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Review Article

Mimiviridae, Marseilleviridae, and virophages as emerging human pathogens causing healthcare-associated infections

Mimiviridae, Marseilleviridae und Virophagen als Erreger von Healthcare-assoziierten Infektionen mit wachsender Bedeutung

Abstract

Aim: During the last decade it became obvious that viruses belonging to *Mimiviridae* and *Marseilleviridae* families (order Megavirales), may be potential causative agents of pneumonia. Thus, we have performed a review of the association of *Mimiviridae*, *Marseilleviridae*, and virophages with pneumonia, particularly healthcare-associated pneumonia, and other infections of the respiratory tract.

Results and discussion: According to the analysis of the published articles, viruses belonging to Mimiviridae family can be potential agents of both community-acquired and healthcare-associated pneumonia. In particular, these viruses may be associated with poor outcome in patients of intensive care units.

The exact mechanism of their pathogenicity, however, still remains unclear. The discrepancies between the results obtained by serological and genomic methods could be explained by the high polymorphism of nucleotide sequences of *Mimiviridae* family representatives. Further investigations on the *Mimiviridae* pathogenicity and on the determination of *Mimiviridae*-caused pneumonia risk groups are required.

However, the pathogenicity of the viruses belonging to *Marseilleviridae* family and virophages is unclear up to now.

Keywords: mimivirus, mimiviridae, marseilleviridae, giant viruses, virophages, pneumonia, healthcare-associated infections

Zusammenfassung

Zielsetzung: Im letzten Jahrzehnt wurde vermutet, dass Viren der Familie der *Mimiviridae* und der *Marseilleviridae* (sog. Megavirales) Pneumonien verursachen können. Deshalb wurde eine Literaturrecherche zu den möglichen Zusammenhängen von *Mimiviridae*, *Marseilleviridae*, Virophagen und Pneumonien mit den Schwerpunkten HA-Infektionen und andere Infektionen der Atemwege durchgeführt.

Ergebnisse und Diskussion: Die Analyse ergab, dass Viren aus der Familie der *Mimiviridae* potentielle Verursacher sowohl der CA- als auch der HA-Pneumonie sein können. Diese Viren können zu einem verschlechterten Outcome bei Intensivtherapiepatienten führen.

Der genaue Mechanismus ihrer Pathogenität ist jedoch noch immer nicht geklärt. Die unterschiedlichen Ergebnisse zwischen serologischen und Genommethoden sind wahrscheinlich durch den hohen Polymorphismus der Nucleotidsequenzen der Vertreter der *Mimiviridae* zu erklären. Daher sind weitere Untersuchungen zur Pathogenität der *Mimiviridae* und ihrer Rolle bei der Pneumonieentstehung in Risikogruppen notwendig.

Im Unterschied dazu ist die Pathogenität der Viren der Familie der Marseilleviridae und der Gruppe der Virophagen noch unklar.

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Schlüsselwörter: Mimivirus, Mimiviridae, Marseilleviridae, Riesenviren, Virophagen, Pneumonie, Healthcare-assoziierte Infektionen

Introduction

The existence of viruses with extremely large particle and genome sizes has been predicted since the discovery of jumbo bacteriophages in the 1970s and the *phycodnaviruses* in the early 1980s [1], [2]. An investigation of pneumonia outbreak with no clear causative agent in Bradford, England (1992) by Tim Rowbotham and his team considered water of a cooling tower as a probable origin of the outbreak and amoebae as potential culprits [3] since they were established as Trojan horses due to their ability to harbor multiple agents of human pneumonia that can survive and multiply under the protection from various external physical and chemical agents within the amoebae encyst [4], [5]. This led to an isolation of intra-amoebal pathogenic bacteria, one of which had the appearance of a Gram-positive coccus and was therefore named Bradford coccus [3], [6], [7], [8], [9]. However, it resisted the PCR amplification and 16S ribosomal DNA sequencing. This led to the observation of Bradford coccus using electron microscopy, which revealed that it had a viral icosahedral structure. The viral nature of Bradford coccus was further confirmed by an eclipse phase during its replication cycle [6], and genome sequencing [10]. In 2003, the Bradford coccus was renamed as *Acanthamoeba polyphaga Mimivirus* (APMV) due to its mimicry of a bacterium by its size and appearance by Gram staining [3]. Raoult et al. [3], [10] reported that APMV genome was the largest among all of viruses (1,181 kb), encoding more than 900 proteins, including those never identified previously in viruses. Overall, the *Mimivirus* discovery has resulted in a considerable shift in our understanding of the definition, origin, and evolution of viruses [11], [12]. *Mimiviruses* were classified into a separate group of viruses called *nucleocytoplasmic large DNA viruses* (NCLDVs) which was first described in 2001 [13] and included the families of *Poxviridae, Asfarviridae, Iridoviridae, Ascoviridae*, and *Phycodnaviridae* [14], [15], [16]. In 2007, a first member of the *Marseilleviridae* family also related to NCLDVs, *Acanthamoeba polyphaga* marseillevirus (APMaV), was isolated from water collected from a cooling tower in Paris, France, using a method based on *Acanthamoeba polyphaga* culture [17]. This virus was named in honor of its amoebal host and of the name of the French city, Marseille, where it was discovered [17]. The Marseillevirus was characterized by a 368-kb genome, 457 genes, and a minimum of 49 proteins [17]. Furthermore, the first member of the second branch of *Mimiviridae* family, *Cafeteria roenbergensis* virus (CroV), was described in 2010 as an agent infecting marine zooplankton, and its genome consisted of ≈730 kb of double-stranded DNA [18]. Recently, Colson et al. [19], [20] proposed assigning an official taxonomic rank to the NCLDVs as the order *Megavirales*, due to the large size of the virions and genomes of these viruses, and because of their common ancestral origin [13], [15], [21], [22]. Families and genus belonging to this new tentative order are summarized in Table 1, whilst a brief timeline of discoveries in this field is presented in Table 2. During the last decade, plenty of other giant virus strains belonging to *Mimiviridae* and *Marseilleviridae* families were discovered [23], and their diversity is reflected in Table 3 and Table 4.

For decades, viruses were considered to be a final level of parasitism in living nature. However, in 2008, La Scola et al. [24] described an icosahedral small virus Sputnik (50 nm in size) which was associated with an APMV. Sputnik did not replicate in *Acanthamoeba castellanii* but demonstrated a rapid growth in the giant virus factory revealed in amoebae co-infected with APMV. The most incredible fact was that Sputnik life cycle was harmful for APMV and led to the production of abortive forms and abnormal capsid assembly of the host virus. The authors suggested that Sputnik belongs to a new family of viruses and classified it as a *virophage* [24]. In 2011, Fischer and Suttle [25] described a new virophage called *Mavirus*, and Yau et al. [26] almost simultaneously reported a discovery of Organic Lake *Virophage*. Eighteen months later, Desnues et al. [27] revealed a new Sputnik strain, which had 99% identity to the original Sputnik virophage genome sequence. A recent comprehensive investigation carried out by Zhou et al. [6] suggested an existence of five new virophages, namely *Yellowstone Lake Virophages* 1, 2, 3, 4, and *Ace Lake Mavirus*. Finally, third Sputnik strain was described in 2013 by Gaia et al. [7]. The discovery of virophages revolutionized our understanding of host-parasite interrelations. Features of known virophages are presented in Table 5.

There is a significant lack of knowledge regarding the biology of virophages. Obviously, they have greater importance in living nature then we can suggest at the moment. Virophages perform a control of non-viral host-virus dynamics as the essential regulators of ecological interrelations [26], participate in a transfer of genetic information between various organisms as the mobile genetic elements [25], particularly in an interviral gene transfer [27], may be the pathogens of the multicellular organisms [28], and can possibly be used as a new way to fight with the emerging viral infections. Bacteriophages are being successfully used against bacteria in a clinical practice; presumably, a similar pattern does not seem to be impossible in the case with virophages and human pathogenic viruses. Further research on the phenomenon of virophages will definitely shed light on their role in living nature.

It was suspected that *mimiviruses* may be potential causative agents of pneumonia due to the setting of its initial discovery and to the involvement of some water-associated amoebae-resistant bacteria, including *Legionella pneumophila*, in such infections [3], [4]. Experimentally, *Mimivirus* was found to be capable of inducing

Table 1: Members of the proposed order Megavirales

Family	Subfamily	Genus	Host range
Ascoviridae		*Ascovirus*	Insects
Asfarviridae		*Asfivirus*	Mammals, dinoflagellates
Iridoviridae		*Chloriridovirus*	Insects
		Iridovirus	Insects
		Lymphocystivirus	Fishes
		Megalocytivirus	Fishes
		Ranavirus	Amphibia
Mimiviridae		*Mimivirus*	Amoeba
		Cafeteria roenbergensis virus (CroV)	Amoeba, green algae, heterokonts, haptophyta
Marseilleviridae		*Marseillevirus*	Amoeba
Phycodnaviridae		*Chlorovirus*	Green algae
		Coccolithovirus	Haptophyta
		Phaeovirus	Heterokonts
		Prasinovirus	Green algae
		Raphidovirus	Heterokonts
Poxviridae	*Chordopoxvirinae*	*Avipoxvirus*	Birds
		Capripoxvirus	Mammals
		Cervidpoxvirus	Mammals
		Crocodylidpoxvirus	Reptiles
		Leporipoxvirus	Mammals
		Molluscipoxvirus	Human
		Orthopoxvirus	Mammals
		Parapoxvirus	Mammals
		Suipoxvirus	Mammals
		Yatapoxvirus	Primates
		Unassigned	Animals
	Entomopoxvirinae	*Alphaentomopoxvirus*	Insects
		Betaentomopoxvirus	Insects
		Gammaentomopoxvirus	Insects
		Unassigned	Insects

pneumonia in mice [29] and infecting macrophages through phagocytosis [30]. A number of case reports showing the pathogenicity of viruses belonging to *Mimiviridae* and *Marseilleviridae* families in humans during the last decade (Table 6) [31], [32], [33], [28], [34], [35], [36], [37], [38]). Further, certain reports demonstrated that asymptomatic *Marseillevirus* infection is not rare in healthy persons and may be transmitted by transfusion [39]. In addition, the results of previous studies identified sequences related to members of families of the order *Megavirales* in human blood, nasopharyngeal samples, or stools [40], [41], [42], [43], [44], [45], [46].

Thus, we aimed to perform a review of the association of *Mimiviridae*, *Marseilleviridae*, and virophages with pneumonia, particularly healthcare-associated pneumonia (HAP), and other infections of the respiratory tract.

Materials and methods

To the best of our knowledge, all relevant articles published before December of 2013 and available in PubMed database were included in this review. The generation of search queries was performed by combination of words placing at certain positions in the structure of the query, and all feasible variants were browsed:

First position: "mimivirus", "mimiviruses", "mimiviridae", "marseillevirus", "marseilleviruses", "marseilleviridae", "giant virus", "giant viruses", "nucleocytoplasmic large DNA virus", "nucleocytoplasmic large DNA viruses", or "megavirales".

Second position: "pneumonia", "nosocomial", "community-acquired", "hospital-acquired", "ventilator-associated", "healthcare-associated", or "respiratory".

Reference lists of all relevant articles were also screened for the papers which could elude from our search. According to the results of the search, we identified 11 relevant

Table 2: A brief timeline of discoveries regarding the nucleocytoplasmic large DNA viruses (NCLDVs) superfamily and the Megavirales order

Year	Discovery
2001 [13]	Comparative analysis of viral genomes with identification of a set of conserved genes led to the isolation of *nucleocytoplasmic large DNA viruses* (NCLDVs) into the separate group consisted of four families of viruses (*Poxviridae*, *Asfarviridae*, *Iridoviridae*, and *Phycodnaviridae*) which had a double-stranded DNA genome greater than 200,000 bp in size and sharing 9 genes.
2003 [6], 2004 [10]	Identification of the genome of *Mimivirus*, the largest virus known to the moment (1,181,404 bp), the definition of a new family among NCLDVs: *Mimiviridae*.
2008 [24]	Identification of Sputnik, a member of a new family of viruses that grew in the giant virus factory found in amoebae co-infected with *Mamavirus*, a new *Mimivirus* strain. This virus was considered as a virophage since it presented functional analogy with bacteriophages; it replicated only in the presence of *Mamavirus* and its growth was deleterious to the giant virus. The Sputnik genome consisted of a 18.343-kilobase circular double-stranded DNA.
2009 [17]	Isolation of *Marseillevirus* using amoebal culture of water collected in a cooling tower. Its genome represented a circular, double-stranded DNA molecule of 368,453 bp. It was shown by the phylogenetic analysis that *Marseillevirus* belongs to a new viral family of NCLDVs, *Marseilleviridae*.
2010 [16]	The NCLDVs core genes appear to have various probable origins including eukaryotes, bacteria, and bacteriophages. The results suggested that the NCLDVs originated at an early stage in the evolution of eukaryotes.
2010 [57]	Phylogeny reconstruction of highly conserved proteins revealed three main lineages named A (that includes *Mimivirus*), B (whose leading member is *Moumouvirus*), and C composed of several members including Courdo 11 and Terra1.
2010 [18]	The genome of the *Cafeteria roenbergensis virus* (CroV) was described, with an estimated size of 730 kbp. This virus infects a widespread marine heterotrophic flagellate. Phylogenetic reconstructions indicated that CroV is related to the Mimiviridae family, apart from the group composed by three lineages.
2011 [63]	The genome of Lausannevirus, a close relative of the Marseillevirus, was described in 2011. It was recovered using amoebal co-culture from a water sample collected in the Seine river that runs through Paris, France, had 346-kbp genome, and shared 89% of genes with Marseillevirus.
2012 [19], 2013 [20]	The suggestion to consider *Megavirales* as a separate order consisting of seven families (*Ascoviridae, Asfarviridae, Iridoviridae, Mimiviridae, Marseilleviridae, Phycodnaviridae, Poxviridae*).

articles in which epidemiological investigations were performed.

Results and discussion

Unfortunately, it was not possible to carry out a meta-analysis since due to significant differences in study design, sample types, and methods of detection used in distinct studies. Thus, we performed only the qualitative comparative analysis.

The results of the first investigation on the association of APMV with pneumonia were published in 2005 by La Scola et al. [47]. The researchers collected serum samples from 376 Canadian patients with community-acquired pneumonia (CAP, 121 ambulatory and 255 hospitalized) and 511 healthy control subjects. Microimmunofluorescence assay revealed that patients with CAP were *mimivirus*-positive significantly more frequently compared to controls (9.66% vs. 2.30%, $P<0.01$) (Table 7). Furthermore, the authors identified hospitalization from a nursing home and rehospitalization after discharge as independent risk factors of *mimivirus*-associated CAP ($P<0.05$), possibly due to poor efficacy of standard antimicrobial agents against viruses. In addition, immunoelectron microscopy revealed that antibodies of APMV-positive patients specifically recognized mature APMV particles whilst antibody fixation was not found in serum samples from APMV-negative patients. The authors suggested APMV as a particularly hazardous etiologic agent of pneumonia acquired in institutions [47], [48]. In addition, the investigators recruited a second study sample consisted of 26 French patients with intensive care unit (ICU)-acquired pneumonia and 50 healthy controls, showing that APMV can be found in patients with ICU-acquired pneumonia and multiple populations [47]. Moreover, serological positivity to APMV was associated with a higher risk of ICU-acquired pneumonia (19.2% in cases vs. 0.0% in controls, $P<0.01$) [47] (Table 7). In the third sample (32 French patients with ICU-acquired pneumonia, 21 intubated controls in ICU without ICU-acquired pneumonia), APMV DNA was detected in bronchoalveolar lavage specimen from one of the patients with ICU-acquired pneumonia but in none of the controls, confirming that APMV may reach the respiratory tract of these patients [47] (Table 7). So, La Scola et al. [47] were very first who proposed that APMV should be tested as a possible novel human pathogen, particularly in pneumonia patients.

The second study devoted to this issue was carried out by Berger et al. [49]. This investigation included 157 French ICU patients with 210 episodes of pneumonia (120 episodes of healthcare-associated pneumonia (HAP), 62 episodes of CAP, and 28 episodes of mixed pneumo-

Table 3: Known members of the Mimiviridae family

Group of giant viruses	Virus	Source of identification	Year, country and region of identification
Mimiviridae (44)			
Group I (43)			
Group A (14)	*Acanthamoeba polyphaga Mimivirus* (APMV)	Cooling tower water	2003 [6], 2004 U.K. (Bradford) [10]
	Acanthamoeba castellanii Mamavirus	Cooling tower water	2008, France (Paris) [64]
	Terra2	Soil	2010, France (Marseille) [57]
	Pointe-Rouge2	Seawater	
	Cher	Rivers and lakes	2010, France (Tours) [57]
	Fauteuil	Hospital water	2010, France (Marseille) [57]
	Longchamps	Decorative fountain water	2010, France (Marseille) [57]
	Lactours	Rivers and lakes	2010, France (Tours) [57]
	Pointe-Rouge1	Seawater	2010, France (Marseille) [57]
	Lentille	Lens liquid	2010, France (Marseille) [57]
	Marais	Swamp	2013, France (Aubagne) [23]
	Univirus	Compost	2013, France (Marseille) [23]
	Hirudovirus	Leech	2013, France (Marseille) [23]
	Montadette2	Soil	2013, France (Martigues) [23]
Group B (6)	Moumouvirus	Cooling tower water	2010, France (Rousset) [57]
	Monve	Cooling tower water	2010, France (Puget sur Argens) [57]
	Ochan	Compost	2013, France (Marseille) [23]
	Goulette	Seawater	2000, Tunisia (Tunis) [64]
	Istres	Soil	2013, France (Istres) [23]
	Cassis49	Soil	2013, France (Cassis) [23]
Group C (25)	Courdo7	Rivers and lakes	2010, France (Saint-Raphael) [57]
	Terra1	Soil	2010, France (Marseille) [57]
	Montpellier	Decorative fountain water	2010, France (Montpellier) [57]
	Courdo11	Rivers and lakes	2010, France (Saint-Raphael) [57]
	Courdo5	Rivers and lakes	2010, France (Marseille) [57]
	Bus	Cooling tower water	2010, France (Marseille) [57]
	Mont1	Soil (mountain)	2000, Tunisia (Tunis) [64]
	LBA111	Bronchoalveolar lavage	2013, Tunisia [65]
	Avenue9	Soil	2000, Tunisia (Tunis) [64]
	Afrovirus	Soil	2013, France (Aubagne) [23]
	Montadette1	Soil	2013, France (Martigues) [23]
	Balcon	Soil	2013, France (Marseille) [23]
	Terrain en construction	Soil	2013, France (Marseille) [23]
	Boug1	Chott (hypersaline soil)	2000, Tunisia (Gafsa) [64]
	Shan	Stool	2013, Tunisia (Tunis) [23]
	Cornil	Soil	2013, France (Marseille) [23]
	Saint Pierre	Stagnant water	2013, France (Marseille) [23]
	Borely	Stagnant water	2013, France (Marseille) [23]
	Capucin	Stagnant water	2013, France (Marseille) [23]
	Potager	Soil	2013, France (Marseille) [23]
	Feuillage	Soil	2013, France (Martigues) [23]
	Luminy43	Water	2013, France (Marseille) [23]
	Sete	Soil	2013, France (Sete) [23]
Group II (1)			
Unassigned	*Cafeteria roenbergensis* virus (CroV)	Unicellular marine biflagellate	2010, Coastal waters near the USA (Yaquina Bay, Oregon) [18]

Table 4: Known members of the Marseilleviridae family

Group of giant viruses	Virus	Source of identification	Year, country and region of identification
Marseilleviridae (17)			
Marseillevirus (4)	*Acanthamoeba polyphaga* Marseillevirus (APMaV)	Cooling tower water	2009, France (Cannes) [17]
	Acanthamoeba castellanii Lausannevirus (ACLaV)	River water	2011, France [63]
	Giant blood Marseillevirus	Donor blood	2013, France [66]
	Senegalvirus	Stool	2010, Senegal [18]
Tunisvirus (1)	Fontaine2	Fountain water	2000, Tunisia (Ariana) [64]
Unassigned (14)	Cannes8	Cooling tower water	2010, France (Cannes) [57]
	Cannes9	Cooling tower water	2010, France (Cannes) [57]
	Saint-Charles	Decorative fountain water	2010, France (Marseille) [57]
	Seb1 eau	Sebkha (hypersaline water)	2000, Tunisia (Tunis) [64]
	Seb1 sol	Soil (hypersaline soil)	2000, Tunisia (Tunis) [64]
	Seb6 sol	Soil (hypersaline soil)	2000, Tunisia (Tunis) [64]
	Seb2 sol	Soil (hypersaline soil)	2000, Tunisia (Tunis) [64]
	Oued1	River	2000, Tunisia (Bezert) [64]
	Cite1	Soil	2000, Tunisia (Kef) [64]
	Riviere1	River (Majerda)	2000, Tunisia (Kef) [64]
	Puit1	Well water	2000, Tunisia (Cap Bon) [64]
	Hammam1	Hammam water	2000, Tunisia (Tunis) [64]
	Sidi thabet	Soil	2000, Tunisia (Ariana) [64]
	Insectomime	Diptere larvae	2013, Tunisia [31]

nia (CAP complicated with HAP) [49]. Using the similar microimmunofluorescence approach, the authors showed that 15/210 episodes (7.1%) in 14/157 patients (8.9%) were associated with APMV [49]. In addition, laboratory investigations for amoeba-associated microorganisms (AAMs) revealed 59/210 (28.1%) diagnoses in 40/157 (19.0%) patients [49]. Seroconversion among patients with ventilator-associated pneumonia (VAP) was observed in 13/51 episodes (25.5%), whereas seroconversion among patients with CAP was detected in 2/8 episodes (25.0%) that may demonstrate the possible pathogenic role of APMV in both VAP and CAP [49] (Table 7). However, there was no control group in this study; therefore the prevalence of APMV in a general population remains unknown [49]. In the same year, Arden et al. [50] and Larcher et al. [51] failed to find any APMV-positive individuals among 315 Australian patients with suspected acute respiratory tract infections and 214 Austrian patients with pediatric CAP, respectively; nonetheless, the authors used predominantly nasopharyngeal aspirates as a study material and real-time [50] or nested suicide [51] PCR instead of microimmunofluorescence as a method of APMV detection (Table 7). Similar results were further obtained by Dare et al. [52] who were unable to detect APMV using real-time PCR in 496 patients with pneumonia (249 patients with CAP, 71 patient with HAP, 87 bone marrow transplant recipients with pneumonia, and 89 lung transplant recipients with pneumonia) from 9 epidemiologically varied pneumonia patient populations (Thailand, Canada, USA) (Table 7). The authors suggested that seropositivity may reflect chronic exposure to APMV antigen rather than active infection, and the potential for nonspecific cross-reactions with the serologic assays used may have inflated the true prevalence of APMV colonization/infection [52]. Nevertheless, most of the specimens examined in this study were obtained from the upper respiratory tract but not from the lower respiratory tract where the only reported APMV PCR-positive sample was identified [47]. Distinct composition of the studies' populations could also play a role in the differences between the studies [52]. However, in 2009 Vincent et al. [53] found 59/300 (19.6%) French patients with suspected VAP to be APMV-positive, detected by microimmunofluorescence (Table 7). In addition, APMV-positive patients had longer duration of mechanical ventilation and ICU stay with median excesses of 7 days and 10 days, respectively, so a positive serology for *mimivirus* was associated with a poorer outcome in mechanically ventilated ICU patients [53].

Three years later, Costa et al. [54] investigated the prevalence of APMV in bronchoalveolar lavage (BAL) specimens from 30 ventilated compared to 39 nonventilated Italian patients using real-time PCR but could not detect any signs of APMV colonization/infection among this population (Table 7). Then, Lysholm et al. [41] investigated nasopharyngeal aspirates from 210 Sweden patients with lower respiratory tract infections through metagenomic sequencing approach but detected APMV only in 2/210 (0.95%) cases. Furthermore, Vanspauwen et al. [55] collected 220 sputum and serum samples from

Table 5: Features of known virophages

Year and region of the discovery	Cellular organism infected by the virus	Virus infected by the *virophage*	*Virophage*	Environment
2008, Paris, France [24]	*Acanthamoeba polyphaga* and possibly other protozoa, particularly amoebae	Mimiviruses from all 3 groups (A, B, and C)	*Sputnik virophage*	A cooling tower
2011, Texas, USA [25]	*Cafeteria roenbergensis* (marine phagotrophic flagellate)	*Cafeteria roenbergensis* virus (CroV), a distant relative of *mimiviruses* (the same family of *nucleocytoplasmic large DNA viruses* (NCDLVs)	*Mavirus*	Coastal waters
2011, Antarctica [26]	Prasinophytes (phototrophic algae)	*Phycodna-* or *mimivirus*?	*Organic Lake Virophage*	Organic Lake, a hypersaline meromictic lake, temperature at the surface of the lake can vary from −14 to +15 °C while remaining subzero at depth [67]
2012, France [27]	*Acanthamoeba polyphaga* and possibly other protozoa, particularly amoebae	*Mimiviruses* from all 3 groups (A, B, and C)	*Sputnik virophage 2*	Contact lens fluid of a patient with keratitis [32]
2013, Wyoming, USA [36]	Microalgae?	*Phycodna-* or *mimiviruses*?	*Yellowstone Lake Virophages* (1–4)	Yellowstone Lake, a freshwater lake with a temperature ranging from 12 to 73°C in Yellowstone National Park [69]
2013, Antarctica [68]	Phagotrophic protozoan?	*Mimiviruses*?	*Ace Lake Mavirus*	Ace Lake, a hypersaline meromictic lake, covered with ice for as long as 11 months to an entire year, with an average temperature of approximately 0°C [70]
2013, South of France [65]	*Acanthamoeba polyphaga* and possibly other protozoa, particularly amoebae	*Mimiviruses* from all 3 groups (A, B, and C)	*Sputnik virophage 3*	Soil samples collected in Marseille and surrounding areas

109 Dutch patients with chronic obstructive pulmonary disease (COPD) and analyzed them using the microimmunofluorescence assay and real-time PCR; however, only 3/210 (2.7%) patients were APMV-seropositive and none of the patients were positive for APMV DNA (Table 7). The authors suggested that the low seropositivity might be explained by either a low abundance of the virus or the presence of the virus may depend on the spatiotemporal regional variation as in the case with *Legionella*-caused infections [55], [56]. Negative PCR results could be explained by a number of reasons [55]. The viral load of the samples may have been below the detection limit of the PCR (12 copies/reaction), or a polymorphism in the area of amplification could occur [55]. A wide genomic diversity of *Mimiviridae* family may support the latter suggestion [19], [57], [55], [58], so patients could be positive for other viruses of the *Mimiviridae* family [55]. In addition, sputum is possibly not an appropriate study material compared to BAL sample [55]. In the second study performed by this research group with 260 bronchoalveolar lavage fluid samples from 214 Dutch patients suspected for VAP, no APMV DNA was detected in all of the samples using real-time PCR [59] (Table 7). Finally, in the recent study of Bousbia et al. [60], seroconversion to APMV was observed in 14/71 (19.7%) French pneumonia patients (ICU) with paired serum samples (Table 7). The authors also observed an elevation of the antibody response (both IgG and IgM) to APMV antigens in the convalescent-phase sera in comparison with the admission sera (16/41 (39.0%) patients with HAP and 4/29 (13.8%) controls (ICU patients without pneumonia), respectively, P=0.02) [60].

There are several explanations for the inconsistency observed between the results of the above-mentioned studies. The most evident explanation is that *Mimiviridae* family DNA detection could possibly have been hampered in studies that used genomic methods of detection. PCR primers used in these studies targeted only APMV genome, whilst a number of APMV relatives exhibiting considerable genetic diversity have been described (Table 3). Recently developed modern real-time PCR systems targeting giant viruses and their *virophages* are able to accurately detect all or most of the members of the currently delineated lineages of giant viruses infecting *Acanthamoebae* as well as the *virophages* [61]; hence, this obstacle may be overcome in the near future. Other reasons for the disparities may include differences in prevalence of giant viruses in distinct populations along

Table 6: Cases of human infections caused by giant viruses

Year and country	Virus	Case description	Sample type	Method of diagnostics
2006, France [33]	Family *Mimiviridae*, lineage A, *Acanthamoeba polyphaga Mimivirus*	28-year-old laboratory technician who handled large amounts of *Mimivirus* to perform Western blot assays with suspected pneumonia	Serum	Seroconversion to *Mimivirus* (against 23 *Mimivirus* proteins, including four unique proteins)
2011, France [32]	Family *Mimiviridae*, lineage A, *Lentillevirus*	17-year-old myopic woman suffering from keratitis with soft contact lenses	Contact lens storage case liquid	Culture isolation on *Acanthamoeba* spp.
2012, France [28]	*Sputnik virophage* of *Acanthamoeba polyphaga mimivirus* (family *Mimiviridae, lineage A*)	29-year-old woman and her 32-year-old husband suffering from asthenia, nausea, myalgia, low-grade fever	Serum	Seroconversion to *virophage*
2012, 2013, Senegal [34], [35]	Family *Marseilleviridae*, Senegalvirus	20-year-old Senegalese man living in rural Senegal. No clinical symptoms	Stool	Metagenomics, culture isolation on *Acanthamoeba* spp.
2013, France [36]	Family *Marseilleviridae*, *Giant blood* Marseillevirus	blood donor, no clinical symptoms	Serum	Metagenomics, PCR, culture isolation on lymphocyte T cells, transmission electron microscopy, fluorescence in situ hybridization
2013, Tunisia [31]	Family *Mimiviridae*, lineage C, LBA111	72-year-old Tunisian woman with pneumonia	Bronchoalveolar fluid	Culture isolation on *Acanthamoeba spp.*, serology
2013, Tunisia [37]	Family *Mimiviridae*, lineage C, Shan virus	17-year-old girl suffering from pneumonia	Stool	Culture isolation, serology
2013, France [38]	Family *Marseilleviridae*, Marseillevirus	11-month-old child with adenitis	Blood and stool	Fluorescence in situ hybridization (FISH), serology, PCR

with spatiotemporal regional variation as well as the use of inappropriate study material (for instance, samples from upper respiratory tract instead of bronchoalveolar lavage (BAL) specimens). In some cases, giant viruses possibly could not be identified due to the too small viral load for the PCR detection in some cases, insufficient amount of specimens. In addition, APMV was shown to contain up to 23 proteins that may cause immune response resulting in a production of antibodies [33], so proteins of other *Mimiviridae* family members may cross-react with those of APMV [71]. In this case, molecular detection of APMV could be negative [62]. Exposure to APMV, since it is an AAM, most likely occurs from environmental sources such as contaminated hospital water supplies [52], which is the case in ICU patients. The high rate of seroconversion in pneumonia patients in certain studies [47], [49], [53] suggests that they may have had a contact with APMV or a cross-reacting agent which could possibly be other member of *Mimiviridae* family.

Conclusion

Viruses belonging to *Mimiviridae* family can be potential agents of both CAP and HAP. In particular, these viruses may be associated with poorer outcome in ICU patients. The exact mechanism of their pathogenicity, however, still remains unclear. The discrepancies between the results obtained by serological and genomic methods could be explained by the high polymorphism of nucleotide sequences of *Mimiviridae* family representatives. Further investigations on the Mimiviridae pathogenicity and on the determination of *Mimiviridae*-caused pneumonia risk groups are required. However, pathogenicity of the viruses belonging to *Marseilleviridae* family is unclear.

Table 7: Studies on the association of the giant viruses with infections of the respiratory tract

Year and country	Sample type	Method of detection	Number of cases and controls	Number and share of positive cases and controls	Odds ratio (OR) with 95% confidence interval (95% CI) and P-value
2005, 1) Canada 2) France 3) France [47]	1) Serum 2) Serum 3) Bronchoalveolar lavage (BAL) specimens	1, 2) *Micro-immunofluorescence* 1) Seroconversion from <1:50 to ≥1:100 between acute-phase and convalescent-phase serum samples 2) 4-fold rise in antibody titer between acute-phase and convalescent-phase serum samples 3) Single or stable titer ≥1:400 3) *Molecular detection* Nested suicide PCR	1) 376 patients with community-acquired pneumonia (CAP) (121 ambulatory and 255 hospitalized), 511 healthy controls 2) 26 patients with intensive care unit (ICU)-acquired pneumonia and 50 healthy controls 3) 32 patients with ICU-acquired pneumonia, 21 intubated controls in ICU	1) 36/376 cases (9.66%) 12/511 controls (2.3%) Then, 14 *Mimivirus*-seropositive patients were compared to 90 *Mimivirus*-negative patients; 2) 5/26 cases (19.2%) 0/50 controls (0.0%) 3) 1/32 cases (3.1%) 0/21 controls (0.0%)	1) P<0.01; hospitalization from a nursing home (3/14 vs. 3/90) and re-hospitalization after discharge (6/14 vs. 16/90) were associated with anti-*Mimivirus* antibodies P<0.05 2) P<0.01 3) no significant
2006, France [49]	Serum	*Micro-immuno-fluorescence* 1) Seroconversion from <1:50 to ≥1:100 between acute-phase and convalescent-phase serum samples 2) 4-fold rise in antibody titer between acute-phase and convalescent-phase serum samples 3) Single or stable titer ≥1:400	157 patients with 210 episodes of pneumonia (ICU), 120 episodes of hospital-acquired pneumonia (HAP), 62 episodes of CAP, 28 episodes of mixed pneumonia (CAP complicated with HAP)	*Mimivirus*: 15/210 episodes (7.1%) in 14/157 patients (8.9%). 59/210 (28.1%) of episodes in 40/157 patients (19.0%) were associated with amoeba-associated microorganisms (AAMs)	Seroconversion among patients with ventilator-associated pneumonia (VAP): 13/51 episodes (25.5%), seroconversion among patients with CAP: 2/8 (25.0%), no sign. difference
2006, Australia [50]	Predominantly (92.4%) Nasopharyngeal aspirates	*Molecular detection* Real-Time PCR	477 specimens from 315 patients with suspected acute respiratory tract infections	0/477 (0.0%)	Not detected
2006, Austria [51]	Nasopharyngeal aspirates	*Molecular detection* Nested suicide PCR	214 hospitalized patients with pediatric CAP	0/214 (0.0%)	Not detected

(Continued)

Table 7: Studies on the association of the giant viruses with infections of the respiratory tract

Year and country	Sample type	Method of detection	Number of cases and controls	Number and share of positive cases and controls	Odds ratio (OR) with 95% confidence interval (95% CI) and P-value
2008, USA, Canada, Thailand [52]	Nasal wash and swabs, nasopharyngeal swabs and aspirates, oropharyngeal swabs, BAL samples, sputum, endotracheal aspirates, lower respiratory samples	*Molecular detection* Real-Time PCR	496 patients with pneumonia, 249 patients with CAP, 71 patients with HAP, 87 bone marrow transplant recipients with pneumonia, 89 lung transplant recipients with pneumonia	0/496 (0.0%)	Not detected
2009, France [53]	Serum	*Micro-immuno-fluorescence* 1) Seroconversion from <1:50 to ≥1:100 between acute-phase and convalescent-phase serum samples 2) 4-fold rise in antibody titer between acute-phase and convalescent-phase serum samples 3) Single or stable titer ≥1:400	55 seropositive patients with suspicion of VAP, 55 seronegative patients (ICU)	59/300 patients with suspected VAP (19.6%)	Patients with a positive serology for *mimivirus* had longer duration of mechanical ventilation and ICU stay with median excesses of 7 days and 10 days, respectively
2012, Italy [54]	BAL samples	*Molecular detection* Real-Time PCR	30 patients on mechanical ventilation and 39 nonventilated patients	0/69 (0.0%)	Not detected
2012, Netherlands [55]	Sputum, serum	*Micro-immuno-fluorescence* 1) Seroconversion from <1:50 to ≥1:100 between acute-phase and convalescent-phase serum samples 2) 4-fold rise in antibody titer between acute-phase and convalescent-phase serum samples 3) Single or stable titer ≥1:400 *Molecular detection* Real-Time PCR	220 sputum samples from 109 patients with chronic obstructive pulmonary disease (COPD)	3/109 (2.7%) according to the micro-immuno-fluorescence assay 0/109 (0.0%) according to real-time PCR	Almost not detected
2012, Sweden [41]	Nasopharyngeal aspirates	*Molecular detection* Metagenomic sequencing	210 patients with lower respiratory tract infections	2/210 (0.95%)	Almost not detected

(Continued)

Table 7: Studies on the association of the giant viruses with infections of the respiratory tract

Year and country	Sample type	Method of detection	Number of cases and controls	Number and share of positive cases and controls	Odds ratio (OR) with 95% confidence interval (95% CI) and P-value
2013, France [60]	Serum	*Micro-immuno-fluorescence* 1) Seroconversion from <1:50 to ≥1:100 between acute-phase and convalescent-phase serum samples 2) 4-fold rise in antibody titer between acute-phase and convalescent-phase serum samples 3) Single or stable titer ≥1:400	88 patients with pneumonia (ICU): 55 patients with VAP, 17 patients with CAP, 8 patients with aspiration pneumonia (AP), 8 patients with non-ventilator ICU-acquired pneumonia. 29 controls from ICU	Both IgG and IgM: 9/88 cases (10.2%) IgG: 1/29 controls (3.45%) IgM: 3/29 controls (10.34%) *In acute phase sera:* 55 patients with VAP – IgG: 5/55 (9.1%) IgM: 7/55 (12.7%) 17 patients with CAP – both IgG and IgM: 2/17 (11.8%) 8 patients with AP – both IgG and IgM: 0/8 (0.0%) 8 patients with non-ventilator ICU-acquired pneumonia – IgG: 2/8 (25%) IgM: 0/8 (0.0%) *In convalescent phase sera:* IgG: 7/41 cases with HAP (17.1%) IgM: 9/41 cases with HAP (22.0%) *In controls:* IgG: 1/29 controls (3.4%) IgM: 3/29 controls (10.3%) *Seroconversion:* 14/71 (19.7%) patients (ICU) with paired serum samples, 9/48 (18.7%) patients with VAP, 3/9 (33.3%) patients with CAP, 2/14 (14.3%) controls	Antibody response (both IgG and IgM) was increased in convalescent phase sera compared to control sera P=0.02
2013, Netherlands [59]	BAL samples	*Molecular detection* Real-time PCR	260 bronchoal-veolar lavage fluid samples from 214 patients suspected for VAP	0/260 (0.0%)	Not detected

Notes

Competing interests

The authors declare that they have no competing interests.

Funding

There was no funding for this paper.

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Please cite as
Kutikhin AG, Yuzhalin AE, Brusina EB. Mimiviridae, Marseilleviridae, and virophages as emerging human pathogens causing healthcare-associated infections. GMS Hyg Infect Control. 2014;9(2):Doc16.
DOI: 10.3205/dgkh000236, URN: urn:nbn:de:0183-dgkh0002365

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Published: *2014-08-19*