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1 **Title: *Parachlamydia* and *Rhabdochlamydia*: emerging agents of community-acquired**
2 **respiratory infections in children**

3

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8

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13

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24 Dear Editor,

25 Besides viruses, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are common causes of
26 community-acquired respiratory infections (CARI) in children. However, the causal agent of
27 CARI remains unknown in many cases (1). Growing evidence suggests that *Chlamydia*-
28 related bacteria might have a pathogenic role in humans (2;3). *Parachlamydia*
29 *acanthamoebae* and *Protochlamydia naegleriophila* have been detected in respiratory clinical
30 samples (4;8) and their role in pneumonia is supported by *in vitro* studies and animal models
31 (5). *Rhabdochlamydia crassificans* and *Rhabdochlamydia porcellionis* are intracellular
32 pathogens of arthropods that also belong to the *Chlamydiales* order (6;7). A recent analysis
33 suggests that *Rhabdochlamydia* spp. might affect morbidity and mortality in premature
34 newborns (9), but their role in respiratory infections is unknown.

35 Using three previously described real-time PCRs for the detection of *P. acanthamoebae*, *P.*
36 *naegleriophila* and *Rhabdochlamydia* spp. (4;8;9), we aimed at assessing the prevalence and
37 clinical significance of these bacteria in respiratory secretions of children. All available
38 respiratory samples of children hospitalized between September 2004 and October 2006 with
39 a diagnosis of CARI were retrospectively tested. Tracheobronchitis was defined by the
40 presence of a new cough with at least one of the following signs (dyspnea, sputum, fever
41 $\geq 38^{\circ}\text{C}$) or a diagnosis of upper respiratory tract infection in the medical record. Pneumonia
42 was considered in the presence of the above criteria and a new infiltrate on chest X-ray. As
43 controls, we used respiratory samples of six children hospitalized during the same period
44 without evidence of respiratory infection at time of sampling. Multiplex PCR assay for the
45 detection of *M. pneumoniae* and *C. pneumoniae* was also performed using previously reported
46 primers and probes (10).

47 Twenty-nine patients were included (13 males, 16 females, median age: 5 years, range 3
48 months-18 years). Most (90%) respiratory samples were nasopharyngeal secretions. Positive

49 results for *Chlamydia*-related bacteria were obtained in 14 of 29 (48%) patients with CARI (2
50 *Parachlamydia*, 11 *Rhabdochlamydia*, 1 both *Para-* and *Rhabdochlamydia*; *Protochlamydia*
51 was not recovered) and 0/6 (0%) controls ($p=0.06$). Considering only cases of documented
52 pneumonia ($n=21$), the rate of positive results was 52% ($p=0.05$ when compared to controls).
53 Clinical characteristics of the 14 patients with CARI and positive PCR results for
54 *Parachlamydia* or *Rhabdochlamydia* spp. are summarized in the Table. An alternative causal
55 agent of pneumonia was documented in two cases (*M. pneumoniae* and *S. pneumoniae*). Of
56 the 12 patients without alternative etiology, 5 (42%) received a macrolide (to which
57 *Chlamydia*-related bacteria are susceptible). Interestingly, one patient who did not respond to
58 initial beta-lactam monotherapy experienced a rapid improvement after start of
59 clarithromycin.

60 In conclusion, our study revealed a high prevalence of positive respiratory samples for
61 *Parachlamydia* and *Rhabdochlamydia* spp.. A similar prevalence has been recently reported
62 in premature neonates with respiratory distress syndrome (9), which suggests that airways
63 colonization with these *Chlamydia*-related bacteria is common. Their pathogenic role in
64 CARI is supported by the fact that these bacteria were not recovered from respiratory
65 samples of patients without evidence of respiratory infection and were the only possible
66 causal agents of pneumonia in 12 of 14 cases.

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72 This study was approved by the ethics committee of the University of Lausanne.

73 Authors have no conflict of interests to declare.

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106

107 **Table. Clinical characteristics of respiratory infection in children with positive PCR results for *Chlamydia*-related bacteria**

| Sex / age / underlying condition | Type of pulmonary infection | Other symptoms/signs | Alternative etiology | Supportive measures | Treatment (response) |
|--|-----------------------------------|---------------------------------|---------------------------------------|----------------------|--|
| <i>Parachlamydia acanthamoebae</i> | | | | | |
| F / 13 y / pinealoblastoma (neutropenia) | Bilateral interstitial pneumonia | Enterocolitis | - | - | Meropenem, vancomycin (complete) |
| M / 15 y / - | Unilateral alveolar pneumonia | Pleural effusion | - | - | Amoxicillin/clavulanate, clarithromycin (complete) |
| <i>Rhabdochlamydia spp.</i> | | | | | |
| F / 1 y / - | Tracheobronchitis | - | <i>S.pneumoniae</i> (urinary antigen) | Invasive ventilation | Ceftriaxone, clarithromycin (complete) |
| F / 2 y / - | Unilateral alveolar pneumonia | - | - | Oxygen supply | Amoxicillin/clavulanate (complete) |
| M / 2 y / - | Unilateral alveolar pneumonia | Rhinitis, pleural effusion | - | - | Amoxicillin/clavulanate, clarithromycin (complete) |
| M / 2 y / cystic fibrosis | Bilateral alveolar pneumonia | - | - | - | Amoxicillin/clavulanate (complete) |
| F / 3 y / - | Bilateral alveolar pneumonia | Rhinitis, pharyngitis, seizures | <i>M. pneumoniae</i> (nose swab, PCR) | - | Clarithromycin (complete) |
| M / 5 y / osteosarcoma (neutropenia) | Unilateral alveolar pneumonia | Rhinitis | - | - | Ceftriaxone, amikacin (complete) |
| F / 9 y / methylmalonic acidemia | Unilateral interstitial pneumonia | - | - | - | Amoxicillin/clavulanate (no response) Then: clarithromycin (complete) |
| F / 11 y / - | Unilateral interstitial pneumonia | Otitis media | - | Oxygen supply | Clarithromycin (complete) |

| | | | | | |
|---|-------------------------------|------------------|---|-------------------------------------|--|
| F / 14 y / cystic fibrosis | Unilateral alveolar pneumonia | - | - | Non-invasive mechanical ventilation | Imipenem, ciprofloxacin (complete) |
| F / 15 y / - | Unilateral alveolar pneumonia | Pleural effusion | - | Oxygen supply | Amoxicillin/clavulanate, clarithromycin (complete) |
| M / 17 y / - | Tracheobronchitis | - | - | - | No treatment (complete) |
| <i>Parachlamydia acanthamoebae</i> and <i>Rhabdochlamydia</i> spp. | | | | | |
| M / 1 month / - | Tracheobronchitis | Conjunctivitis | - | - | No treatment (complete) |

108

109 y = year-old

110