

Review

Airborne Interindividual Transmission of *Pneumocystis jirovecii*Laurence Pougnet^{1,2,*}, Solène Le Gal^{1,3}, Gilles Nevez^{1,3,*}

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Received: December 17, 2018**Accepted:** May 15, 2019**Published:** May 22, 2019**Abstract**

Pneumocystis pneumonia (PCP) is the most frequent AIDS-defining disease among HIV-infected individuals in developed countries, and also affects immunocompromised non-HIV patients. Experimental studies on rodent models carried out in the early eighties have shown that *Pneumocystis* spp. can be transmitted via the airborne route. Unfortunately, this mode of acquisition and transmission has long been overlooked by physicians because PCP in immunosuppressed patients was considered to result from reactivation of a latent endogenous infection. This hypothesis was further investigated and, at present, PCP is considered to frequently result from the *de novo* acquisition of the fungus. This paradigm shift is correlated with the development of highly sensitive detection techniques and molecular characterization of *Pneumocystis* spp. in animal models and humans. This review article describes the milestones that have been achieved on the knowledge on the airborne interindividual transmission of *Pneumocystis jirovecii*.



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Keywords

Pneumocystis jirovecii; hospital hygiene; airborne transmission; outbreaks; *Pneumocystis pneumonia*

1. Introduction

Pneumocystis jirovecii is an opportunistic, transmissible fungus that infects humans [1]. It causes severe pneumonia (*Pneumocystis pneumonia* or PCP) in immunocompromised patients. PCP is the most frequent AIDS-defining disease in developed countries and approximately 30% of the AIDS cases (1,200) in France were related to PCP during 2013 [2]. These data are consistent with the report on opportunistic infections in a multicohort analysis of 63,541 North-American HIV-infected patients between 2000 and 2010. During this period, PCP was the most frequent AIDS-defining disease. There were about 1,000 PCP cases per 100,000 person-years between 2000 and 2004 regardless of the immune status or antiretroviral therapy. This incidence decreased gradually to about 250 PCP cases per 100,000 person-years in 2010 [3]. PCP incidence in the world might have exceeded 400,000 cases per year in 2012 with more than 52,000 deaths per year [4]. Patients with other immune deficiencies also develop PCP. The patients who are receiving cytostatic and immunomodulatory treatments and those with solid organ transplants or with malignancies are at the highest risk [5]. The number of PCP cases in France is estimated to be 300 per year in HIV-infected patients and 600 per year in other immunocompromised patients [2, 6]. The fatality rate of PCP in France increased from 5% to 15% between 2001 and 2010 [7]. Moreover, according to the national database of the Medicalization of Information Systems in Medicine, Surgery, and Obstetrics, the number of inpatient hospitalizations due to PCP increased by 60% between 2010 and 2017, from 526 to 846, mostly due to PCP in non-HIV patients [8]. Torpid *P. jirovecii* infections may occur in patients with chronic bronchial and pulmonary diseases, such as chronic obstructive pulmonary disease (COPD). Moreover, *P. jirovecii* infections have been linked to severe COPD [9]. Therefore, *P. jirovecii* infection is a public health issue.

Pneumocystis is an atypical fungus that cannot be routinely cultured, and therefore, animal models are to be used to study the transmission mode and pathogenicity. Moreover, animal models are worth investigating since the clinical presentation of PCP is similar in animals and in humans. The experimental studies on rodent models have shown that *Pneumocystis* spp. can be transmitted via the airborne route [10, 11]. Despite these studies, this mode of acquisition and transmission has long been overlooked by physicians due to PCP infection in immunocompromised adult patients was believed to be mostly from endogenous latent *P. jirovecii* organisms that are carried within alveoli since childhood [12]. However, recent studies have indicated that PCP occurs due to *de novo* acquisition rather than reactivation of latent infection [12]. Host specificity of *Pneumocystis* spp. has led to the naming of different species in the genus according to the binominal system [13]. For instance, *Pneumocystis carinii*, *Pneumocystis murina*, and *Pneumocystis jirovecii* infects rats, mice, and humans, respectively [13]. Considering this host specificity, an animal reservoir for *P. jirovecii* was excluded.

In this context, our aim was to compile the latest available information on the epidemiology of *Pneumocystis* spp. established in rodent models and humans, specifically on the airborne interindividual transmission of the fungus and to provide a rationale for hygiene measures to prevent *P. jirovecii* transmission in hospitals.

2. Contribution of Rodent Models

The results of the main studies on *Pneumocystis* sp. airborne acquisition and/or transmission using rodent models are summarized (Table 1).

Airborne acquisition and transmission of *P. carinii* were established in the 1980s [11,14]. Later, Choukri and colleagues. described the kinetics of *P. carinii* exhalation by the immunocompromised rats developing PCP [15]. A correlation between lung fungal burdens of rats and air fungal burdens was highlighted during the first month of PCP development with a ratio of approximately $10^6:1$. The kinetics of *P. carinii* exhalation in immunocompetent rats developing primary infection and reinfection was also investigated, which suggested that the immune response impacts the pulmonary fungal burden as well as *P. carinii* exhalation [16]. Further investigation on the relationship between *P. carinii* pulmonary burden and the immune status [17] suggested a correlation between the airborne acquisition of *P. carinii* and the level of immunosuppression.

Some experiments in mice [11, 18, 19] revealed that immunocompromised mice developing PCP can transmit *P. murina* via the airborne route to other susceptible immunosuppressed mice and to immunocompetent mice. Immunocompetent mice can be colonized by *P. murina* that can transmit *P. murina* to immunosuppressed susceptible mice as well as to other immunocompetent mice [18, 19]. In order to identify the putative infectious stage of *Pneumocystis* sp., experiments were conducted with echinocandin-treated mice, and the findings showed that ascus is necessary for *P. murina* transmission [20]. A recent study on *Pneumocystis* life cycle suggested that the ascospores located in the asci could be the putative infectious stage [21].

In summary, both immunosuppressed rodents and immunocompetent rodents can acquire *Pneumocystis* sp. and exhale the fungus into the surrounding air. Nonetheless, the level of *Pneumocystis* sp. acquisition and exhalation seems to be correlated to the level of immunosuppression and the severity of the infection. The putative infectious stage may be the ascus or the ascospore.

Table 1 Main studies on *Pneumocystis* sp. airborne acquisition and/or transmission using rodent models.

Model	References	Immune status	Main points
Rats	Hughes WT [10] Hughes et al. [14]	Immunosuppression (corticosteroid treatment)	The rats did not acquire <i>P. carinii</i> when maintained in filtered air conditions, but acquired <i>P. carinii</i> and developed PCP when they were exposed to the air from the animal facilities. They also acquired <i>P. carinii</i> and developed PCP when exposed to the exhaled air from conventional Sprague-Dawley rats.
	Choukri et al. [15]	Immunosuppression (Lou nu/nu rats, corticosteroid treatment)	The objective was to describe the kinetics of <i>P. carinii</i> exhalation by athymic Lou nu/nu rats developing PCP after intratracheal inoculation of the fungus. The Coriolis® µ air sampler (Bertin Technologies, France) was used to collect air samples from a HEPA-filtered air chamber containing one rat developing PCP. <i>P. carinii</i> was detected and quantified using a qPCR assay at the mtLSUrRNA gene in air samples over a period of at least 7 weeks after inoculation. The results showed that the <i>P. carinii</i> quantity in the air increased for up to 4-5 weeks. Moreover, there was a correlation between <i>P. carinii</i> burdens in the lungs and in air samples during the first month of PCP development with a 10 ⁶ /1 ratio.
	Menotti et al. [16]	Immunocompetency	The objective was to describe the kinetics of <i>P. carinii</i> exhalation by immunocompetent Sprague-Dawley rats developing primary infection and re-infection. <i>P. carinii</i> was detected in the air surrounding the rats developing primary infection between the 2 nd and 3 rd weeks of infection, with a correlation between <i>P. carinii</i> burdens in air and pulmonary samples. <i>P. carinii</i> was not detected in the surrounding air of re-infected immunocompetent rats, which harbored low fungal burdens.
	Khalife et al. [17]	Immunosuppression (Lou nu/nu rats, corticosteroid treatment)	Sprague Dawley rats were treated with different doses of dexamethasone (receivers) and cohoused during 2 weeks with athymic Lou nu/nu rats developing PCP (seeders). The first population of rats undergoing gradual immunosuppression levels acquired <i>P. carinii</i> from the second one. In receiver rats, there was an inverse correlation between <i>P. carinii</i> pulmonary burdens and the CD4+ cell and CD8+ cell counts in

			blood. The results suggested a correlation between the airborne acquisition of <i>P. carinii</i> and the level of immunosuppression.
Mice	Soulez et al. [11]	Immunosuppression (SCID mice, corticosteroid treatment)	A colony of twenty <i>P. murina</i> -free SCID mice shared the same air during one day with a Balb/c mouse developing corticosteroid-induced PCP. The colony acquired <i>P. murina</i> and later developed PCP. The results showed <i>P. murina</i> is highly transmissible in mice.
	Dumoulin et al. [18]	Immunosuppression (SCID mice) Immunocompetency (Balb/c mice)	<i>P. murina</i> -infected SCID mice were co-housed with <i>P. murina</i> -free Balb/c mice for 1, 5, or 20 days. These immunocompetent Balb/c mice acquired <i>P. murina</i> , were transiently colonized by <i>the fungus</i> , but did not develop PCP. They were then co-housed with <i>P. murina</i> -free immunosuppressed SCID mice which then acquired <i>P. murina</i> and later developed PCP. Thus, immunocompetent mice were able to acquire, to be transiently colonized, and to transmit <i>P. murina</i> to susceptible immunosuppressed <i>P. murina</i> -free mice.
	Gigliotti et al. [19]	Immunocompetency (Balb/c mice)	<i>P. murina</i> -exposed Balb/c mice were co-housed with <i>P. murina</i> -free Balb/c mice. The latter mouse population seroconverted to <i>P. murina</i> antigens secondarily to the exposure which is consistent with <i>P. murina</i> acquisition.
	Cushion et al. [20]	Immunosuppression (CH/HeN mice corticosteroid treatment)	The echinocandins inhibit (1,3)- β -D-glucan synthesis, which is the major component of the cell wall of most fungi, including the asci of <i>Pneumocystis</i> sp. Infected mice treated with anidulafungin only harbored <i>P. murina</i> trophic forms since (1, 3)- β -D-glucan is assumed to be absent in these stages. In this study, infected mice treated with echinocandins were not able to transmit <i>P. murina</i> to susceptible immunosuppressed mice, while untreated mice developing PCP and harboring both asci and trophic forms were able to do so. These results strongly suggest that the ascus was necessary for <i>Pneumocystis</i> sp. transmission.

3. Transmission of *Pneumocystis jirovecii* in Hospitals

PCP outbreaks occurring in hospitals over the past 60 years favor the hypothesis of interindividual transmission of *P. jirovecii*. Between 1968 and 2019, almost 60 outbreaks were described worldwide, mainly in renal transplant recipients as well as in HIV-infected and cancer patients [22-41]. Although interindividual transmission of *P. jirovecii* was suggested, it remained hypothetical until 1998 due to the absence of genotyping methods. Several other studies of outbreaks, which combined the concordance of *P. jirovecii* genotypes in index patients and susceptible patients with the analysis of patient encounters, supported the nosocomial acquisition and interindividual transmission of the fungus. In 2012, Le Gal and colleagues showed that both PCP patients and *P. jirovecii* colonized patients may be possible infectious sources of the fungus [23]. These results were confirmed by two other investigations on *P. jirovecii* outbreaks, one in renal transplant recipients and another in heart transplant recipients [29, 32]. Interestingly, during the course of the latter outbreak, a *P. jirovecii* cytochrome b mutant was observed exclusively in the heart transplant recipients and not in the control patients; the mutation may provide putative resistance to atovaquone, an anti-infectious agent targeting the cytochrome b [28]. Outbreaks in liver transplant recipients have also been investigated, which provided additional information on the putative interindividual transmission of *P. jirovecii* [35, 42].

The main findings on *P. jirovecii* exhalation from PCP patients and colonized patients into the surrounding air in hospitals are summarized in Table 2.

By the end of the 1990s, two important studies detected and identified *P. jirovecii* genotypes from patient rooms [43, 44]. A perfect or partial similarity was observed in *P. jirovecii* genotypes of clinical and air samples. These results are consistent with the findings on *P. jirovecii* exhalation from PCP patients and the subsequent putative airborne transmission of *P. jirovecii*. Another study demonstrated *P. jirovecii* exhalation in an intubation system by a patient developing PCP and monitored in an Intensive Care Unit [49].

In 2010, *P. jirovecii* DNA was detected at 1, 5, and 8 m distance from PCP patients and *P. jirovecii* DNA burdens in air samples decreased with the distance of sampling [45]. A perfect or partial similarity was observed in *P. jirovecii* genotypes of clinical and air samples [46]. The spread of *P. jirovecii* from both PCP patients and colonized patients was investigated using the same method [47, 48]. *P. jirovecii* burdens in the air samples from colonized patients appeared lower than those collected from the air surrounding PCP patients. This indicates that *P. jirovecii* can be exhaled and spread from both PCP patients and colonized patients. However, whether colonized patients represent infectious sources at the same level as PCP patients is still an open question considering the difference in pulmonary fungal burden [47, 50]. The major findings of *P. jirovecii* genotyping clinical samples and air samples are summarized (Table 2).

Table 2 Main studies on *Pneumocystis jirovecii* genotyping in clinical and air samples.

References	Clinical presentation of <i>P. jirovecii</i> infection	Main points
Bartlett <i>et al.</i> [43]	<i>Pneumocystis pneumonia</i>	<i>P. jirovecii</i> DNA was amplified by PCR with primers specific for the internal transcribed spacer (ITS) regions of rRNA. <i>P. jirovecii</i> DNA was found in 17 of 30 air samples (57%) from the rooms of Pneumocystis-infected patients. It was also found in 6 of 21 other hospital rooms sampled (29%) but was not found in any of the offices, storage areas, or control homes. Genotyping results were available for 14 pairs of clinical/air samples with a perfect match in 10 of 14, a partial match in 2 of 14, and a discordance in 2 of 14. The results suggested the airborne presence of <i>P. jirovecii</i> organisms within the hospital environment.
Olsson <i>et al.</i> [44].	<i>Pneumocystis pneumonia</i>	<i>P. jirovecii</i> DNA was amplified by PCR with primers specific for the mitochondrial large-subunit rRNA (mtLSU rRNA) gene in pulmonary samples from seven PCP patients and in some air samples (five out of seven PCP patients' rooms and two of four air filtrations from the ward corridors). The <i>P. jirovecii</i> genotypes at the ITSs were available for five pairs of clinical/air samples, resulting in a perfect match in 3 of 5, a partial match in 1 of 5, and discordance in 1 of 5. The results suggested a risk of person-to-person transmission of <i>P. jirovecii</i> from PCP patients and airborne presence of <i>P. jirovecii</i> organisms within the hospital environment.
Choukri <i>et al.</i> [45]. Damiani <i>et al.</i> [46].	<i>Pneumocystis pneumonia</i>	The experiments were conducted using the Coriolis μ air sampler (Bertin Technologies, France), which concentrates aerial particles in a liquid medium to facilitate the DNA extraction process and consequently the subsequent PCR assays. <i>P. jirovecii</i> DNA was amplified using a real-time PCR assay with primers specific for the mtLSU rRNA gene in 4 of the 12 air samples collected at an 8-meter distance, in 5 of the 12 samples collected at a 5-meter distance, 9 of the 13 samples collected at a 3-meter distance, and 15 of the 19 samples collected at a one-meter distance from PCP patients' heads. <i>P. jirovecii</i> DNA quantities decreased with distance from the patients ($P < .002$). Forty control samples were collected and remained negative. In a second

		<p>study investigating the same patients and air samples, <i>P. jirovecii</i> genotypes at the ITS and DHPS loci were available for 6 of 7 pairs of clinical samples and air samples with a perfect match in 4 of 6, and a partial match in 2 of 6. These studies provided the first quantitative data on the spread of <i>P. jirovecii</i> in exhaled air from PCP patients.</p>
Le Gal <i>et al.</i> [47]	<i>Pneumocystis pneumonia</i> Pulmonary colonization	<p>In this study, <i>P. jirovecii</i> was detected and characterized in the air surrounding the patients with <i>Pneumocystis</i> pulmonary colonization. Using the same methods as described by Choukri and colleagues. <i>P. jirovecii</i> DNA was detected in 5 of 10 air samples collected at 1 m from patients' heads and in 5 of the 10 other air samples collected at 5 m from patients' heads. <i>P. jirovecii</i> genotypes at the mtLSU rRNA gene were available in 4 pairs or triplets of air and pulmonary samples. Full genotype matches were observed in 3 of the 4 pairs or triplets of air and pulmonary samples. <i>P. jirovecii</i> burdens in the air samples from colonized patients appeared lower than those from PCP patients. These results provided original data supporting <i>P. jirovecii</i> exhalation from colonized patients and hypothesized the risk of <i>P. jirovecii</i> nosocomial transmission from this patient population.</p>
Fréalles <i>et al.</i> [48]	Pulmonary colonization	<p><i>P. jirovecii</i> DNA was detected using the same methods as described by Choukri et al. in 3 of 17 air samples at a one-meter distance, and in none of 17 air samples at a 5-meter distance from three colonized patients. <i>P. jirovecii</i> genotypes at the mtLSU rRNA gene were available in the three couples of clinical and air samples with a perfect match. These data brought additional arguments for putative exhalation of <i>P. jirovecii</i> by colonized patients.</p>

4. Prevention of *Pneumocystis jirovecii* Transmission in Hospitals

High pulmonary tropism of *P. jirovecii* combined with the data on *P. jirovecii* exhalation from infected patients as well as the occurrence of clusters of PCP cases are consistent with the airborne acquisition in humans and emphasize the risk of patient-to-patient transmission through this mode. Chemoprophylaxis is essential to prevent *P. jirovecii* infection. However, the measures based on chemoprophylaxis alone may not be sufficient to ensure PCP prevention.

Measures to prevent healthcare-associated infections are usually classified as standard, droplet, or airborne. This classification is based on transmission mode, transmitted particle size, and microorganism infectivity over time and distance. Droplet precaution procedures consist of i) placing the patient in a single room, ii) use of surgical masks by health-care workers and visitors, iii) limiting patient movement out of the room, and iv) use of masks by patients when out of their rooms [51]. Airborne precaution procedures consist of i) placing the patient in a single room with doors closed or with special air treatment, ii) use of respirator masks (e.g., N95) by health-care workers, iii) limiting patient movement out of the room, and iv) use of masks by patients when out of their rooms [51].

Centers for Disease Control and Prevention recommend chemoprophylaxis for susceptible persons to prevent PCP [52]. It is also recommended to implement standard precautions and avoid placement of a PCP patient with an immunocompromised patient in the same room [51]. Considering the knowledge gained on *Pneumocystis* transmission over the past ten years, these recommendations should be updated. The transmissible stage of *P. jirovecii* is assumed to be the ascus or the ascospores [20, 21]. Unfortunately, the median size of the ascus (5 μm) is precisely the threshold value for distinguishing droplet and air precaution measures. Moreover, whether *Pneumocystis* transmission occurs through Flüggé droplets or because *Pneumocystis* aerosolizes itself through the ascospores remains unknown.

Nonetheless, the data pertaining to the transmission of *Pneumocystis* spp. in rodent models and humans are now sufficient to recommend preventive measures, either airborne or droplet. *P. jirovecii* detection in the surrounding air at 5 m (or even 8 m) distance [45, 47] favors air precautions. However, air precautions are tough to implement. When the engineering resources are limited, preventing airborne transmission consists of placing a patient in a single room with doors closed and wearing respirator masks when in contact with the patient [51].

The application of droplet precautions was proposed in France in the late nineties [53, 54]. However, these recommendations have been poorly applied and at least 10 clusters of PCP cases occurred in France over the past two decades [23, 29, 30, 32, 33, 35, 40, 41, 55, 56]. Since the exhalation of *P. jirovecii* by infected patients can be observed beyond 1 m distance [45, 47, 48], airborne precautions may be more suitable.

Nonetheless, whichever precaution is implemented, no study has reported their duration. As an initial approach to address this issue, we investigated the longitudinal *P. jirovecii* air exhalation by a patient developing PCP and efficiently treated with cotrimoxazole [57]. Five air samples were collected after treatment initiation on five consecutive days in the patient's room at 1 m distance from the patient head. *P. jirovecii* DNA was detected in the five air samples. This study showed that PCP treatment dramatically decreased *P. jirovecii* exhalation, which suggests maintaining preventive measures, whatever they may be, for at least five days following PCP treatment initiation [57].

Further, precautions should be proposed to prevent *P. jirovecii* transmission from patients developing PCP who may be highly contagious. Whether precautionary measures should be implemented for colonized patients or healthcare workers who may have a role in the transmission chain remains a subject of debate [33, 50, 58]. Through In a different approach, the French Hygiene Society recommends that susceptible patients should wear a mask when encountering all other patients [59].

In conclusion, *P. carinii* and *P. murina* transmission via the airborne route has been clearly established in rodents, and *P. jirovecii* airborne transmission is highly probable in humans. Chemoprophylaxis is essential in susceptible patients; however, it may not be sufficient to completely prevent *P. jirovecii* infection. Measures must be implemented to prevent interindividual transmission of *P. jirovecii* specifically from PCP patients in hospitals who seem to be highly infectious. At present, there are strong arguments in favor of air precautions. However, considering the challenges in their implementation, at least droplet precautions must be implemented. Nonetheless, these measures are still subject to debate; therefore, an update through a consensus conference is recommended.

Author Contributions

The three authors contributed equally to this work.

Competing Interests

The authors have declared that no competing interests exist.

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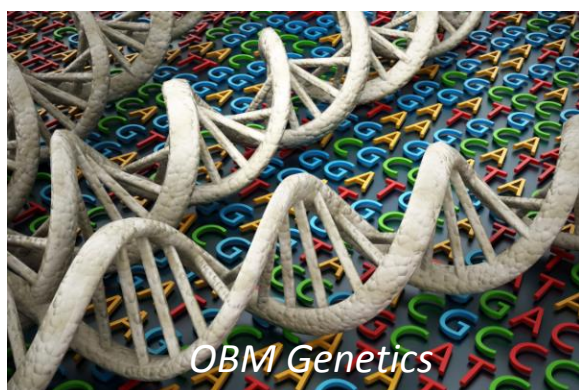
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