28] and 12 of diverse non-HIV populations.[27,33,36,41,54,57–63] Prophylaxis was protective against PJP, except in one study of children receiving glucocorticoids, in whom incidences of PJP were non-significantly

Table 2. Mortality associated with *Pneumocystis jirovecii* pneumonia.

Author	Year	Study design	Study period	Country	Level of care	Population description	No. of patients (*n*, %)	Mortality (type, *n/N*, %)
Báez-Saldaña et al.	2015	RCS SC	January 2010–December 2011	Mexico	Tertiary	Adults with HIV-AIDS and infectious respiratory disease	Total: 308 PJP: 142 (46.1%)	Inpatient ACM in PJP cases *n* = 17/54 (31.5%)
Chen et al.	2020	RCSSC	July 2015–December 2017	Taiwan	Tertiary	Hospitalised patients aged ≥20 years with PJP	170	60-day ACM *n* = 58/170 (34.1%)
Choi et al.	2018	RCS SC	January 2013–December 2015	South Korea	Tertiary	HIV-negative patients with PJP admitted to ICU for respiratory failure	81	ACM *n* = 52/81 (64.2%)
Coyle et al.	2012	RCS MC	July 2008–July 2011	Northern Ireland	Multiple	Patients with laboratory confirmed PJP	53	ACM *n* = 16/53 (30.2%)
Creemers-Schild et al.	2016	RCS SC	January 2003–July 2013	Netherlands	Tertiary	Adult patients diagnosed with PJP and treated with TMP–SMX	104	30-day ACM *n* = 14/104 (13.5%)
Evernden et al.	2020	RCSSC	January 2008–June 2017	Canada	Tertiary	Adult allogenic HSCT patients receiving anti-thymocyte globulin for GVHD prophylaxis	Total: 649 PJP cases: 21 (32.4%)	ACM in PJP cases *n* = 3/21 (14.3%)
Gaborit et al.	2019	PCSSC	January 2012–January 2017	France	Tertiary	Patients with confirmed PJP	107	90-day ACM *n* = 29/107 (27.1%)
Garg et al.	2018	CCSSC	January 1994–December 2016	USA	Tertiary	Adult recipients of kidney or kidney-pancreas transplantation	Total: 112 Cases: 28 (25.0%) Controls: 84 (75.0%)	3-month ACM–PJP cases *n* = 62.3% 2-year ACM – PJP cases *n* = 37.9% *Raw numbers NS*
Inoue and Fushimi	2019	RCS MC	April 2010–March 2016	Japan	Tertiary	HIV-negative adults with PJP	1299	60-day ACM in patients (PaO2 > 60 mmHg) *n* = 58/546 (10.6%) 60-day ACM in patients (PaO2 ≤ 60 mmHg) *n* = 189/732 (25.8%)
Kim et al.	2014	RCS MC	January 2004–July 2011	South Korea	Tertiary	Immunocompromised HIV-negative patients with PJP	173	In-hospital ACM *n* = 62/173 (62%) Mortality attributable to PJP *n* = 56/173 (32.4%)
Kim et al.	2015	RCS SC	May 2007–January 2013	South Korea	Tertiary	Hospitalised patients with laboratory confirmed PJP	95	Overall 30-day ACM *n* = 25/95 (26.3%) 30-day ACM: hospital-onset PJP *n* = 7/16 (43.8%) 30-day ACM: community-onset PJP *n* = 18/79 (22.8%)
Kim et al.	2017	PCS SC	January 2014–December 2015	South Korea	Tertiary	HIV-negative adults with PJP with or without pulmonary CMV	Total: 76 With CMV: 34 (44.7%) Without CMV: 42 (55.3%)	Overall 30-day ACM *n* = 8/76 (10.5%) 30-day ACM (CMV) *n* = 6/34 (17.7%) 30-day ACM (without CMV) *n* = 2/42 (47.6%)

Table 2. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description	No. of patients (*n*, %)	Mortality (type, *n/N*, %)
Lee et al.	2019	RCS SC	February 2003–April 2017	South Korea	Tertiary	Patients with laboratory-confirmed PJP with and without HIV-AIDS	Total: 424 HIV-negative: 362 (85.4%) HIV-AIDS: 62 (14.6%)	30-day ACM (HIV-negative) *n* = 118/362 (32.6%) 90-day ACM (HIV-AIDS) *n* = 11/62 (17.7%) *Authors used different definitions of mortality between cohorts*
Lee et al.	2021	RCS SC	May 2004–January 2019	South Korea	Tertiary	Adults with diffuse large B-cell lymphoma receiving R-CHOP who did or did not receive PJP prophylaxis	Total: 739 PJP prophylaxis: 137 (18.5%) No prophylaxis: 602 (81.5%)	PJP-related mortality *n* = 8/49 (16.3%)
Lee et al.	2020	RCS SC	January 1997–March 2019	South Korea	Tertiary	Kidney transplant recipients diagnosed with PJP	Total: 52 PJP only: 38 (73.1%) PJP and CMV: 14 (26.9%)	ACM (PJP only) *n* = 8/38 (21.0%) ACM (PJP and CMV) *n* = 3/14 (21.4%)
Li et al.	2020	RCS MC	January 2013–December 2019	China	Tertiary	Patients aged ≥16 years with pneumonia treated with glucocorticoids	Total: 716 PJP cases: 134 (18.7%)	30-day ACM (PJP) *n* = 45/134 (33.6%) 90-day ACM (PJP) *n* = 51/134 (38.1%)
Li et al.	2017	RCS SC	November 2003–June 2014	China	Tertiary	Patients with inflammatory or autoimmune disease receiving immunosuppressive therapy who had suspected PJP	Total: 123 Confirmed PJP: 52 (42.3%) Possible PJP: 22 (17.8%) Negative PJP: 49 (39.9%)	28-day mortality *n* = 26/52 (50%)
Liu et al.	2020	RCS SC	December 2013–December 2018	China	Tertiary	Patients with nephrotic syndrome who were diagnosed with PJP.	57	Mortality attributable to PJP *n* = 19/57 (33.3%)
Lopez-Sanchez et al.	2015	RCS SC	January 2000–December 2013	Spain	Tertiary	Adult patients with HIV-AIDS diagnosed with PJP	136	In-hospital ACM *n* = 15/136 (11.0%) 5-year ACM in patients available for follow-up *n* = 20/121 (16.5%)
Matsumura et al.	2014	PCS SC	January 2008–July 2011	Japan	Tertiary	Immunocompromised patients with suspected PJP	190	Overall 30-day ACM *n* = 41/190 (21.6%) 30-day ACM (treated for PJP) *n* = 17/85 (20.0%) 30-day ACM (untreated) *n* = 24/105 (22.9%)

Table 2. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description	No. of patients (*n*, %)	Mortality (type, *n/N*, %)
Mundo et al.	2020	RCS SC	1995–2019	USA	Tertiary	Patients with laboratory confirmed PJP	Total: 71 HIV-negative: 28 (39.4%) HIV-AIDS: 43 (60.6%)	Overall in-hospital ACM *n* = 27/71 (38.0%) In-hospital ACM (HIV-AIDS) *n* = 7/43 (16.3%) In-hospital ACM (HIV-negative) patients *n* = 20/28 (71.4%) 90-day ACM (HIV-AIDS) *n* = 3/(7.14%) 90-day ACM (HIV-negative) *n* = 16/(59.62%) 1-year ACM (HIV-AIDS) *n* = 3/(7.69%) 1-year ACM (HIV-negative) *n* = 19/(76.0%)
Neofytos et al.	2018	RCS MC	2008–2016	Switzerland	Multiple	All patients in the national SOT registry of Switzerland	Total: 2842 PJP: 41	12-week ACM (PJP cases) *n* = 2/41 (4.9%) 1-year ACM (PJP cases) *n* = 6/41 (14.6%)
Ohmura et al.	2019	RCS MC	January 2004–October 2017	Japan	Tertiary	Patients with SRD diagnosed with PJP and treated with TMP—SMX	81	30-day ACM *n* = 3/81 (3.7%)
PERCH Study Group	2019	CCS MC	August 2011–January 2014	Bangladesh, The Gambia, Kenya, Mali, South Africa, Thailand, Zambia	Multiple	Cases: children aged 1–59 months hospitalised with severe pneumonia. Controls: age-group-matched children randomly selected from local.	Total: 9351 Cases: 4232 (45.3%) Controls: 5119 (54.7%)	30-day ACM *n* = 292/4000 (7.3%) *PJP specific data NS*
Rego de Figueiredo et al.	2019	RCS SC	2011–2016	Portugal	Tertiary	Adult patients diagnosed with PJP	Total: 129 HIV-AIDS: 75 (58.1%) HIV-negative: 54 (41.9%)	In-hospital ACM (HIV-AIDS) *n* = 10/75 (13.3%) In-hospital ACM (HIV-negative) *n* = 20/54 (37.0%)
Schmidt et al.	2018	RCS SC	January 2000–June 2017	Germany	Tertiary	Patients with microbiological confirmation of PJP	240	In-hospital ACM *n* = 61/240 (25.4%)

Table 2. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description	No. of patients (*n*, %)	Mortality (type, *n/N*, %)
Schoffelen et al.	2013	RCS MC	June 1996–January 2011	The Netherlands	Multiple	Patients in a national HIV-AIDS registry who developed PJP	PJP: 1055	ACM during follow-up *n* = 125/1055 (11.9%)
Shi et al.	2020	RCS SC	January 2014–December 2018	China	Tertiary	Adults with SRD admitted to the ICU due to acute respiratory failure	Total: 259 Confirmed PJP: 103 (39.8%)	ACM while in ICU (PJP cases) *n* = 69/103 (70.0%)
Singh et al.	2019	RCS SC	March 2014–March 2017	India	Tertiary	Patients with HIV-AIDS and PJP	Total: 76 PCR and microscopy confirming PJP: 17	In-hospital mortality due to respiratory failure in patients with confirmed PJP *n* = 3/17 (17.7%)
Solodokin et al.	2016	RCS SC	January 2009–July 2014	USA	Tertiary	Patients aged <22 years admitted to haematology or oncology who received ≥1 dose of IV pentamidine for PJP prophylaxis	121	ACM during follow-up *n* = 25/121 (20.6%) *PJP-specific mortality NS*
Wang et al.	2019	CCSSC	March 2014–July 2016	China	Tertiary	Patients with HIV-AIDS diagnosed with PJP	80	ACM *n* = 14/80 (17.5%)
Wei et al.	2018	RCSMC	January 2006–December 2013	Taiwan	Multiple	HIV-negative patients with non-Hodgkin's lymphoma	Total: 12 158 Treated with rituximab and developed PJP: 223/7554 (2.95%) Not treated with rituximab and developed PJP: 61/4604 (1.33%)	30-day ACM (treated with rituximab and developed PJP) *n* = 27/223 (12.1%) 60-day ACM (treated with rituximab and developed PJP) *n* = 37/223 (16.6%) 90-day ACM (treated with rituximab and developed PJP) *n* = 48/223 (21.5%)
Yu et al.	2017	RCSSC	January 2009–January 2016	China	Tertiary	HIV-negative patients diagnosed with PJP with or without CMV	Total: 70 CMV-positive: 38 (54.3%) CMV-negative: 32 (45.7%)	Overall ACM *n* = 26/70 (37.1%) ACM (CMV-positive BAL) *n* = 17/38 (44.7%) ACM (CMV-negative BAL) *n* = 9/32 (28.2%)

ACM, all-cause mortality; BAL, bronchioalveolar lavage; CCS, case control study; CMV, cytomegalovirus; GVHD, graft versus host disease; HSCT, haematopoietic stem cell transplant; ICU, intensive care unit; IV, intravenous; MC, multicentre; NS, not stated (by authors); PCS, prospective cohort study; PJP, *Pneumocystis jirovecii* pneumonia; R-CHOP, rituximab/cyclophosphamide/hydroxydaunorubicin/prednisone; RCS, retrospective cohort study; SC, single centre; SOT, solid organ transplant; SRD, systemic rheumatic disease; TMP–SMX, trimethoprim–sulfamethoxazole.
Data reported as it appears in the source papers.

Table 3. Studies describing inpatient care with length of stay associated with *Pneumocystis jirovecii* pneumonia.

Author	Year	Study design	Study period	Country	Level of care	Population description	No. of patients	No. of days in hospital
Báez-Saldaña et al.	2015	RCS SC	January 2010–December 2011	Mexico	Tertiary	Adult patients with HIV-AIDS diagnosed with infectious respiratory disease	Total: 308 Patients with PJP: 142 (46.1%)	13 (IQR: 10–23)
Creemers-Schild et al.	2016	RCS SC	January 2003–July 2013	Netherlands	Tertiary	Adult patients diagnosed with PJP and treated with TMP–SMX	104	Low-dose TMP–SMX: 15 (IQR: 9–24) Intermediate-dose TMP–SMX: 15 (IQR: 8–33)
Lee et al.	2020	RCS SC	January 1997–March 2019	South Korea	Tertiary	Kidney transplant recipients diagnosed with PJP	Total: 1994 Patients with PJP only: 38 (1.9%) Patients with PJP + CMV: 14 (0.7%)	PJP only: 19 (SD: 14.7) PJP plus CMV: 29.7 (SD: 10.8)
Rego de Figueiredo et al.	2019	RCS SC	2011–2016	Portugal	Tertiary	Adult patients diagnosed with PJP	Total: 129 HIV-AIDS: 75 (58.1%) HIV-negative: 54 (41.9%)	Total: 28.3 (SD: 20.8) HIV-AIDS: 27.8 (SD: 22.6) HIV-negative: 29.1 (SD: 18.2)
Shi et al.	2020	RCS SC	January 2014–December 2018	China	Tertiary	Adults with SRD admitted to the ICU due to acute respiratory failure	Total: 259 Confirmed PJP: 103 (39.8%)	22 (IQR: 8–37)
Singh et al.	2019	RCS SC	March 2014–March 2017	India	Tertiary	Patients with HIV-AIDS who developed laboratory-confirmed PJP	PJP diagnosed: 76 Both PCR and microscopic confirmation of PJP: 17 (22.4%)	<4 weeks $n = 12/12$ (100.0%)

CMV, cytomegalovirus; ICU, intensive care unit; IQR, interquartile range; MC, multicentre; PCR, polymerase chain reaction; PJP, *Pneumocystis jirovecii* pneumonia; RCS, retrospective cohort study; SC, single centre; SRD, systemic rheumatic disease; TMP–SMX, trimethoprim–sulfamethoxazole.
Data reported as it appears in the source papers. Numbers of days in hospital reported as median (IQR) or mean (SD) as per source.

Table 4. Studies describing complications and sequelae associated with *Pneumocystis jirovecii* pneumonia.

Author	Year	Study design	Study period	Country	Level of care	Population description	No. of patients	Complications
Kim et al.	2019	RCS SC	2000–2017	South Korea	Tertiary	Kidney transplant recipients aged ≥18 years	Total: 1502 PJP: 68 (4.53%)	Graft failure HR 3.33 (95% CI 1.30–8.53)

PJP, *Pneumocystis jirovecii* pneumonia; RCS, retrospective cohort study; SC, single centre.

Table 5. Studies describing antimicrobial resistance in *Pneumocystis jirovecii.*

Author	Year	Resistance mechanism	Antifungal agent affected	Clinical significance
Argy et al.	2018	Cytochrome *b* (cyt *b*) mutation (A144V)	Atovaquone	Failure of atovaquone prophylaxis in heart transplant patients
Singh et al.	2019	DHPS mutations: novel non-synonymous nucleotide substitution at position 288 (G → A), resulting in amino acid change (Val96Ile)	Trimethoprim–sulfamethoxazole	3 of 12 (25%) HIV-positive adult patients with HIV and PJP were found to have this mutation and died despite treatment with trimethoprim–sulfamethoxazole, while the other 9 survived
Singh et al.	2015	Mutations (nucleotide substitutions) in the dihydrofolate reductase (DHFR) gene	Trimethoprim–sulfamethoxazole	Among a mixed population (HIV-positive and HIV-negative), treated for PJP with trimethoprim–sulfamethoxazole, 2/14 (14%) of patients with DHFR mutations died; both had co-infections, and the DHFR mutations were of uncertain significance

DHFR, dihydrofolate reductase; DHPS, dihydropteroate synthase; HIV, human immunodeficiency virus; PJP, *Pneumocystis jirovecii* pneumonia.

different at 0.61 and 0.53 per 10 000 patient-years in children exposed versus those unexposed to PJP prophylaxis.[60]

In addition, 25 papers reported on underlying risk factors for PJP, and these are shown in Supplementary Table 1.[23,27,31,33,34,36,39,46,54,57,60,62,64–76] Risk factors included HIV infection and various types of immunosuppression, including iatrogenic immunosuppression with SOT patients, particularly kidney transplants, those with autoimmune and inflammatory disease, nephrotic syndrome, and patients with malignancy treated with chemotherapy. Lower CD4 + lymphocyte count was a risk factor in those with HIV (especially <200 cells/mm^3).[71] In older adults, corticosteroids and other immunosuppressants, including biological agents such as rituximab, were reported as associated with a risk of PJP or a poor outcome from PJP across risk groups.[36,74]

Annual incidence

Annual incidence of PJP was reported in 16 studies in various geographical regions and patient populations, as shown in Table 7.[25,27,33,45,49,60,70,77–85] This ranged from 0% in single-centre renal transplant or haematological malignancy patients to 1.2% in one single-centre study of patients with first allogeneic HSCT.[33] National annual incidence varied from 0.67/100 000 in Vietnam (2012)[79] to 22/100 000 in Tanzania (2012),[82] while incidence was estimated in national HIV-positive populations as 230/100 000 in Uruguay (2016)[78] and 15.8/100 000 in the Republic of Congo (2017).[77]

Global distribution

Distribution of PJP was described in 39 studies listed in Table 8.[21,22,24,25,27,30,31,33,36,40,42,45–49,54,55,57,60,64–66,68,70,72,73,76,78,80–84,86–91] *Pneumocystis jirovecii* is globally endemic in the human population and has been reported in patients of all ages and in all regions. Although most studies focused on specific high-risk populations, one multisite case-control study of patients in seven African and Southeast Asian hospitals identified *P. jirovecii* as the causative organism of pneumonia in approximately 2% of paediatric cases.[21] A retrospective multicentre study of patients receiving corticosteroids in the USA from 2000 to 2013 noted a PJP incidence of <1%,[60] compared to 25.9% in a similar patient population in China in a retrospective study from 2013 to 2019.[22]

Emergence trends in the past 10 years

Although, as noted in the introduction, substantial declines in PJP incidence have been reported in HIV-positive individuals over the past decades, with new risk groups emerging, the following studies identified here reported on trends in specific population groups during the past 10 years. In a US study of renal transplant patients, given 1 month of prophylaxis, PJP remained rare with 4 cases among 1352 cases between 2003 and 2009.[57] A Spanish study noted a significant decline in incidence from 13.4 cases per 1000 per year in 2000 to 3.3 cases per 1000 per year in 2013.[25] Decreasing incidence was reported in two studies: one in HIV-positive populations in Brazil, with a reduction from 0.8% over the time period 1987–2002 to 0.3% during the sub-period of 2009–2002,[80] and a Swiss study of SOT recipients reported that transplantation in 2013–2016 was protective compared with transplantation in 2008–2012, transplantation during 2013–2016 (OR: 0.14, 95% CI 0.03–0.6).[27] Increasing incidence in non-HIV settings was reported in one study of immunocompromised patients in Northern Ireland: 6/43 tested in July–December 2008 had PJP (14% positive), compared with 21/230 (9% positive) in January–July 2011[31] and another study of non-HIV patients in Korea in a 2700-bed hospital: annual average cases increased from 12.2 (2003–2007) to 42.2 (2012–2016), with an increasing proportion of infections in non-HIV patients.[40]

Table 6. Studies describing preventatability and prophylaxis against *Pneumocystis jirovecii* pneumonia.

Author	Year	Study design	Study period	Country	Level of care	Population description	Number of patients	Preventative measure	Effectiveness
Anand et al.	2011	RCS SC	2003–2009	USA	Tertiary	Kidney or kidney-pancreas transplant recipients	Total: 1352 Patients with laboratory confirmed PJP: 4 (0.3%)	PJP prophylaxis <30 days	No difference in short vs. long prophylaxis
Awad et al.	2020	RCS SC	January 2014–September 2018	Jordan	Tertiary	Adult HSCT patients receiving IV pentamidine	187	IV pentamidine prophylaxis	No confirmed PJP cases
Báez-Saldaña et al.	2015	RCS SC	January 2010–December 2011	Mexico	Tertiary	Adult patients with HIV-AIDS diagnosed with infectious respiratory disease	Total: 308 PJP: 142 (46.1%)	HAART >180 days	Reduced risk of PJP aOR: 0.245 95% CI 0.08–0.8 ($P = .02$).
Basiaga et al.	2018	RCS MC	May 2000–June 2013	USA	Multiple	Patients aged ≤18 years receiving ≥2 prescriptions of glucocorticoids in <60 days	Total: 119 399 PJP: 6 (0.005%)	TMP–SMX	PJP incidence lower in 0.61 and 0.53 per 10 000 patient-years
Evernden et al.	2020	RCS SC	January 2008–June 2017	Canada	Tertiary	Adult allogenic HSCT patients receiving anti-thymocyte globulin for GVHD prophylaxis	Total: 649 PJP: 21 (32.4%) No PJP: 624 (96.1%)	Adherence to guidelines for prophylaxis	Non-adherence preceded the diagnosis of PJP in 6/8 (75.0%) of patients with GVHD.
Gabardi et al.	2012	RCS SC	January 2004–December 2008	USA	Tertiary	Kidney transplant patients aged ≥18 years	Total: 185 TMP–SMX prophylaxis: 160 Atovaquone prophylaxis: 25	TMP–SMX or atovaquone	No PJP on either drug 12 months post-transplant.
Haeusler et al.	2013	RCS SC	March 2009–June 2012	Australia	Tertiary	Patients who received FCR	Total: 66 PJP: 8/66 (12.1%)	Post-treatment prophylaxis $n = 7/38$ (18.4%, 95% CI 7.7–34.3)	
Kim et al.	2019	RCS SC	2000–2017	South Korea	Tertiary	Kidney transplant recipients aged ≥18 years	Total: 1502 PJP: 68 (4.53%)	TMP–SMX >4 weeks in the post-transplant	Lowered the risk of PJP

Table 6. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description	Number of patients	Preventative measure	Effectiveness
Kitazawa et al.	2019	RCS SC	October 2014–October 2016	Japan	Tertiary	Adults with connective tissue diseases on corticosteroids and PJP prophylaxis	Total:96 TMP–SMX: 55 (57.3%) Pentamidine: 28 (29.2%) Atovaquone: 7 (7.3%)	TMP–SMX daily Aerosolised pentamidine monthly Atovaquone oral daily	No PJP in all prophylaxis groups Well-tolerated
Lee et al.	2021	RCS SC	May 2004–January 2019	South Korea	Tertiary	Adults with diffuse large B-cell lymphoma treated with R-CHOP ± PJP prophylaxis	Total: 739 PJP prophylaxis: 137 (18.5%) No PJP prophylaxis: 602 (81.5%)	PJP prophylaxis	No PJP incidence in prophylaxis group
Neofytos et al.	2018	RCS MC	2008–2016	Switzerland	Multiple	All patients within the national SOT registry of Switzerland	Total: 2842 Diagnosed with PJP: 41 (1.4%)	PJP prophylaxis	Protective for PJP OR: 0.4, 95% CI 0.17–0.9 (P-value = .04)
Nunokawa et al.	2019	NCCS	2005–2014	Japan	Tertiary	RA patients from a national database	Total: 753 60 (8.0%) PJP cases 356 (47.3%) unmatched controls 337 (44.8%) matched controls	Sulfasalazine use RA patients	Lower risk of PJP (unmatched) aOR 0.18, 95% CI 0.00–0.92 Lower risk of PJP (matched) aOR 0.08, 95% CI 0.00–0.36 in the matched study
Wei et al.	2018	RCS MC	January 2006–December 2013	Taiwan	Multiple	HIV-negative patients receiving chemotherapy in a national database	Total: 12 158 Treated with rituximab: 7554 (62.1%) Not treated with rituximab: 4604 (37.9%)	TMP–SMX	First-year survival rate improved 38% vs. 73%

CCS, case control study; CI, confidence interval; GVHD, graft versus host disease; FCR, fludarabine/cyclophosphamide/rituximab; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HSCT, haematopoietic stem cell transplant; IV, intravenous; MC, multicentre; NS, not stated (by authors); PCS, prospective cohort study; PJP, *Pneumocystis jirovecii* pneumonia; R-CHOP, rituximab/cyclophosphamide/hydroxydaunorubicin/prednisone; RA, rheumatoid arthritis; RCS, retrospective cohort study; SC, single centre; SOT, solid organ transplant; TMP–SMX, trimethoprim–sulfamethoxazole.

Table 7. Studies describing annual incidence of *Pneumocystis jirovecii*.

Author	Year	Study design	Study period	Country	Level of care	Population description	No. of patients	Annual incidence
Amona et al.	2020	NPS MC	2018	Republic of Congo	Multiple	Population of the Republic of Congo	5244 000 estimated	Estimated incidence based on cases of HIV-AIDS 15.8/100 000 people
Báez-Saldaña et al.	2015	RCS SC	January 2010–December 2011	Mexico	Tertiary	Adults with HIV-AIDS diagnosed with infectious respiratory disease	Total: 308	PJP cases $n = 142$ (46.1%)
Beardsley et al.	2015	CSS MC	2012	Vietnam	Multiple	Population of Vietnam	Estimated number of PJP cases: 608	Estimated incidence based on cases of HIV-AIDS 0.67/100 000 people
Coelho et al.	2014	RCS SC	1987–2012	Brazil	Multiple	Patients with HIV/AIDS aged ≥18 years with opportunistic infections	Total opportunistic infections: 3378 Opportunistic infections (2009–2012): 268	PJP cases (2009–2012) $n = 22/268$ (8.2%) IRR (2012–2009 vs. 1987–1990) 0.03 ($P < .001$)
Evernden et al.	2020	RCS SC	January 2008–June 2017	Canada	Tertiary	Adult allogenic HSCT patients receiving anti-thymocyte globulin for GVHD prophylaxis	Total receiving PJP prophylaxis: 649	PJP cases 21/649 (3.24%) 3-year cumulative PJP incidence 3.52%
Faini et al.	2015	NPS MC	2012	Tanzania	Multiple	Population of Tanzania	43.6 million estimated. Adults with HIV-AIDS: 1500 000	Estimated incidence based on cases of HIV-AIDS $n = 9600$ ~22/100 000 people
Lagrou et al.	2015	NPS MC	2013	Belgium	Multiple	Population of Belgium	11 million estimated. People with HIV-AIDS ~20 000	Estimated incidence $n = 120$ 1.1/100 000 people

Table 7. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description	No. of patients	Annual incidence
Lopez-Sanchez et al.	2015	RCS SC	January 2000–December 2013	Spain	Tertiary	Adults with HIV-AIDS and PJP	PJP cases: 136	1.3–3.3/1000 person-years
Macedo-Viñas and Denning	2018	CSS MC	2016	Uruguay	Multiple	Population of Uruguay	Population of Uruguay: 3444 006 estimated People with HIV-AIDS ~12 000	Estimated incidence based on cases of HIV-AIDS $n = 48$ 1.4/100 000 people
Neofytos et al.	2018	RCS MC	2008–2016	Switzerland	Multiple	All patients within the national SOT registry of Switzerland	Total: 2842 Diagnosed with PJP: 41	Overall incidence 0.01/1000 person-days (95% CI 0.009–0.02)
Özenci et al.	2019	CSS MC	2016	Sweden	Multiple	Population of Sweden	Population of Sweden: 9995 153 estimated	3/100 000 people
Quinn et al.	2018	RCS SC	January 2007–August 2014	USA	Tertiary	Paediatric oncology patients receiving ≥1 dose of pentamidine	Total: 754 Suspected PJP: 4 (0.5%)	Rate 0.03/1000 patient-days (95% CI 0.009–0.07)
Schmidt et al.	2018	RCS SC	January 2000–June 2017	Germany	Tertiary	Confirmed PJP	Total: 240 HIV-AIDS: 125 (52.1%) SOT: 39 (16.3%) Chemotherapy: 38 (15.8%)	PJP cases annually $n = 13 \pm 5$
Tufa et al.	2019	CSS MC	2017	Ethiopia	Multiple	Population of Ethiopia	105 000 000 estimated People with HIV-AIDS: 12 700 estimated	Estimated incidence 12.1/100 000 person-years IR (HIV-AIDS vs. HIV-negative) 1/6.1

CCS, case control study; CI, confidence interval; GVHD, graft versus host disease; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HSCT, haematopoietic stem cell transplant; IR, incidence ratio; IRR, incidence rate ratio; IV, intravenous; MC, multicentre; NPS, national prevalence study; NS, not stated (by authors); PCS, prospective cohort study; PJP, *Pneumocystis jirovecii* pneumonia; R-CHOP, rituximab/cyclophosphamide/hydroxydaunorubicin/prednisone; RA, rheumatoid arthritis; RCS, retrospective cohort study; SC, single centre; SOT, solid organ transplant; TMP–SMX, trimethoprim–sulfamethoxazole.

Table 8. Studies describing global distribution of *Pneumocystis jirovecii* pneumonia.

Author	Year	Study design	Study period	Country	Level of care	Population description	No. of patients	Prevalence
Anand et al.	2011	RCS SC	2003–2009	USA	Tertiary	Kidney or kidney-pancreas transplant recipients.	Total: 1352	Laboratory confirmed PJP $n = 4/1352$ (0.3%)
Attia et al.	2015	RCS MC	1996–2009	USA	Tertiary	National registry of veterans with HIV-AIDS	Total: 41 993	Incidence of PJP (2006–2009) 0.8% *Raw data NS*
Azoulay et al.	2018	PCSMC	January 2000–December2015	France	Tertiary	ICU patients with haematological malignancies in acute respiratory failure	Total: 1338	Confirmed PJP cases $n = 134/1338$ (10.0%)
Barreto et al.	2016	RCSSC	January 2006–04/2014	USA	Tertiary	Patients aged ≥18 years with B-cell lymphoma receiving R-CHOP	689	PJP cases $n = 10/689$ (1.51%) 95% CI 0.57–2.43
Basiaga et al.	2018	RCSMC	May 2000–June 2013	USA	Multiple	Patients aged ≤18 years receiving ≥2 prescriptions of glucocorticoids in <60 days with or without TMP–SMX.	Total: 119 399	PJP cases $n = 6/119\,399$ (0.005%)
Choi et al.	2018	RCS SC	January 2013–December 2015	South Korea	Tertiary	HIV-negative patients with PJP admitted to ICU for respiratory failure	81	$n = 81$
Coelho et al.	2014	RCSSC	1987–2012	Brazil	Multiple	Patients with HIV/AIDS aged ≥18 years with opportunistic infections	3378	22/7735 2009–2012; 140/18 137 total 1987–2012
Coyle et al.	2012	RCS MC	July 2008–July 2011	Northern Ireland	Multiple	Laboratory confirmed PJP	Total: 53	Clinically significant PJP $n = 51/53$ (96.2%)
Evernden et al.	2020	RCSSC	January 2008–June 2017	Canada	Tertiary	Adult allogenic HSCT recipients receiving anti-thymocyte globulin for GVHD prophylaxis	Total receiving PJP prophylaxis: 649	Confirmed PJP patients $n = 21/649$ (32.4%)
Faini et al.	2015	NPSMC	2012	Tanzania		Tanzanian population	43.6 million estimated Adults with HIV-AIDS 1500 000	Estimated incidence based on cases of HIV-AIDS $n = 9600 \sim 22/100\,000$ people
Figueiredo-Mello et al.	2017	PCSSC	September 2012–July 2014	Brazil	Tertiary	HIV patients with CAP	143	Diagnosed PJP $n = 52/143$ (36%)
Kim et al.	2016	RCSMC	December 2006–July 2013	South Korea	Multiple	Patients aged >18 years with HIV-AIDS	Total: 1086	PJP cases $n = 121/1086$ (11.1%)

Table 8. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description	No. of patients	Prevalence
Kim et al.	2019	RCSSC	2000–2017	South Korea	Tertiary	Kidney transplant recipients aged ≥18 years	Total: 1502	PJP cases *n* = 68/1502 (4.53%)
Lagrou et al.	2015	NPSMC	2013	Belgium	Multiple	Population of Belgium	11 million estimated.People with HIV-AIDS~20 000	Estimated incidence *n* = 1201.1/100 000 people
Lee et al.	2019	RCS SC	February 2003–April 2017	South Korea	Tertiary	Laboratory confirmed PJP with and without HIV-AIDS	Total: 424	*n* = 424
Lee et al.	2020	RCS SC	January 1997–March 2019	South Korea	Tertiary	Kidney transplant recipients	Total: 1994 PJP only: 38PJP and CMV: 14	*n* = 52/1994 (2.6%)
Li et al.	2020	RCS MC	January 2013–December 2019	China	Tertiary	Patients aged ≥16 years with pneumonia treated with glucocorticoids	Total: 716	Total confirmed PJP *n* = 134/716 (18.7%) CAP *n* = 128/635 (20.2%) HAP *n* = 21/81 (25.9%)
Liu et al.	2020	RCS SC	December 2013–December 2018	China	Tertiary	Patients with nephrotic syndrome diagnosed with PJP	57	*n* = 57
Lopez-Sanchez et al.	2015	RCS SC	January 2000–December 2013	Spain	Tertiary	Adult patients with HIV-AIDS diagnosed with PJP	136	*n* = 136 Incidence (2013) 3.3 cases/1000 patients-year
Lum et al.	2020	RCSMC	January 2015–December 2016	USA	Tertiary	SOT recipients aged ≥18 years prescribed PJP prophylaxis	Total: 1173	*n* = 2/1173 (0.2%)
Maartens et al.	2018	PCSMC	November 2011–October 2014	South Africa		Patients aged ≥18 years with HIV-AIDS	500	*n* = 56/500 (11.2%)

Table 8. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description	No. of patients	Prevalence
Macedo-Viñas and Denning	2018	CCSMC	2016	Uruguay	Multiple	Population of Uruguay	Population of Uruguay: 3444 006 estimated People with HIV-AIDS ~12 000	Estimated incidence based on cases of HIV-AIDS $n = 481.4/100\,000$ people
Nam et al.	2020	CCSSC	June 1989–December 2016	South Korea	Tertiary	Cases: immunosuppressed patients with IBD and PJP. Controls: immunosuppressed patients with IBD without PJP.	6803	$n = 6/6803$ (0.09%) 10.4/100 000 person-years
Neofytos et al.	2018	RCS MC	2008–2016	Switzerland	Multiple	All patients within the national SOT registry of Switzerland	Total: 2842	$n = 41/2842$ (1.4%)
Özenci et al.	2019	CSSMC	2016	Sweden	Multiple	Population of Sweden	9995 153 estimated	$n = 297/9995\,153$ (0.003%)
Park et al.	2020	CSSSC	1999–2015	South Korea	Tertiary	Cases: Patients with kidney or kidney-pancreas transplant and PJP Controls: Patients with kidney or kidney-pancreas transplants	Total: 161 Cases: 67/161 (41.6%) Controls: 94/161 (58.4%)	$n = 67/161$ (41.6%)
PERCH Study Group	2019	CCS MC	August 2011–January 2014	Bangladesh, The Gambia, Kenya, Mali, South Africa, Thailand, Zambia	Multiple	Cases: children aged 1–59 months admitted to hospital with severe pneumonia. Controls: age-group-matched children randomly selected from communities surrounding study sites.	Total: 9351 Cases: 4232 Controls: 5119	PJP in NP/OP specimens $n = 692/8894$ (7.8%)
Quinn et al.	2018	RCSSC	January 2007–August 2014	USA	Tertiary	Paediatric oncology patients who received ≥1 dose of pentamidine for PJP prophylaxis	754	$n = 4/754$ (0.5%)
Rekhtman et al.	2019	RCSMC	December 2012–December 2017	USA	Multiple	Patients aged ≥18 years treated with immunosuppressive drugs or corticosteroids who had neither HIV-AIDS or cancer	3366 086	$n = 406/3366\,086$ (0.012%)

Table 8. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description	No. of patients	Prevalence
Saeed et al.	2015	RCSSC	January 2009–May 2013	Bahrain	Tertiary	HIV-AIDS patients with or without opportunistic infections	194	Total $n = 10/194$ (5.1%) HIV-AIDS with opportunistic infection $n = 10/66$ (15.1%)
Schmidt et al.	2018	RCS SC	January 2000–June 2017	Germany	Tertiary	Patients with microbiological confirmation of PJP	240	$n = 240$
Schoffelen et al.	2013	RCS MC	June 1996–January 2011	The Netherlands	Multiple	Patients in a national HIV-AIDS registry who developed PJP	Patients in registry $n = 13\,844$	PJP $n = 1055/13\,844$ (7.6%)
Shi et al.	2020	RCS SC	January 2014–December 2018	China	Tertiary	Adults with SRD admitted to the ICU due to acute respiratory failure	259	$n = 103/259$ (39.8%)
Singh et al.	2015	RCSSC	NS	India	Tertiary	Patients with clinical suspicion of PJP	Total $n = 180$ Adults $n = 150$ (83.3%) Children $n = 30$ (16.7%)	PJP confirmed by PCR $n = 18/180$ (10.0%)
Singh et al.	2019	RCS SC	March 2014–March 2017	India	Tertiary	Patients with HIV-AIDS and PJP	Clinically suspected PJP $n = 76$	PJP confirmed by both microscopy and PCR $n = 17/76$ (22.4%)
Wei et al.	2018	RCSMC	January 2006–December 2013	Taiwan	Multiple	HIV-negative patients with NHL who did or did not receive rituximab	Total $n = 12\,158$ Rituximab treated $n = 7554$ (62.1%) No rituximab $n = 4604$ (37.9%)	PJP in rituximab treated $n = 223/7554$ (2.95%) PJP in no rituximab $n = 61/4604$ (1.33%)
Yukawa et al.	2018	CCSSC	January 2010–December 2014	Japan	Tertiary	Patients with RA who did not receive TMP–SMX	$n = 2640$	$n = 19/2640$ (0.7%)

CAP, community acquired pneumonia; CCS, case control study; CI, confidence interval; GVHD, graft versus host disease; HAART, highly active antiretroviral therapy; HAP, hospital acquired pneumonia; HIV, human immunodeficiency virus; HSCT, haematopoietic stem cell transplant; IV, intravenous; MC, multicentre; NPS, national prevalence study; NS, not stated (by authors); PCS, prospective cohort study; PJP, *Pneumocystis jirovecii* pneumonia; RA, rheumatoid arthritis; RCS, retrospective cohort study; SRD, systemic rheumatic diseases; SC, single centre; SOT, solid organ transplant; TMP–SMX, trimethoprim–sulfamethoxazole.

Discussion

This review examines the epidemiology and global impact of *P. jirovecii* and the associated disease, *P. jirovecii* pneumonia, and was initially performed to inform the WHO FPPL.[17] Due to the extensive scope of the review and its inclusion/exclusion criteria, 41% of included studies were classified as unclear or at high risk of bias, which may influence the reliability of some results.

Most studies reported a stable incidence of PJP over the past 10 years, but declines among people with HIV were counterbalanced by increasing infections in some new at-risk populations, including SOT patients and those on newer immunosuppressive therapies. Variability of incidence among various geographical regions and patient populations reflects different at-risk populations and prevention strategies. A more recent study reported stable incidence in France, but this study was published after our search window closed.[92]

Mortality with PJP was substantial but highly variable, ranging from 4% to over 75%. In general, mortality in persons with PJP was lower in HIV-positive populations than in non-HIV populations. Assessment of the burden of mortality and disease is, however, complex for PJP, due not only to important differences in comorbidities among those at risk but also to the impact of early diagnosis and antiretroviral therapy in HIV-infected individuals. A meta-analysis on HIV-associated PJP from 2016 conducted in Sub-Saharan Africa found attributable mortality of ∼7%, with an overall mortality of 19%.[6] In our review, inpatient care and LOS were also variable, with LOS ranging from 0 to 123 days, again reflecting different populations and healthcare systems. We reported on sequelae of graft failure following PJP in renal transplant patients,[54] and more recently, complications of restrictive lung disease, bronchiectasis, and pulmonary cysts have been reported in patients with HIV and PJP, emphasising the importance of prevention of this disease.[93]

Risk factors for PJP included HIV infection and various other forms of immunosuppression, including iatrogenic immunosuppression with SOT, especially renal transplantation, patients with autoimmune and inflammatory disease, those with nephrotic syndrome, and patients with malignancy receiving chemotherapy. Extensive data on PJP prophylaxis, principally with TMP–SMX, demonstrates it is highly efficacious but not always taken. In one study identified in our search, but later excluded as no patients developed PJP, 24% of renal transplant patients (21/88) discontinued TMP–SMX prophylaxis within 1 year, with a variety of side effects reported.[94] Our review identified one study in which adjunctive corticosteroids were associated with reduced mortality in severe but not moderate-severe PJP in HIV-negative individuals.[37] While the use of these agents for severe HIV-associated PJP is standard, it should be noted that adjunctive therapy in non-HIV-associated disease remains controversial.[95] More recently, combination antifungal therapy with echinocandins or ibrexafungerp has also shown potential benefit as either adjunctive therapy in observational studies or as single-agent prophylaxis in animal models, with clinical trials awaited.[96–98]

TMP–SMX is generally the first-line treatment for PJP: TMP targets dihydrofolate reductase (DHFR) and SMX targets dihydropteroate synthase (DHPS), two key enzymes in *P. jirovecii* folate synthesis. Phenotypic susceptibility testing is not available for *P. jirovecii*, so minimum inhibitory concentrations cannot be estimated and clinical breakpoints cannot be established. Researchers have therefore attempted to identify molecular markers of 'resistance', and several studies have reported on mutations with a theoretical role in resistance to TMP–SMX or atovaquone (the target of which is cytochrome B). However, no clear link has yet been established between the presence of specific mutations and treatment failure or mortality. In fact, a 2016 consensus guideline reviewed the evidence for screening for DHPS mutations and recommended against use, concluding that mutations are not associated with TMP–SMX treatment failure at the doses given.[10] It is important that the role of TMP–SMX is not undermined without strong evidence, since it is accessible and affordable globally and often provided in HIV treatment programmes. Alternative medications, critical for patients who cannot tolerate TMP–SMX, are much less available in low- and middle-income countries.

Diagnostics for PJP remain limited and variable, affecting the interpretation of results in reports using different methods. The significance of molecular mutations remains to be further explored. *Pneumocystis jirovecii* colonisation is a major challenge in determining diagnostic cut-offs for colonisation versus disease. The development of novel diagnostics, preferably point-of-care, is urgently required.

Given changing epidemiology among at-risk groups and ongoing challenges with diagnosis, areas for further research include risk factors for PJP acquisition and mortality, especially in at-risk populations other than people living with HIV. Most patients included in studies are adults, while specific paediatric PJP population data is relatively sparse. The availability of drugs for the early treatment of HIV as well as advanced treatment for cancer and biological drugs also affects preventability, risk factors, and outcomes. Methods to account for these are needed. Information on annual incidence is limited worldwide, and established surveillance systems for fungal infections in immunocompromised patients are generally lacking. A standardised approach to assess the incidence of PJP and fungal infections more generally in at-risk populations is needed.

This systematic review has limitations. Including the exclusion of studies published in languages other than English and important studies published prior to 2011, given important trends in HIV management prior to this time, and the effects of this on PJP epidemiology. The exclusion of conference abstracts and pre-prints may have biased the findings, and the exclusion of review articles may mean missed opportunities to identify further relevant articles. The substantial heterogeneity of studies, reflected somewhat in the variability of results, limits the ability to draw universally generalisable conclusions. Nonetheless, this review does present a comprehensive effort to assess the epidemiology and global impact of an important infection.

Conclusion

Pneumocystis jirovecii causes substantial morbidity and mortality globally as an opportunistic infection causing pneumonia in immunocompromised individuals, including persons with HIV and those with non-HIV immunosuppression. Infections due to this organism are generally preventable and treatable if at-risk groups receive appropriate prophylaxis and infected individuals are promptly diagnosed. Access to diagnostics, prevention, and treatment is, however, variable. Increased test availability and affordability, better characteri-

sation of non-HIV risk groups, and provision of alternative medicines for persons who cannot receive TMP–SMX, due to allergy or side effects, are required. *Pneumocystis jirovecii* remains an important pathogen in HIV-positive persons and in new risk groups, highlighting the importance of collaborative efforts in mitigating the impact of these infections on global health.

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Author contributions

Brendan McMullan (Data curation, Formal analysis, Investigation, Project administration, Validation, Writing – original draft), Hannah Yejin Kim (Data curation, Formal analysis, Investigation, Project administration, Writing – review & editing), Ana Alastruey-Izquierdo (Conceptualization, Data curation, Writing – review & editing), Evelina Tacconelli (Formal analysis, Writing – review & editing), Aiken Dao (Data curation, Project administration, Writing – review & editing), Rita Oladele (Data curation, Writing – review & editing), Daniel Tanti (Data curation, Writing – review & editing), Nelesh P. Govender (Data curation, Writing – review & editing), Jong-Hee Shin (Data curation, Writing – review & editing), Jutta Heim (Data curation, Writing – review & editing), Nathan Paul Ford (Data curation, Writing – review & editing), Benedikt Huttner (Data curation, Writing – review & editing), Marcelo Galas (Data curation, Writing – review & editing), Saskia Andrea Nahrgang (Data curation, Writing – review & editing), Valeria Gigante (Data curation, Project administration, Writing – review & editing), Hatim Sati (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Writing – review & editing), Jan Willem Alffenaar (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – review & editing), C. Orla Morrissey (Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Writing – review & editing), and Justin Beardsley (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing)

Supplementary material

Supplementary material is available at *Medical Mycology* online.

Conflict of interest

The authors declare no conflict of interest.

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