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A DIFFERENT VIEW

The role of rhinoviruses is overestimated in the aetiology of community-acquired pneumonia in children

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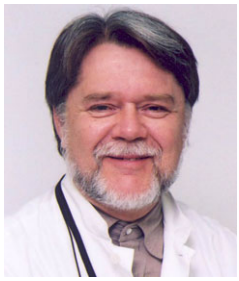

Until the 1990s, viral cultures, antigen detection and antibody assays were used to diagnose virus-specific respiratory infections (1). The introduction of polymerase chain reaction (PCR) increased the number of viral findings, revealed that multiple viral aetiological findings are common, confirmed that viruses are often found in nonsymptomatic children and even detected new viruses (2–4). Rhinoviruses were discovered in 1956, but the slow, nonsensitive viral culture was the only diagnostic method for decades, and the development of antigen or antibody assays did not help, as there are now more than 100 rhinovirus serotypes. In the 2000s, PCR highlighted the role of rhinoviruses in paediatric community-acquired pneumonia (CAP) (1) and identified other agents, such as the metapneumovirus, bocavirus and certain coronaviruses (2,3). Multiple viral findings and the presence of viral carriage raised questions about which virus was the real cause of clinical infections in each case (4).

A systematic review and meta-analysis published in 2015 covered 23 controlled or quasi-controlled hospital studies on acute respiratory infections in children (5), including 19 (83%) from developing countries. The case definitions included pneumonia in eight cases (35%) and bronchiolitis in one case. All the studies contained inpatient data, three studies provided outpatient data and three included population-based community controls. PCR data for only one virus were reported in 10 (44%) studies: one respiratory syncytial virus (RSV), two rhinoviruses, two metapneumovirus, two coronaviruses and three bocavirus.

The virus-specific results showed strong evidence for a causal attribution of RSV, influenza viruses, parainfluenza viruses and metapneumovirus, and less strong evidence for rhinoviruses (Table 1) (5). The combined odds ratio (OR) for rhinoviruses was 1.43 with a 95% confidence interval (95% CI) of 1.03–1.97. The analysis probably overestimated the role of rhinoviruses, as upper respiratory infections were also included. Other picornaviruses, like enteroviruses, were not reported separately from the rhinoviruses. When influenza viruses were analysed separately, the differences between cases and controls were significant for influenza A but not influenza B (5). When parainfluenza viruses type 1–4 were analysed separately, there were no significant differences between the cases and controls (5). Subgroup analyses like these carry the risk of a type-2 statistical error.

The results of three case–control studies on the role of respiratory viruses in paediatric CAP (6–8), which were not included in the above meta-analysis (5), are summarised in Table 2. The controls were apparently healthy, nonsymptomatic children from the community, and the statistical analyses used conditional logistic regression to retain the case–control pairs in the analyses.

A three-years case–control study from Stockholm, Sweden, comprised 121 CAP cases (60% boys) of less than six years of age, including 93 who met the World Health Organization (WHO) criteria for radiological pneumonia and 240 controls from child health units matched for birth month and year (6). Three-quarters (76%) were treated in hospital, and their median age was 21 months. Nasopharyngeal aspirates were analysed by real-time PCR for 15

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Table 1 Virus-specific odds ratios (ORs) and 95% confidence interval (95% CIs) from the meta-analysis (5), comparing the frequency of viral findings between children with acute respiratory infections and controls

Virus	Number of studies	Combined OR	95% CI
Respiratory syncytial virus	13	9.79	4.98–19.27
Influenza viruses	10	5.10	3.19–8.14
Parainfluenza viruses	11	3.37	1.59–7.15
Metapneumovirus	10	3.76	2.45–5.78
Adenovirus	10	1.13	0.71–1.80
Rhinoviruses	11	1.43	1.03–1.97
Bocavirus	8	1.20	0.36–3.98
Coronaviruses	8	1.03	0.80–1.33

Table 2 Odds ratios and 95% confidence intervals between community-acquired pneumonia cases and matched apparently healthy nonsymptomatic controls, based on conditional logistic regression analyses

Virus	Rhedin et al. (6)	Zar et al. (7)	Spichak et al. (8)
Adenovirus	2.1 (1.0–4.3)	2.2 (1.3–3.5)	15.5 (1.6–152.0)
Bocavirus	0.5 (0.3–0.8)	2.3 (1.3–4.2)	0.7 (0.1–5.8)
Coronaviruses	0.3 (0.1–0.9)	1.2 (0.8–2.0)	2.5 (0.6–10.5)
Enterovirus	0.5 (0.1–2.9)	0.9 (0.6–1.5)	0.5 (0.1–4.3)
Influenza virus	4.2 (1.2–14.5)	4.1 (2.1–8.3)	16.4 (3.2–83.5)
Metapneumovirus	6.5 (3.0–14.1)	1.1 (0.7–1.9)	21.1 (2.3–192.3)
Parainfluenza virus	0.9 (0.2–3.6)	2.0 (1.2–3.4)	0.4 (0.1–1.9)
Respiratory syncytial virus	10.1 (4.8–21.2)	8.1 (4.2–15.4)	7.7 (2.3–25.9)
Rhinoviruses	0.8 (0.5–1.4)	0.9 (0.6–1.2)	0.4 (0.2–0.9)

viruses found in 98 (81%) of cases and 134 of (56%) controls. RSV (OR 10.1), metapneumovirus (OR 6.5) and influenza viruses (OR 4.2) were significantly associated with CAP (6). The bocavirus (OR 0.5) and coronaviruses (OR 0.3) were significantly more common in controls than cases (6). There were no significant differences in the adenovirus, parainfluenza virus or rhinovirus findings between the cases and controls (6).

A nested two-years case–control study from Paarl, South Africa, comprised 284 CAP cases (68% boys) aged less than three-and-a-half years who met the WHO criteria and 418 controls from the same birth cohort, matched for birth date and site (7). The CAP cases in this population-based study were actively recruited. A third (32%) were treated in hospital, and the patients' median age was five months. The diagnosis was confirmed by chest radiography in hospitalised patients. Multiplex real-time PCR was used to detect 18 viruses in nasopharyngeal swabs and induced sputum samples in cases and in nasopharyngeal swabs in controls. RSV (OR 8.1), influenza viruses (OR 4.1), parainfluenza viruses (OR 2.0), adenoviruses (OR 2.2), bocavirus (OR 2.3) and cytomegalovirus (OR 1.6) were significantly associated with CAP (7), but there were no significant differences in metapneumovirus, coronavirus or rhinovirus findings between the cases and controls (7).

A 13-month case–control study from Moscow, Russia, comprised 56 radiologically confirmed CAP cases (54% boys) aged more than 12 months and 280 apparently healthy controls from schools and kindergartens matched for sex and birth month and year (8). All patients were treated at home, and their mean age was six-and-a-half years. Real-time PCR was used to detect 17 viruses in nasopharyngeal and oropharyngeal swaps in both groups. RSV (OR 7.7), metapneumovirus (OR 21.1), influenza A virus (OR 16.4) and adenoviruses (OR 15.5) were significantly associated with CAP (8). Rhinoviruses were more common in controls than in cases (OR 0.4, 95% CI 0.2–0.9), but no significant associations were found with parainfluenza viruses, coronaviruses, enteroviruses and bocavirus (8).

The three CAP studies agreed with each other on the adenovirus, influenza virus and RSV findings and disagreed on the bocavirus, coronavirus, metapneumovirus and parainfluenza virus findings (6–8). Rhinoviruses were more common in controls than cases in all the studies, and only the Russian study showed any significant differences (8).

A two-and-a-half years controlled multi-centre American study comprised 2222 children (55% boys), with a median age of two years, who had radiologically confirmed CAP, and 521 nonsymptomatic hospital-based controls (9). Nasopharyngeal and oropharyngeal swaps and paired serum samples were obtained from both groups. At least one virus was detected in 1,472 (66%) of the CAP cases: RSV in 28%, rhinovirus in 27%, metapneumovirus in 13%, adenovirus in 11%, influenza virus in 7% and coronavirus in 5% (9). After adjustments for age, rhinoviruses were found in 17% of the controls and 22% of the cases. All the other pathogens were detected in 3% or less of the controls (9). Another study included 832 children hospitalised for CAP at <18 years of age and 521 asymptomatic controls from two outpatient surgery units (10). Nasopharyngeal and oropharyngeal swaps were studied by real-time PCR for 12 viruses. In the logistic regression adjusted for age, month and hospital, rhinovirus detection did not increase the risk of CAP (aOR 1.13, 95% CI 0.84–1.51), whereas RSV (aOR 15.2), metapneumovirus (aOR 10.4), parainfluenza viruses (aOR 2.3) and coronaviruses (aOR 3.2) increased.

Although the studies reviewed here were carried out well, with adequate population-based healthy controls (Table 2), they were from three different environments: a suburban area of a high-income country (6), an urban area of a middle-income country (8) and a rural area of a low-income country (7). In addition, the age distribution of the patients and the study settings – inpatients (6), outpatients (8) or both (7) – influenced the results. The sample collections were identical between the cases and controls in the Swedish and Russian studies (7,9), but induced sputum was only collected from cases in the South-African study, which may have increased the positive findings (8). The study results were surprisingly similar, highlighting the well-established role of RSV, influenza viruses, parainfluenza viruses and adenoviruses in paediatric CAP and showing higher metapneumovirus levels in CAP than found in the

2015 meta-analysis (5). They also suggested a minor role for picornaviruses, namely rhinovirus and enteroviruses, and coronaviruses. The impact of the bocavirus was less clear, as it was found significantly more often in the Swedish controls (6), but significantly more often in the South-African CAP cases (7).

CONCLUSION

There is no doubt that rhinoviruses and other picornaviruses are the real causes of paediatric CAP, but the frequency is probably much less than the levels suggested by noncontrolled observational studies. Therefore, controlled studies are needed, preferably with case–control designs that contain nonsymptomatic, healthy population-based controls and appropriate analyses.

CONFLICT OF INTEREST

No conflicts of interest to declare.

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